CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125516Orig1s000

MEDICAL REVIEW(S)

ADDENDUM TO CLINICAL REVIEW

Application Type	Biologics License Application
Application Number(s)	125516
Priority or Standard	Priority
Submit Date(s)	April 11, 2014
Received Date(s)	April 11, 2014
Revised PDUFA Goal Date (Due to Major Amendment)	March 10, 2015
Division / Office	DOP2/OHOP
Reviewer Name(s)	Martha Donoghue
Addendum Completion Date	March 5, 2015
Established Name	Dinutuximab
(Proposed) Trade Name	Unituxin
Therapeutic Class	Chimeric monoclonal antibody
Applicant	United Therapeutics
Formulation(s)	Injection for intravenous infusion
Dosing Regimen	17.5 mg/m^2/day for four consecutive days for five cycles
Indication(s)	High-risk neuroblastoma
Intended Population(s)	Pediatric patients

Reference ID: 3711777

Background

Late in the original review cycle, United Therapeutics Corporation (UTC) provided additional data on antibody-dependent cell-mediated (ADCC) cytotoxicity indicating that recent drug substance and drug product lots had consistently higher ADCC activity compared to early drug product lots of UTC material that were used in the analytical comparability assessment (Table 1, adapted from information provided by UTC). This information prompted concern among the clinical, nonclinical, and quality review teams that that these differences in ADCC activity could adversely affect the safety and tolerability of dinutuximab. In particular, there was a concern that increased ADCC activity could result in increased neuropathic effects such as severe pain, sensory neuropathy, and motor neuropathy. The wide variability in ADCC activity also raised concerns regarding process consistency.

Table 1: Relative ADCC Potency by UTC Lot

Lot Number	(b) (4) Date	Clinical Study	Relative ADCC Potency
S110601[a]	11/1/2011	DIV-NB-201	100
2600429	9/4/2012	DIV-NB-302	170
2600477	11/6/2012	DIV-NB-302	217
2600542	11/20/2012	DIV-NB-302	147
2600562	10/15/2013	DIV-NB-302	197

[a] S110601 is the UTC reference standard and the comparator sample for ADCC. All potency is expressed relative to S110601 activity.
Source: Applicant BLA submission

After a discussion of the status of the BLA review at an internal meeting held with Dr. John Jenkins, Director of the Office of New Drugs (OND), on October 21, 2014, the BLA review team decided that additional clinical and product quality data would be required to address the potential safety concerns associated with the increased ADCC activity observed in recently manufactured drug product lots. The Division of Oncology Products 2 (DOP2) decided that these data would constitute a major amendment that would extend the review timeline of the BLA.

On October 29, 2014, DOP2 notified UTC in an ad hoc teleconference that UTC would be receiving requests for information that would constitute a major amendment to the BLA. On this date, the DOP2 clinical team also issued an information request for datasets with domains permitting analysis of serious and severe adverse events by lot number for patients exposed to dinutuximab from January 2014 through October 21, 2014 in Study 302.

Additionally, DOP2 requested that UTC provide analyses comparing the per-patient incidence of severe and serious adverse events per cycle and overall for each dinutuximab lot with the per-patient incidence (per cycle and overall) of these adverse events in patients exposed to ch14.18 in the integrated summary of safety (ISS) previously submitted to the BLA. Patient narratives for serious adverse events were also requested. The Division requested submission of the same information on an updated, cumulative basis by December 15, 2014 and February 15, 2015 (using a data cutoff date of January 31, 2015 or later).

DOP2 also submitted information requests for substantive additional information on behalf of the chemistry and manufacturing (CMC) and product microbiology teams on October 29, 2014 and November 19, 2014.

On December 7, 2014, DOP2 issued a letter formally informing UTC that the amendments to the BLA received on November 14th, 17th, and 21st, 2014 in response to these information requests constituted major amendments to the application and that the goal date for action on the application would therefore be extended by three months (revised PDUFA action goal date March 10, 2015). As a result, the timeline for communicating labeling changes and postmarketing requirements and commitments was revised in accordance with *PDUFA Reauthorization Performance Goals and Procedures – Fiscal Years 2013 through 2017*.

UTC submitted the updated cumulative clinical safety information outlined in DOP2's October 29, 2014 information request to the BLA on November 14, 2014, December 15, 2014, and February 18, 2015.

Clinical Review of Additional Safety Information Submitted to the BLA

Review Summary

Clinical review of the updated safety information submitted to the BLA did not result in identification of additional safety signals from use of dinutuximab provided by UTC to patients enrolled in Study DIV-NB-302 over the approximately one year time period covered by the information request (from January 21, 2014, when NCI-provided ch14.18 was permanently replaced by dinutuximab produced by UTC, through January 31, 2015). Overall, the toxicity profile of dinutuximab (UTC) appears comparable to the toxicity profile of NCI-provided ch14.18 (hereafter referred to as "ch14.18"). Additionally, analyses of these data did not uncover a trend for increased toxicity in the dinutuximab lots with higher ADCC activity compared to the lots with lower ADCC activity.

Notably, peripheral sensory neuropathy was reported in 3/249 (1%) of patients exposed to dinutuximab over the reporting period (two Grade 3 and one Grade 2) and there were no cases of peripheral motor neuropathy reported with dinutuximab. The cases of peripheral sensory neuropathy appeared to be related to the infusion, improved with medical management, and decreased in severity over time.

However, the results of these analyses should be interpreted with caution due to the relatively small number of patients who received dinutuximab over this one year time period, and the smaller numbers of patients who were exposed to a given lot. Notably, only 63 patients received at least one dose of dinutuximab from Lot 2600477 and only 40 patients received at least one dose of dinutuximab from Lot 2600562, the two lots with the highest relative ADCC potency. Because analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to further assess whether variations in ADCC activity alter the safety and tolerability of dinutuximab and the new pharmacovigilance system that FDA is required to establish under 505(k)(3) of the FDCA will not be sufficient to assess this serious risk, the clinical review team recommends that the Applicant conduct the following study as a postmarketing requirement:.

> *Provide a comparison of comprehensive exposure and safety data from approximately 220 patients who complete treatment with dinutuximab, pooling across dinutuximab lots and by individual lot, with the historical experience observed in approximately 1100 patients treated with ch14.18 (manufactured by SAIC for the National Cancer Institute). Based on these data, provide thoughtful analyses of the safety and tolerability of the marketed product, Unituxin, and an assessment regarding whether variations in antibody-dependent cell-mediated toxicity across dinutuximab lots alter the safety and tolerability of dinutuximab.*

Additionally, the data submitted to the BLA are inadequate to fully characterize the risk of hypersensitivity reactions, including anaphylaxis (which would require permanent discontinuation of dinutuximab) versus infusion reactions (which can usually be managed by infusion rate reductions and supportive management). Because the clinical presentations of infusion reactions and hypersensitivity reactions can be similar, the majority of cases consistent with severe infusion reactions were reported as allergic reactions, hypersensitivity reactions, or anaphylaxis. However, many patients who experienced these reactions were able to tolerate subsequent infusions. Additional information is needed to support

product labeling and guide healthcare providers on the management and identification of hypersensitivity reactions and infusion reactions related to dinutuximab. Because analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess the known serious risk of hypersensitivity, including anaphylaxis, and the new pharmacovigilance system that FDA is required to establish under 505(k)(3) of the FDCA will not be sufficient to assess this serious risk, the clinical review team recommends that the Applicant conduct the following study as a postmarketing requirement:

> *Submit datasets and safety analyses of laboratory data including serum complement, IgE, tryptase, histamine, and human anti-chimeric antibody levels obtained in patients with documented Grade 4 allergic reactions or anaphylaxis from a sufficient number of patients with neuroblastoma to allow for improved characterization of these adverse reactions to better inform product labeling. For each case identified, provide a narrative description that includes a summary of the allergic reaction or anaphylaxis adverse reaction, rechallenge information, and an assessment of whether the clinical presentation and laboratory data obtained were consistent with an allergic reaction or an infusion reaction.*

Finally, late in the review cycle a safety report describing a well-documented case of atypical hemolytic uremic syndrome (aHUS) was submitted by the Cancer Therapy Evaluation Program to IND 4308. This case is supported by a less well documented case that occurred in 2011 with ch14.18. In response to these cases, the clinical reviewer asked the Applicant to contact the clinical site to elucidate whether the patient who experienced the first case of aHUS received additional treatment with ch14.18. According to UTC, the clinical site confirmed that this patient received an additional treatment with ch14.18 upon satisfactory resolution of the aHUS; however, aHUS recurred following retreatment so ch14.18 was subsequently permanently discontinued.
Although both cases are confounded by prior treatment, which included radiation therapy and consolidation myeloablative chemotherapy with autologous stem cell transplant, there is strong temporal relationship between development of aHUS and receipt of ch14.18/dinutuximab and this causal relationship is reinforced by the positive rechallenge observed in the earlier case. Therefore, the risk of aHUS should be communicated in product labeling.

Summary of Exposure to Dinutuximab

From January 21, 2014 through January 31, 2015, a total of 249 patients received at least one dose of dinutuximab (Table 2). The majority of patients received lot 2600429 (relative ADCC potency of 170).

Table 2: Dinutuximab exposure summary

Dinutuximab lot	No. of Patients	Median (range) of cycle received
2600429	154	3 (1,5)
2600429 and 2600477	11	1 (1,2)
2600429 and 2600542	6	1 (1,1)
2600429 and 2600562	1	1 (1,1)
2600477	63	2 (1,3)
260047 and 2600542	8	1 (1,1)
2600542	102	2 (1,5)
2600542 and 2600562	9	1 (1,1)
2600562	40	1 (1,3)
L0602009 (NCI lot) and 2600542	1	1 (1,1)
Overall	249	4 (1,5)

A total of 36 patients (14%) prematurely discontinued study therapy. The primary reported reason for discontinuation of study therapy was progressive disease (15 patients, or 6% of patients treated with dinutuximab), followed by withdrawal of consent for additional treatment (11 patients, or 4% of treated patients), adverse reactions (6 patients, or 2%), and physician decision (3 patients, or 1%), and death (1 patient, or 0.4%). All six patients who discontinued study therapy prematurely due to adverse reactions discontinued due to adverse reactions consistent with severe infusion reactions or hypersensitivity reactions/anaphylaxis. Review of the adverse event database revealed that the majority of patients who discontinued study therapy prematurely due to physician or parental/guardian decisions had adverse reactions that are known to be related to dinutuximab, including capillary leak syndrome, hypotension, infusion reactions, hypersensitivity reactions, or infection.

Reviewer note: Interpretation of comparison of the rate of premature study therapy discontinuation observed with dinutuximab with the rate of premature discontinuation with ch14.18 is difficult because treatment was ongoing at the time of data cutoff for approximately 88 of the 249 patients treated with dinutuximab as of January 31, 2015, and because some patients received both NCI- and UTC-manufactured products during the course of their treatment. However, the 14% incidence of premature

discontinuation of study therapy observed among the 249 patients treated with dinutuximab is reassuring because 29% discontinued study therapy with ch14.18 in Study DIV-NB-301. Additionally, the incidence of premature discontinuation due to dinutuximab toxicity or physician or parental decision, 8%, compares favorably to the 19% incidence of premature discontinuation of study therapy due to toxicity observed in Study DIV-NB-301.

Dose reductions or infusion rate reductions resulting in receipt of at least 25% less than the recommended dose of dinutuximab were reported in 16 (6%) of patients. In Study DIV-NB-303, the only study of ch14.18 in which dose modifications were systematically recorded, 78% of patients required at least one dose interruption and 31% of received less than 90% of the planned dose of ch14.18.

Analyses of Dinutuximab Adverse Events

Table 3 presents the per-patient incidence of severe (≥ Grade 3) treatment-emergent adverse events by Preferred Term (PT) and System Organ Class (SOC) for each UTC lot and overall for dinutuximab in comparison with the integrated summary of safety (ISS) population treated with ch14.18 provided by the NCI. Adverse events of Grade 3 or greater severity occurring in at least 5% of patients treated with dinutuximab or ch14.18 are included in Table 3.

Decreased urine output was the sole adverse event of Grade 3 or greater severity with a per-patient incidence notably higher in patients receiving dinutuximab in comparison to the per-patient incidence in the integrated summary of safety (8% vs. 2%).

Reviewer note: Comparisons of the per-patient incidence of severe adverse events should be interpreted with caution because of the relatively small number of patients who received dinutuximab in comparison to the number of patients who received ch14.18, the smaller numbers of patients who were exposed to a given lot, and because treatment was ongoing at the time of data cutoff for approximately 88 of the 249 patients treated with dinutuximab as of January 31, 2015, whereas safety data comprising the ISS are mature.

Reference ID: 3711777

Table 3: Comparison of Severe Adverse Events Experienced by Patients Treated with Dinutuximab (UTC) and ch14.18 (NCI)

Adverse Reaction	Lot 26000429 N=154	Lot 2600477 N=63	Lot 2600542 N=102	Lot 2600562 N=40	[1]All UTC Lots N=249	[2]Ch14.18 Integrated Summary of Safety N=1101
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**16**	**5**	**11**	**0**	**14**	**36**
Anemia	15	5	11	0	14	33
Gastrointestinal Disorders	**17**	**11**	**6**	**5**	**15**	**27**
Abdominal pain	10	3	2	0	7	14
Diarrhea	7	8	4	3	7	10
General Disorders and Administration Site Conditions	**38**	**25**	**28**	**20**	**40**	**51**
Pyrexia	28	21	21	15	31	39
Pain	14	11	14	8	17	21
Immune System Disorders	**10**	**8**	**11**	**10**	**15**	**21**
Anaphylactic reaction	5	6	5	10	8	17
Hypersensitivity	7	3	7	5	8	6
Infections and Infestations	**20**	**13**	**12**	**13**	**22**	**33**
Device-related infection	7	5	5	5	9	15
Investigations	**34**	**18**	**26**	**18**	**33**	**61**
Lymphopenia	12	3	10	5	11	28
Thrombocytopenia	13	5	6	0	12	27
Neutropenia	8	5	7	3	8	25

Adverse Reaction	Lot 26000429 N=154	Lot 2600477 N=63	Lot 2600542 N=102	Lot 2600562 N=40	[1]All UTC Lots N=249	[2]Ch14.18 Integrated Summary of Safety N=1101
	Per-patient Incidence (%)					
Increased alanine aminotransferase	13	2	6	3	10	17
Increased aspartate aminotransferase	9	2	4	3	8	10
Increased gamma-glutamyl transferase	7	0	1	3	4	7
Decreased urine output	8	2	3	10	8	2
Metabolism and Nutrition Disorders	**36**	**24**	**28**	**23**	**39**	**51**
Hypokalemia	23	13	12	13	23	32
Hyponatremia	12	5	6	0	10	20
Decreased appetite	7	3	4	5	7	7
Hypophosphatemia	5	2	5	3	6	6
Musculoskeletal and Connective Tissue Disorders	**5**	**0**	**1**	**0**	**3**	**10**
Pain in extremity	3	0	1	0	2	6
Nervous System Disorders	**3**	**0**	**1**	**0**	**3**	**10**
Neuralgia	1	0	0	0	0	7
Respiratory and Thoracic and Mediastinal Disorders	**21**	**10**	**13**	**5**	**21**	**21**
Hypoxia	14	8	11	5	16	13
Skin and Subcutaneous Tissue Disorders	**7**	**5**	**6**	**10**	**8**	**11**
Urticaria	5	2	5	8	6	8
Vascular Disorders	**15**	**18**	**13**	**8**	**20**	**28**

Adverse Reaction	Lot 26000429 N=154	Lot 2600477 N=63	Lot 2600542 N=102	Lot 2600562 N=40	[1]All UTC Lots N=249	[2]Ch14.18 Integrated Summary of Safety N=1101
	Per-patient Incidence (%)					
Hypotension	12	16	13	8	17	19
Capillary Leak Syndrome	4	3	2	3	5	13

[1] Some patients received more than one lot of dinutuximab overall, and some patients received different lots of dinutuximab in the same cycle.
[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study.

Tables 4 through 8 present the per-patient incidence of severe (≥ Grade 3) treatment-emergent adverse events by Preferred Term (PT) and System Organ Class (SOC) for each UTC lot and overall for dinutuximab in comparison with the integrated summary of safety (ISS) population treated with ch14.18 provided by the NCI by treatment cycle. Adverse events of Grade 3 or greater severity occurring in at least 5% of patients treated with dinutuximab or ch14.18 are included. As these tables illustrate, there do not appear to be any consistent clinically relevant differences in the toxicity profile of the different dinutuximab lots in comparison with the overall toxicity profile of dinutuximab and the toxicity profile of ch14.18.

Reviewer note: Comparisons of the per-patient incidence of severe adverse events should be interpreted with caution because of the relatively small number of patients who received dinutuximab in comparison to the number of patients who received ch14.18, and the even smaller numbers of patients who were exposed to a given lot.

Table 4: Per-Patient Incidence of Severe Adverse Reactions in Cycle 1

Adverse Reactions Cycle 1	Lot 26000429 N=87	Lot 2600477 N=36	Lot 2600542 N=40	Lot 2600562 N=14	[1]All UTC Lots N=181	[2]Ch14.18 Integrated Summary of Safety N=1101
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**10**	**3**	**15**	**0**	**9**	**20**
Anemia	10	3	15	0	9	18
Gastrointestinal Disorders	**16**	**6**	**3**	**7**	**10**	**15**
Abdominal pain	10	3	3	0	6	10
General Disorders and Administration Site Conditions	**23**	**25**	**33**	**29**	**25**	**23**
Pain	12	14	20	14	14	12
Pyrexia	14	19	15	14	15	11
Infections and Infestations	**6**	**8**	**8**	**14**	**8**	**11**
Device-related infection	1	6	5	0	3	5
Investigations	**21**	**3**	**20**	**21**	**17**	**39**
Thrombocytopenia	9	3	8	0	7	18
Lymphopenia	12	0	8	7	8	17
Neutropenia	1	0	3	0	1	7
Increased alanine aminotransferase	6	0	3	0	3	6
Decreased urine output	7	0	5	14	6	1
Metabolism and Nutrition Disorders	**14**	**14**	**23**	**21**	**16**	**15**
Hypokalemia	6	8	10	14	8	8
Nervous System Disorders	**2**	**0**	**0**	**0**	**1**	**7**
Neuralgia	0	0	0	0	0	6

Adverse Reactions Cycle 1	Lot 26000429 N=87	Lot 2600477 N=36	Lot 2600542 N=40	Lot 2600562 N=14	[1]All UTC Lots N=181	[2]Ch14.18 Integrated Summary of Safety N=1101
	Per-patient Incidence (%)					
Respiratory and Thoracic and Mediastinal Disorders	**10**	**14**	**13**	**14**	**12**	**9**
Hypoxia	9	11	10	14	11	7
Vascular Disorders	**7**	**8**	**8**	**14**	**8**	**10**
Hypotension	5	8	8	14	7	7

[1] Some patients received more than one lot of dinutuximab during the same cycle; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study. Study POG-9347 not included in the ISS because per course information was not available from this study.

Table 5: Per-Patient Incidence of Severe Adverse Reactions in Cycle 2

Adverse Reactions Cycle 2	Lot 26000429 N=82	Lot 2600477 N=26	Lot 2600542 N=46	Lot 2600562 N=11	[1]All UTC Lots N=174	[2]Ch14.18 Integrated Summary of Safety N=1042
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**13**	**4**	**13**	**0**	**10**	**21**
Anemia	13	4	13	0	10	19
Gastrointestinal Disorders	**7**	**12**	**7**	**0**	**7**	**12**
Diarrhea	5	8	7	0	5	5

Adverse Reactions Cycle 2	Lot 26000429 N=82	Lot 2600477 N=26	Lot 2600542 N=46	Lot 2600562 N=11	[1]All UTC Lots N=174	[2]Ch14.18 Integrated Summary of Safety N=1042
	Per-patient Incidence (%)					
General Disorders and Administration Site Conditions	**33**	**31**	**28**	**9**	**30**	**35**
Pyrexia	26	27	24	9	24	29
Pain	12	8	13	0	11	8
Immune System Disorders	**4**	**15**	**7**	**18**	**8**	**11**
Anaphylactic reaction	1	12	4	18	6	9
Investigations	**35**	**31**	**28**	**18**	**31**	**48**
Lymphopenia	10	0	11	0	8	22
Thrombocytopenia	16	12	7	0	11	21
Neutropenia	10	8	7	9	8	17
Increased alanine aminotransferase	10	0	2	0	5	7
Decreased urine output	7	4	4	0	5	1
Metabolism and Nutrition Disorders	**44**	**23**	**26**	**27**	**34**	**38**
Hypokalemia	24	8	13	18	18	20
Hyponatremia	13	4	7	0	9	15
Hypophosphatemia	7	4	9	9	8	5
Respiratory, Thoracic, and Mediastinal Disorders	**20**	**8**	**9**	**9**	**13**	**9**
Hypoxia	13	4	4	0	8	6
Vascular Disorders	**15**	**19**	**15**	**0**	**14**	**16**
Hypotension	12	15	13	0	12	9
Capillary Leak Syndrome	4	8	2	0	3	8

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.

[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study. Study POG-9347 not included in the ISS because per course information was not available from this study.

Table 6: Per-Patient Incidence of Severe Adverse Reactions in Cycle 3

Adverse Reactions Cycle 3	Lot 26000429 N=84	Lot 2600477 N=17	Lot 2600542 N=55	Lot 2600562 N=9	[1]All UTC Lots N=173	[2]Ch14.18 Integrated Summary of Safety N=986
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**6**	**0**	**0**	**0**	**4**	**9**
Anemia	6	0	0	0	4	8
General Disorders and Administration Site Conditions	**12**	**12**	**4**	**22**	**9**	**9**
Pain	8	6	4	11	6	6
Investigations	**11**	**0**	**9**	**0**	**9**	**24**
Thrombocytopenia	4	0	0	0	2	8
Lymphopenia	2	0	0	0	1	7
Decreased urine output	6	0	4	0	5	0

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study. Study POG-9347 not included in the ISS because per course information was not available from this study.

Table 7: Per-Patient Incidence of Severe Adverse Reactions in Cycle 4

Adverse Reactions Cycle 4	Lot 26000429 N=84	Lot 2600477 N=17	Lot 2600542 N=52	Lot 2600562 N=11	[1]All UTC Lots N=169	[2]Ch14.18 Integrated Summary of Safety N=931
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**8**	**12**	**10**	**0**	**8**	**16**
Anemia	7	12	10	0	8	15
General Disorders and Administration Site Conditions	**20**	**12**	**17**	**18**	**19**	**21**
Pyrexia	16	6	15	9	14	15
Pain	5	6	6	9	7	8
Immune System Disorders	**10**	**6**	**8**	**9**	**8**	**7**
Anaphylactic reaction	4	6	2	9	4	6
Investigations	**19**	**12**	**15**	**18**	**18**	**35**
Lymphopenia	6	6	4	9	5	13
Neutropenia	5	6	6	0	5	13
Thrombocytopenia	2	0	2	0	2	10
Increased alanine aminotransferase	6	6	8	9	7	6
Metabolism and Nutrition Disorders	**26**	**35**	**17**	**18**	**24**	**26**
Hypokalemia	14	29	8	0	12	14
Hyponatremia	5	6	6	0	5	9
Respiratory, Thoracic, and Mediastinal Disorders	**12**	**0**	**10**	**0**	**9**	**6**
Hypoxia	7	0	10	0	7	4

Adverse Reactions Cycle 4	Lot 26000429 N=84	Lot 2600477 N=17	Lot 2600542 N=52	Lot 2600562 N=11	[1]All UTC Lots N=169	[2]Ch14.18 Integrated Summary of Safety N=931
	Per-patient Incidence (%)					
Vascular Disorders	**7**	**17**	**12**	**0**	**10**	**10**
Hypotension	6	18	12	0	9	6
Capillary Leak Syndrome	1	6	2	0	2	6

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study. Study POG-9347 not included in the ISS because per course information was not available from this study.

Table 8: Per-Patient Incidence of Severe Adverse Reactions in Cycle 5

Adverse Reactions Cycle 5	Lot 26000429 N=83	Lot 2600477 N=14	Lot 2600542 N=43	Lot 2600562 N=9	[1]All UTC Lots N=159	[2]Ch14.18 Integrated Summary of Safety N=882
	Per-patient Incidence (%)					
General Disorders and Administration Site Conditions	**10**	**9**	**0**	**0**	**8**	**7**
Pain	8	7	0	0	6	4
Pyrexia	9	9	0	0	2	2
Investigations	19	9	0	0	14	14
Urine output decreased	7	0	0	11	5	1

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Patients included in the overall ISS were primarily treated with NCI manufactured ch14.18, but there were 28 patients included in this population that were treated with both ch14.18 and dinutuximab in the DIV-NB-201 study. Study POG-9347 not included in the ISS because per course information was not available from this study.

Table 9 presents the per-patient incidence of serious treatment-emergent adverse events by Preferred Term (PT) and System Organ Class (SOC) for each UTC lot and overall for dinutuximab in comparison with the integrated summary of safety (ISS) population treated with ch14.18 provided by the NCI. Serious adverse events were defined as those adverse events meeting NCI's Adverse Event Expedited Reporting System (AdEERS) criteria (see main Clinical Review of this BLA for details regarding AdEERS reporting requirements). Serious adverse event data presented below were derived from DIV-NB-301, DIV-NV-302, and DIV-NB-303, because these studies shared common serious adverse event reporting procedures. Serious Adverse events of Grade 3 or greater severity occurring in at least 3% of patients treated with dinutuximab or ch14.18 are included.

Tables 10 through 14 Tables 4 through 8 present the per-patient incidence of serious treatment-emergent adverse events by Preferred Term (PT) and System Organ Class (SOC) for each UTC lot and overall for dinutuximab in comparison with the integrated summary of safety (ISS) population treated with ch14.18 by treatment cycle. Serious adverse events of Grade 3 or greater severity occurring in at least 3% of patients treated with dinutuximab or ch14.18 are included. As these tables illustrate, there do not appear to be any consistent clinically relevant differences in the incidence and types of serious adverse events reported for the different dinutuximab lots in comparison with dinutuximab overall and the ISS for ch14.18.

Reviewer note: Comparisons of the per-patient incidence of serious adverse events should be interpreted with caution because of the relatively small number of patients who received dinutuximab in comparison to the number of patients who received ch14.18, and the even smaller numbers of patients who were exposed to a given lot.

Table 9: Comparison of Serious Adverse Events Experienced by Patients Treated with Dinutuximab (UTC) and ch14.18 (NCI)

Serious Adverse Reaction	Lot 26000429 N=154	Lot 2600477 N=63	Lot 2600542 N=102	Lot 2600562 N=40	[1]All UTC Lots N=249	[2]Ch14.18 Integrated Summary of Safety N=1028
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**3**	**0**	**2**	**0**	**2**	**7**
Anemia	1	0	2	0	1	6
Gastrointestinal Disorders	**7**	**5**	**1**	**0**	**6**	**10**
Diarrhea	2	5	1	0	3	4
Abdominal pain	1	2	0	0	1	3
General Disorders and Administration Site Conditions	**4**	**3**	**7**	**0**	**6**	**19**
Fever	3	2	5	0	4	13
Pain	1	2	0	0	1	4
Immune System Disorders	**9**	**10**	**10**	**10**	**14**	**15**
Anaphylactic reaction	4	6	5	10	8	10
Allergic Reaction	5	8	7	3	8	6
Infections and Infestations	**12**	**8**	**7**	**3**	**13**	**24**
Unspecified	0	0	0	0	0	11
Catheter-related infection	4	2	0	0	3	10
Sepsis	1	2	6	3	4	2
Investigations	**8**	**3**	**5**	**3**	**8**	**17**
Lymphopenia	0	0	0	0	0	6
Neutropenia	1	0	0	0	0	6
Thrombocytopenia	1	0	2	0	1	4

Serious Adverse Reaction	Lot 26000429 N=154	Lot 2600477 N=63	Lot 2600542 N=102	Lot 2600562 N=40	[1]All UTC Lots N=249	[2]Ch14.18 Integrated Summary of Safety N=1028
	Per-patient Incidence (%)					
Increased alanine aminotransferase	1	0	0	0	1	3
Decreased urine output	5	2	3	3	5	1
Metabolism and Nutrition Disorders	**9**	**10**	**7**	**0**	**11**	**21**
Hypokalemia	1	3	1	0	2	9
Hyponatremia	3	2	3	0	4	6
Hypocalcemia	1	2	0	0	1	4
Hypophosphatemia	2	2	1	0	2	4
Dehydration	4	2	1	0	3	2
Respiratory and Thoracic and Mediastinal Disorders	**9**	**3**	**4**	**5**	**9**	**13**
Hypoxia	3	0	3	5	4	6
Skin and Subcutaneous Tissue Disorders	**5**	**3**	**4**	**5**	**6**	**6**
Urticaria	4	3	4	5	6	4
Vascular Disorders	**15**	**18**	**11**	**5**	**19**	**23**
Hypotension	12	16	10	5	17	15
Capillary Leak Syndrome	6	6	2	3	7	11

[1] Some patients received more than one lot of dinutuximab overall, and some patients received different lots of dinutuximab in the same cycle.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

Table 10: Per-Patient Incidence of Serious Adverse Reactions in Cycle 1

Serious Adverse Reactions Cycle 1	Lot 26000429 N=87	Lot 2600477 N=36	Lot 2600542 N=40	Lot 2600562 N=14	[1]All UTC Lots N=181	[2]Ch14.18 Integrated Summary of Safety N=1028
	Per-patient Incidence (%)					
Blood and Lymphatic System Disorders	**2**	**0**	**0**	**0**	**1**	**3**
Anemia	1	0	3	0	1	3
Immune System Disorders	**5**	**6**	**3**	**7**	**4**	**4**
Allergic reaction	3	3	3	7	3	2
Investigations	6	0	8	7	6	8
Lymphopenia	0	0	0	0	0	3
Decreased urine output	5	0	5	7	4	1
Vascular Disorders	**8**	**8**	**3**	**14**	**8**	**8**
Hypotension	8	8	3	14	7	5

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

Table 11: Per-Patient Incidence of Serious Adverse Reactions in Cycle 2

Serious Adverse Reactions Cycle 2	Lot 26000429 N=82	Lot 2600477 N=26	Lot 2600542 N=46	Lot 2600562 N=11	[1]All UTC Lots N=174	[2]Ch14.18 Integrated Summary of Safety N=976
	Per-patient Incidence (%)					
General Disorders and Administration Site Conditions	**4**	**8**	**9**	**0**	**5**	**12**
Pyrexia	2	4	7	0	3	9
Immune System Disorders	**2**	**15**	**4**	**18**	**7**	**8**
Anaphylactic reaction	1	12	4	18	6	5
Allergic reaction	1	12	0	0	3	3
Infections and Infestations	**6**	**8**	**4**	**0**	**5**	**8**
Unspecified	0	0	0	0	0	**4**
Investigations	**5**	**8**	**2**	**0**	**5**	**9**
Neutropenia	1	0	0	0	1	3
Metabolism and Nutrition Disorders	**10**	**8**	**9**	**0**	**8**	**13**
Hypokalemia	2	4	2	0	2	5
Hyponatremia	4	0	4	0	3	4
Hypocalcemia	2	0	0	0	1	3
Skin and Subcutaneous Disorders	**4**	**8**	**0**	**9**	**3**	**3**
Urticaria	**4**	**8**	**0**	**9**	**3**	**2**
Vascular Disorders	**15**	**19**	**9**	**0**	**12**	**12**
Hypotension	11	15	9	0	10	8
Capillary Leak Syndrome	6	12	0	0	5	5

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

Table 12: Per-Patient Incidence of Serious Adverse Reactions in Cycle 3

Serious Adverse Reactions Cycle 3	Lot 26000429 N=84	Lot 2600477 N=17	Lot 2600542 N=55	Lot 2600562 N=9	[1]All UTC Lots N=173	[2]Ch14.18 Integrated Summary of Safety N=923
	Per-patient Incidence (%)					
Infections and Infestations	**7**	**0**	**2**	**0**	**5**	**5**
Catheter related infection	5	0	0	0	3	2
Vascular Disorders	**2**	**6**	**0**	**0**	**3**	**3**
Hypotension	2	6	0	0	2	1

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

Table 13: Per-Patient Incidence of Serious Adverse Reactions in Cycle 4

Serious Adverse Reactions Cycle 4	Lot 26000429 N=84	Lot 2600477 N=17	Lot 2600542 N=52	Lot 2600562 N=11	[1]All UTC Lots N=169	[2]Ch14.18 Integrated Summary of Safety N=877
	Per-patient Incidence (%)					
General Disorders and Administration Site Conditions	**0**	**0**	**2**	**0**	**1**	**5**
Fever	0	0	2	0	1	4
Immune System Disorders	**8**	**0**	**8**	**9**	**7**	**5**
Anaphylaxis	4	0	2	9	3	3
Allergic reaction	4	0	6	0	4	1
Infections and Infestations	**7**	**0**	**2**	**0**	**4**	**7**
Unspecified	0	0	0	0	0	3
Catheter related infection	1	0	0	0	1	3
Skin and Subcutaneous Tissue Disorders	**4**	**0**	**6**	**0**	**4**	**2**
Urticaria	4	0	6	0	4	2
Vascular Disorders	**7**	**18**	**15**	**0**	**11**	**7**
Hypotension	6	12	14	0	9	4
Capillary Leak Syndrome	2	12	4	9	4	4

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

Table 14: Per-Patient Incidence of Serious Adverse Reactions in Cycle 5

Serious Adverse Reactions Cycle 5	Lot 26000429 N=83	Lot 2600477 N=14	Lot 2600542 N=43	Lot 2600562 N=9	[1]All UTC Lots N=159	[2]Ch14.18 Integrated Summary of Safety N=837
	Per-patient Incidence (%)					
Immune System Disorders	**2**	**0**	**5**	**11**	**3**	**2**
Allergic reaction	1	0	5	0	2	1
Anaphylaxis	1	0	5	0	1	1
Infections and Infestations	**1**	**7**	**2**	**0**	**2**	**5**
Catheter related infections	0	0	0	0	0	2
Sepsis	0	7	2	0	1	0
Device related infection	1	0	0	0	1	0

[1] Some patients received more than one lot of dinutuximab; for these patients, the adverse event was not ascribed to a particular lot.
[2]As of December 2013. Includes data from DIV-NB-301, DIV-NB-302, and DIV-NB-303 because these studies shared common AdEERS reporting criteria and procedures.

.

Deaths

Four patients died within 60 days of dinutuximab treatment, including three patients who died due to progressive disease and one patient who died of respiratory failure in the setting of sepsis due to *Klebsiella pneumoniae* approximately two days following receipt of the third day of treatment with dinutuximab in Cycle 2.

Reviewer note: In response to an information request, the sponsor indicated that the dinutuximab infusion bags were not cultured. Infection is a known risk of treatment with dinutuximab, and will be included in the Warnings and Precautions section of the dinutuximab package insert. To mitigate the risk of infection, dinutuximab product labeling will instruct healthcare providers to discard diluted dinutuximab solution 24 hours after preparation to decrease the risk of microbacterial overgrowth in the infusion bag. Additionally, a postmarketing requirement is under negotiation a study to confirm compatibility of the drug product with the use of an in-line filter during administration.

Additional Safety Information

On February 24, 2015 the sponsor of IND 4308, the Cancer Therapy Evaluation Program (CTEP) submitted a safety report describing a well-documented case of atypical hemolytic uremic syndrome (aHUS) occurring in a one year old boy approximately 4 days following receipt of the first cycle of treatment with dinutuximab. This patient presented with hypertension, hematuria, proteinuria, hemolytic anemia, and elevated blood urea nitrogen and creatinine A search of the safety database for ch14.18 uncovered one additional case of HUS that occurred in a 5 year old girl approximately four days following receipt of the first cycle of ch14.18 (2011, Study DIV-NB-302). This patient presented with hypertension, proteinuria, intravascular hemolysis, and progressive renal insufficiency. The AdEERS report indicated that the patient did not discontinue study therapy following this adverse event. According to UTC, the clinical site confirmed that this patient received an additional treatment with ch14.18 upon satisfactory resolution of the aHUS; however, aHUS recurred following retreatment so ch14.18 was subsequently permanently discontinued.

Reviewer note: Both cases are confounded by prior treatment, which included radiation therapy and consolidation myeloablative chemotherapy with autologous stem cell transplant. However, there is strong temporal relationship between development of aHUS and receipt of ch14.18/dinutuximab in both cases, and the causal relationship between ch14.18/dinutuximab and aHUS is reinforced by the positive rechallenge observed in the first case. Therefore, the risk of aHUS should be communicated in product labeling.

Consultation with Special Government Employees

This BLA was not the subject of an advisory committee meeting. As part of the review of this BLA, the clinical review team sought advice from two consultants with expertise in pediatric oncology and one patient representative with oncology expertise. These consultants were designated as Special Government Employees and were cleared for conflict of interest by the Division of Advisory Committee and Consultant Management at CDER prior to discussion of this application. After clearance was granted, DOP2 provided a briefing document summarizing the clinical safety and efficacy data submitted to the BLA and a copy of draft product labeling for Unituxin. Teleconferences were held between the clinical review team and each consultant separately. During these teleconferences, each consultant expressed a definitive opinion that dinutuximab appeared to provide a treatment benefit to patients with high risk neuroblastoma, and that the risk/benefit assessment favors treatment of patients with high risk neuroblastoma with dinutuximab. Each consultant also indicated that the risks of dinutuximab treatment appeared to be acceptable for this patient population, given the life-threatening nature of the disease.

Labeling Review

At the time of completion of this review, text for the proposed label had not been finalized. This section of the review will focus on high-level labeling recommendations. All sections of the proposed label and patient package insert were revised for clarity, brevity, and consistency. Only clinically-relevant, substantive content changes will be discussed in this section (sections pertaining to CMC, clinical pharmacology, or non-clinical issues are not included), with proposed wording for the key clinical sections of the package insert for Unituxin provided in italics.

Boxed Warning

The labeling originally proposed by UTC (b) (4) the clinical review team recommended that the risks of serious infusion reactions and neuropathy (including severe neuropathic pain, sensory neuropathy and motor neuropathy) be communicated in a boxed warning due to their serious nature, and requirement for premedication and close monitoring to prevent or mitigate the risk of these adverse reactions. At the time of this review, DOP2 and UTC agreed on the following text for inclusion in the Unituxin label as a boxed warning:

WARNING: SERIOUS INFUSION REACTIONS AND NEUROPATHY

Infusion Reactions: Serious and potentially life threatening infusion reactions occurred in 26% of patients treated with Unituxin. Administer required prehydration and premedication including antihistamines prior to each Unituxin infusion. Monitor patients closely for signs and symptoms of an infusion reaction during and for at least four hours following completion of each Unituxin infusion. Immediately interrupt Unituxin for severe infusion reactions and permanently discontinue Unituxin for anaphylaxis (2.2, 2.3, 5.1).

Neuropathy: Unituxin causes severe neuropathic pain in the majority of patients. Administer intravenous opioid prior to, during, and for 2 hours following completion of the Unituxin infusion. In clinical studies of patients with high-risk neuroblastoma, Grade 3 peripheral sensory neuropathy occurred in 2% to 9% of patients. In clinical studies of Unituxin and related GD2-binding antibodies, severe motor neuropathy was observed in adults. Resolution of motor neuropathy was not documented in all cases. Discontinue Unituxin for severe unresponsive pain, severe sensory neuropathy, or moderate to severe peripheral motor neuropathy (2.2, 2.3, 5.2).

Section 1: INDICATIONS AND USAGE

UTC originally proposed that Unituxin be indicated for (b) (4) Because the extent to which GM-CSF, IL-2, and RA contributed to the observed treatment effect in Study DIV-NB-301 is uncertain and because these therapies are not approved for the treatment of neuroblastoma, DOP2 recommended that these therapies not be specified in the indication statement. DOP2 also proposed adding a sentence following the indication statement to inform healthcare providers that approval of Unituxin was based on data derived from a trial that studied dinutuximab in combination with GM-CSF, IL-2, and RA in patients who achieved at least a partial response to prior therapy. DOP2 also recommended that the indication statement specify that Unituxin is approved as part of a multiagent multimodality regimen for the first line treatment of high risk neuroblastoma. Finally, because there are limited safety and efficacy data from the use of ch14.18/dinutuximab in adult patients with neuroblastoma (n<10), DOP2 recommended specifying that Unituxin was indicated in the pediatric population.

At the time of this review, DOP2 and UTC agreed on inclusion of the following indication statement in the Unituxin package insert:

Unituxin (dinutuximab) is indicated for (b) (4) .

Section 2: DOSAGE AND ADMINISTRATION

This section was extensively reorganized and reworded for clarity and readability. DOP2 recommended omitting [redacted (b) (4)] and instead provided references to the CLINICAL STUDIES and ADVERSE REACTIONS sections of the Unituxin package insert, which provide information regarding their use in combination with dinutuximab. Additionally, DOP2 recommended including a table of adverse reactions that require permanent discontinuation of dinutuximab. Additional language was added instructing healthcare providers to initiate the dinutuximab infusion within 4 hours of preparation of the diluted solution, and to discard the diluted Unituxin solution within 24 hours after preparation to minimize the risk of transmission of infection through bacterial overgrowth.

At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the DOSAGE AND ADMINISTRATION section of the package insert:

2 DOSAGE AND ADMINISTRATION

- *Verify that patients have adequate hematologic, [redacted (b) (4)], hepatic, and renal function prior to initiating each course of Unituxin [see Clinical Studies (14)].*
- *Administer required premedication and hydration prior to initiation of each Unituxin infusion [see Dosage and Administration (2.2)].*

2.1 Recommended Dose

- *The recommended dose of Unituxin is 17.5 mg/m^2/day administered as an intravenous infusion over 10 to 20 hours for 4 consecutive days for a maximum of 5 cycles (Tables 1 and 2) [see Dosage and Administration (2.4), Clinical Studies (14)].*
- *Initiate at an infusion rate of 0.875 mg/m^2/hour for 30 minutes. The infusion rate can be gradually increased as tolerated to a maximum rate of 1.75 mg/m^2/hour. Follow dose modification instructions for adverse reactions [see Dosage and Administration (2.3)].*

Table 1: Schedule of Unituxin Administration for Cycles 1, 3, and 5

Cycle Day	1 through 3	4	5	6	7	8 through 24*
Unituxin		X	X	X	X	

**Cycles 1, 3, and 5 are 24 days in duration.*

Table 2: Schedule of Unituxin Administration for Cycles 2 and 4

Cycle Day	***1 through 7***	***8***	***9***	***10***	***11***	***12 through 32****
Unituxin		*X*	*X*	*X*	*X*	

**Cycles 2 and 4 are 32 days in duration.*

2.2 Required Pre-treatment and Guidelines for Pain Management

Intravenous Hydration

- *Administer 0.9% Sodium Chloride Injection, USP 10 mL/kg as an intravenous infusion over one hour just prior to initiating each Unituxin infusion.*

Analgesics

- *Administer morphine sulfate (50 mcg/kg) intravenously immediately prior to initiation of Unituxin and then continue as a morphine sulfate drip at an infusion rate of 20 to 50 mcg/kg/hour during and for two hours following completion of Unituxin.*
- *Administer additional 25 mcg/kg to 50 mcg/kg intravenous doses of morphine sulfate as needed for pain up to once every 2 hours followed by an increase in the morphine sulfate infusion rate in clinically stable patients.*
- *Consider using fentanyl or hydromorphone if morphine sulfate is not tolerated.*
- *If pain is inadequately managed with opioids, consider use of gabapentin or lidocaine in conjunction with intravenous morphine.*

Antihistamines and Antipyretics

- *Administer an antihistamine such as diphenhydramine (0.5 to 1 mg/kg; maximum dose 50 mg) intravenously over 10 to 15 minutes starting 20 minutes prior to initiation of Unituxin and as tolerated every 4 to 6 hours during the Unituxin infusion.*
- *Administer acetaminophen (10 to 15 mg/kg; maximum dose 650 mg) 20 minutes prior to each Unituxin infusion and every 4 to 6 hours as needed for fever or pain. Administer ibuprofen (5 to 10 mg/kg) every 6 hours as needed for control of persistent fever or pain.*

2.3 Dosage Modifications

Manage adverse reactions by infusion interruption, infusion rate reduction, dose reduction, or permanent discontinuation of Unituxin (Table 3 and Table 4) [see Warnings and Precautions (5), Adverse Reactions (6), Clinical Studies (14)].

Table 3: Adverse Reactions Requiring Permanent Discontinuation of Unituxin

Grade 3 or 4 anaphylaxis
Grade 3 or 4 serum sickness
Grade 3 pain unresponsive to maximum supportive measures
Grade 4 sensory neuropathy or Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks
Grade 2 peripheral motor neuropathy
Subtotal or total vision loss
Grade 4 hyponatremia despite appropriate fluid management

Table 4: Dose Modification for Selected Unituxin Adverse Reactions

Infusion-related reactions *[see Warnings and Precautions (5.1)]*	
Mild to moderate adverse reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to symptomatic treatment	
Onset of reaction:	*Reduce Unituxin infusion rate to* (b) (4) *and monitor closely.*
After resolution:	*Gradually increase infusion rate up to a maximum rate of 1.75 mg/m^2/hour.*
Prolonged or severe adverse reactions such as mild bronchospasm without other symptoms, angioedema that doesn't affect the airway	
Onset of reaction:	*Immediately interrupt Unituxin.*
After resolution:	*If signs and symptoms resolve rapidly, resume Unituxin at* (b) (4) *and observe closely.*
First recurrence:	*Discontinue Unituxin until the following day.* *If symptoms resolve and continued treatment is warranted, premedicate with hydrocortisone 1 mg/kg (maximum dose 50 mg) intravenously and administer Unituxin at a rate of 0.875 mg/m^2/hour in an intensive care unit.*
Second recurrence:	*Permanently discontinue Unituxin.*

Capillary leak syndrome *[see Warnings and Precautions (5.3)]*	
Moderate to severe but not life threatening capillary leak syndrome	
Onset of reaction:	*Immediately interrupt Unituxin.*
After resolution:	*Resume Unituxin infusion at* (b) (4) .
Life threatening capillary leak syndrome	
Onset of reaction:	*Discontinue Unituxin for the current cycle.*
After resolution:	*In subsequent cycles, administer Unituxin at* (b) (4) .
First recurrence:	*Permanently discontinue Unituxin.*
Hypotension requiring medical intervention* *[see Warnings and Precautions (5.4)]*	
Onset of reaction:	*Interrupt Unituxin infusion*
After resolution:	*Resume Unituxin infusion at* (b) (4) . *If blood pressure remains stable for at least 2 hours, increase the infusion rate as tolerated up to a maximum rate of 1.75 mg/m^2/hour.*
Severe systemic infection or sepsis [see *Warnings and Precautions (5.5)*]	
Onset of reaction:	*Discontinue Unituxin until resolution of infection, and then proceed with subsequent cycles of therapy.*
Neurological Disorders of the Eye *[see Warnings and Precautions (5.6)]*	
Onset of reaction:	*Discontinue Unituxin infusion until resolution.*
After resolution:	*Reduce the Unituxin dose by 50%.*
First recurrence or if accompanied by visual impairment:	*Permanently discontinue Unituxin.*

**Symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP decreased by more than 15% compared to baseline.*

2.4 Instructions for Preparation and Administration

Preparation

- *Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F). Protect from light by storing in the outer carton.* ***DO NOT FREEZE OR SHAKE*** *vials.*
- *Inspect visually for particulate matter and discoloration prior to administration. Do not administer Unituxin and discard the single-use vial if the solution is cloudy, has pronounced discoloration, or contains particulate matter.*
- *Aseptically withdraw the required volume of Unituxin from the single-use vial and inject into a 100 mL bag of 0.9% Sodium Chloride Injection, USP. Mix by gentle inversion. Do not shake. Discard unused portions of the vial.*
- *Store the diluted Unituxin solution under refrigeration (2°C to 8° C). Initiate infusion within 4 hours of preparation.*
- *Discard diluted Unituxin solution 24 hours after preparation.*

Administration

- *Administer Unituxin as a diluted intravenous infusion only [see Dosage and Administration (2.1)].* ***Do not administer Unituxin as an intravenous push or bolus.***

Section 5: WARNINGS AND PRECAUTIONS

UTC originally proposed that the following adverse reactions be described in Section 5 of the Unituxin package insert:

- (b) (4)
- capillary leak syndrome
- hypotension
- infection or sepsis
- pain
- peripheral neuropathy
- neurological disorders of the eye.

DOP2 recommended the following changes:

- Inclusion of the risk of serious infusion reactions, with description of anaphylaxis in two patients, because the vast majority of patients that had adverse reactions characterized as severe or serious hypersensitivity, allergic reactions, or anaphylaxis tolerated additional treatments with ch14.18 following infusion rate reductions and with additional premedication.
- Discussion of the risk of pain and peripheral neuropathy under the same subheading, because pain and peripheral neuropathy are interrelated and due to the same underlying pathophysiologic mechanism (i.e., binding to GD2 on peripheral

nerves). DOP2 also recommended inclusion of language informing healthcare providers that adult patients may have more severe neuropathic effects with treatment based upon case reports of severe motor neuropathy in adult patients treated with a related anti-GD2 binding antibody.

- Addition of the risks of bone marrow suppression, electrolyte abnormalities including syndrome of inappropriate and antidiuretic hormone secretion (SIADH), and atypical hemolytic uremic syndrome.

At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the WARNINGS AND PRECAUTIONS section of the package insert:

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infusion Reactions

Serious infusion reactions requiring urgent intervention including blood pressure support, bronchodilator therapy, corticosteroids, infusion rate reduction, infusion interruption, or permanent discontinuation of Unituxin included facial and upper airway edema, dyspnea, bronchospasm, stridor, urticaria, and hypotension. Infusion reactions generally occurred during or within 24 hours of completing the Unituxin infusion. Due to overlapping signs and symptoms, it was not possible to distinguish between infusion reactions and hypersensitivity reactions in some cases.

In Study 1, Severe (Grade 3 or 4) infusion reactions occurred in 35 (26%) patients in the Unituxin/13-cis-retinoic acid (RA) group compared to 1 (1%) patient receiving RA alone. Severe urticaria occurred in 17 (13%) patients in the Unituxin/RA group but did not occur in the RA group. Serious adverse reactions consistent with anaphylaxis and resulting in permanent discontinuation of Unituxin occurred in 2 (1%) patients in the Unituxin/RA group. Additionally, 1 (0.1%) patient had multiple cardiac arrests and died within 24 hours after having received Unituxin in Study 2.

Prior to each Unituxin dose, administer required intravenous hydration and premedication with antihistamines, analgesics, and antipyretics [see Dosage and Administration (2.2)]. Monitor patients closely for signs and symptoms of infusion reactions during and for at least 4 hours following completion of each Unituxin infusion in a setting where cardiopulmonary resuscitation medication and equipment are available.

For mild to moderate infusion reactions such as transient rash, fever, rigors, and localized urticaria that respond promptly to antihistamines or antipyretics, decrease the Unituxin infusion rate and monitor closely. Immediately interrupt or permanently discontinue Unituxin and institute supportive management for severe or prolonged infusion reactions. Permanently discontinue Unituxin and institute supportive management for life-threatening infusion reactions [see Dosage and Administration (2.3)].

5.2 Pain and Peripheral Neuropathy

Pain

In Study 1, 114 (85%) patients treated in the Unituxin/RA group experienced pain despite pre-treatment with analgesics including morphine sulfate infusion. Severe (Grade 3) pain occurred in 68 (51%) patients in the Unituxin/RA group compared to 5 (5%) patients in the RA group. Pain typically occurred during the Unituxin infusion and was most commonly reported as abdominal pain, generalized pain, extremity pain, back pain, neuralgia, musculoskeletal chest pain, and arthralgia.
Premedicate with analgesics including intravenous opioids prior to each dose of Unituxin and continue analgesics until two hours following completion of Unituxin. For severe pain, decrease the Unituxin infusion rate to 0.875 mg/m^2/hour. Discontinue Unituxin if pain is not adequately controlled despite infusion rate reduction and institution of maximum supportive measures [see Dosage and Administration (2.3)].

Peripheral Neuropathy

In Study 1, severe (Grade 3) peripheral sensory neuropathy occurred in 2 (1%) patients and severe peripheral motor neuropathy occurred in 2 (1%) patients in the Unituxin/RA group. No patients treated with RA alone experienced severe peripheral neuropathy. The duration and reversibility of peripheral neuropathy occurring in Study 1 was not documented. In Study 3, no patients experienced peripheral motor neuropathy. Among the 9 (9%) patients who experienced peripheral sensory neuropathy of any severity, the median (min, max) duration of peripheral sensory neuropathy was 9 (3, 163) days.
The neuropathic effects of anti-GD2 antibody therapy appear more severe in adult patients compared to pediatric patients. In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients developed severe motor neuropathy. One patient developed lower extremity weakness and inability to ambulate that persisted for approximately 6 weeks. Another patient developed severe lower extremity weakness resulting in an inability to ambulate without assistance that lasted for approximately 16 weeks and neurogenic bladder that lasted for approximately 3 weeks. Complete resolution of motor neuropathy was not documented in this case.
Permanently discontinue Unituxin in patients with Grade 2 peripheral motor neuropathy, Grade 3 sensory neuropathy that interferes with daily activities for more than 2 weeks, or Grade 4 sensory neuropathy.

5.3 Capillary Leak Syndrome

In Study 1, severe (Grade 3 to 5) capillary leak syndrome occurred in 31 (23%) patients in the Unituxin/RA group and in no patients treated with RA alone. Additionally, capillary leak syndrome was reported as a serious adverse reaction in 9 (6%) patients in the Unituxin/RA group and in no patients treated with RA alone. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic or severe capillary leak syndrome [see Dosage and Administration (2.3].

5.4 Hypotension

In Study 1, severe (Grade 3 or 4) hypotension occurred in 22 (16%) patients in the Unituxin/RA group compared to no patients in the RA group.
Prior to each Unituxin infusion, administer required intravenous hydration. Closely monitor blood pressure during Unituxin treatment. Immediately interrupt or discontinue Unituxin and institute supportive management in patients with symptomatic hypotension, systolic blood pressure (SBP) less than lower limit of normal for age, or SBP that is decreased by more than 15% compared to baseline [see Dosage and Administration (2.2, 2.3)].

5.5 Infection

In Study 1, severe (Grade 3 or 4) bacteremia requiring intravenous antibiotics or other urgent intervention occurred in 17 (13%) patients in the Unituxin/RA group compared to 5 (5%) patients treated with RA alone. Sepsis occurred in 24 (18%) of patients in the Unituxin/RA group and in 10 (9%) patients in the RA group.
Monitor patients closely for signs and symptoms of systemic infection and temporarily discontinue Unituxin in patients who develop systemic infection until resolution of the infection [see Dosage and Administration (2.3)].

5.6 Neurological Disorders of the Eye

Neurological disorders of the eye experienced by two or more patients treated with Unituxin in Studies 1, 2, or 3 included blurred vision, photophobia, mydriasis, fixed or unequal pupils, optic nerve disorder, eyelid ptosis, and papilledema.
In Study 1, 3 (2%) patients in the Unituxin/RA group experienced blurred vision, compared to no patients in the RA group. Diplopia, mydriasis, and unequal pupillary size occurred in 1 patient each in the Unituxin/RA group, compared to no patients in the RA group. The duration of eye disorders occurring in Study 1 was not documented. In Study 3, eye disorders occurred in 16 (15%) patients, and in 3 (3%) patients resolution of the eye disorder was not documented. Among the cases with documented resolution, the median duration of eye disorders was 4 days (range: 0, 221 days).
Interrupt Unituxin in patients experiencing dilated pupil with sluggish light reflex or other visual disturbances that do not cause visual loss. Upon resolution and if continued treatment with Unituxin is warranted, decrease the Unituxin dose by 50%. Permanently discontinue Unituxin in patients with recurrent signs or symptoms of an eye disorder following dose reduction and in patients who experience loss of vision [see Dosage and Administration (2.3)].

5.7 Bone Marrow Suppression

In Study 1, severe (Grade 3 or 4) thrombocytopenia (39% vs. 25%), anemia (34% vs. 16%), neutropenia (34% vs. 13%), and febrile neutropenia (4% vs. 0 patients) occurred more commonly in patients in the Unituxin/RA group compared to patients treated with RA alone. Monitor peripheral blood counts closely during therapy with Unituxin.

5.8 Electrolyte Abnormalities

Electrolyte abnormalities occurring in at least 25% of patients who received Unituxin/RA in Study 1 included hyponatremia, hypokalemia, and hypocalcemia. Severe (Grade 3 or 4) hypokalemia and hyponatremia occurred in (b) (4)% and 23% of patients in the Unituxin/RA group respectively compared to 2% and 4% of patients in the RA group. In a study of a related anti-GD2 antibody conducted in 12 adult patients with metastatic melanoma, 2 (13%) patients developed syndrome of inappropriate antidiuretic hormone secretion resulting in severe hyponatremia. Monitor serum electrolytes daily during therapy with Unituxin.

5.9 Atypical Hemolytic Uremic Syndrome

Hemolytic uremic syndrome in the absence of documented infection and resulting in renal insufficiency, electrolyte abnormalities, anemia, and hypertension occurred in two patients enrolled in Study 2 following receipt of the first cycle of dinutuximab. Atypical hemolytic uremic syndrome recurred following rechallenge with Unituxin in one patient. Permanently discontinue Unituxin and institute supportive management for signs of hemolytic uremic syndrome.

5.10 Embryo-Fetal Toxicity

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment, and for two months after the last dose of Unituxin [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)].

Section 6: ADVERSE REACTIONS

DOP2 recommended the following changes to Section 6:

- Inclusion of relevant safety and exposure information from Study DIV-NB-302 (Study 2) and Study DIV-NB-303 (Study 3), including a table of laboratory abnormalities from Study 3, because laboratory data were not comprehensively collected in Study DIV-NB-301 (Study 1).
- Additional exposure information from Study 1, including the percentage of premature discontinuations in the Unituxin/RA and RA groups.
- Correction of the per-patient incidence data in the adverse reaction table for Study 1 that reflect accurate exposure data in the Unituxin/RA and RA groups.
- Based upon information submitted to the BLA indicating that most patients who experienced adverse reactions coded as “allergic reaction” or “hypersensitivity” responded to infusion rate reduction and medical treatment (such as antihistamines) and subsequently received additional treatment with ch14.18, changing (b) (4) to “infusion reactions”. Additionally, because review of

the cases described as “infusion related reaction” revealed that these cases were pain adverse reactions occurring during the infusion, DOP2 recommended that these adverse reactions be included in the preferred term “pain”.

- Inclusion of the per-patient incidence of hemorrhage in the adverse reaction table, using the preferred terms in the MedDRA SMQ for hemorrhage.
- To better inform healthcare providers of the pattern of adverse reactions that occurred during cycles containing GM-CSF and IL-2, inclusion of a table comparing the per-patient incidence of adverse reactions in cycles containing dinutuximab/GM-CSF/RA (Cycles 1, 3, and 5) compared to cycles containing dinutuximab/IL-2/RA (Cycles 2 and 4).

At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the ADVERSE REACTIONS section of the package insert:

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- *Serious Infusion Reactions [see Boxed Warning and Warnings and Precautions (5.1)]*
- *Pain and Peripheral Neuropathy [see Boxed Warning and Warnings and Precautions (5.2)]*
- *Capillary Leak Syndrome [see Warnings and Precautions (5.3)]*
- *Hypotension [see Warnings and Precautions (5.4)]*
- *Infection [see Warnings and Precautions (5.5)]Neurological Disorders of the Eye [see Warnings and Precautions (5.6)]*
- *Bone Marrow Suppression [see Warnings and Precautions (5.7)]*
- *Electrolyte Abnormalities [see Warnings and Precautions (5.8)]*
- *Atypical Hemolytic Uremic Syndrome [see Warnings and Precautions (5.9)]*
- *Embryo-Fetal Toxicity [see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in clinical practice. The data described below reflect exposure to Unituxin at the recommended dose and schedule in 1021 patients with high-risk neuroblastoma enrolled in an open label, randomized (Study 1) or single arm clinical trials (Study 2 and Study 3). Prior to enrollment, patients received therapy consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease. Patients received Unituxin in combination with granulocyte-

macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA). Treatment commenced within 95 days post autologous stem cell transplant in Study 1, within 210 days of autologous stem cell transplant in Study 2, and within 110 days of autologous stem cell transplant in Study 3.

Study 1

In a randomized, open label, multi-center study (Study 1), 134 patients received dinutuximab in combination with GM-CSF, IL-2 and RA (Unituxin/RA group), including 109 randomized patients and 25 patients with biopsy-proven residual disease who were non-randomly assigned to receive dinutuximab. A total of 106 randomized patients received RA alone (RA group) [see Dosage and Administration (2) and Clinical Studies (14)]. Patients had a median age at enrollment of 3.8 years (range: (b) (4) to 15.3 years), and were predominantly male ((b) (4)%) and White ((b) (4)%). In Study 1, adverse reactions of Grade 3 or greater severity were comprehensively collected, but adverse reactions of Grade 1 or 2 severity were collected sporadically and laboratory data were not comprehensively collected.

Approximately 71% of patients in the Unituxin/RA group and 77% of patients in the RA group completed planned treatment. The most common reason for premature discontinuation of study therapy was adverse reactions in the Unituxin/RA group (19%) and progressive disease (17%) in the RA group.
The most common adverse drug reactions (≥ 25%) in the Unituxin/RA group were pain, pyrexia, thrombocytopenia, lymphopenia, infusion reactions, hypotension, hyponatremia, increased alanine aminotransferase, anemia, vomiting, diarrhea, hypokalemia, capillary leak syndrome, neutropenia, urticaria, hypoalbuminemia, increased aspartate aminotransferase, and hypocalcemia. The most common serious adverse reactions (≥ 5%) in the Unituxin/RA group were infections, infusion reactions, hypokalemia, hypotension, pain, fever, and capillary leak syndrome.

Table 5 lists the adverse reactions reported in at least 10% of patients in the Unituxin/RA group for which there was a between group difference of at least 5% (all grades) or 2% (Grade 3 or greater severity).

Table 5: Selected Adverse Reactions Occurring in at Least 10% of Patients in the Unituxin/RA Group in Study 1

	Unituxin/RA (N=134)		***RA (N=106)***	
Adverse Reaction[1,2]	***All Grades (%)***	***Grades 3-4 (%)***	***All Grades (%)***	***Grades 3-4 (%)***
General Disorders and Administration Site Conditions				
Pain[3]	*85*	*51*	*16*	*6*
Pyrexia	*72*	*40*	*27*	*6*
Edema	*17*	*0*	*0*	*0*

Adverse Reaction[1,2]	Unituxin/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Blood and Lymphatic System Disorders[4]				
Thrombocytopenia	66	39	43	25
Lymphopenia[4]	62	51	36	20
Anemia	51	34	22	16
Neutropenia	39	34	16	13
Immune System Disorders				
Infusion reactions	60	25	9	1
Vascular Disorders				
Hypotension	60	16	3	0
Capillary leak syndrome[5]	40	23	1	0
Hemorrhage[6]	17	6	6	3
Hypertension	14	2	7	1
Metabolism and Nutrition Disorders				
Hyponatremia[4]	58	23	12	4
Hypokalemia[4]	43	37	4	2
Hypoalbuminemia[4]	33	7	3	0
Hypocalcemia[4]	27	7	0	0
Hypophosphatemia[4]	20	8	3	0
Hyperglycemia[4]	18	6	4	1
Hypertriglyceridemia[4]	16	1	11	1
Decreased appetite	15	10	5	4
Hypomagnesemia[4]	12	2	1	0
Investigations				
Increased alanine aminotransferase[4]	56	23	31	3
Increased aspartate aminotransferase[4]	28	10	7	0
Increased serum creatinine[4]	15	2	6	0
Increased weight	10	0	0	0
Gastrointestinal Disorders				
Vomiting	46	6	19	3
Diarrhea	43	13	15	1
Nausea	10	2	3	1
Skin and Subcutaneous Tissue Disorders				

Adverse Reaction[1,2]	Unituxin/RA (N=134)		RA (N=106)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Urticaria	37	13	3	0
Respiratory, Thoracic and Mediastinal Disorders				
Hypoxia	24	12	2	1
Cardiac Disorders				
Tachycardia[7]	19	2	1	0
Infections and Infestations				
Sepsis	18	16	9	9
Device related infection	16	16	11	11
Renal and Urinary Disorders				
Proteinuria[4]	16	0	3	1
Nervous System Disorders				
Peripheral neuropathy	13	3	6	0

[1] *Includes adverse reactions that occurred in at least 10% of patients in the Unituxin/RA group with at least a 5% (All Grades) or 2% (Grades 3-5) absolute higher incidence in the Unituxin/RA group compared to the RA group.*
[2] *Adverse drug reactions were graded using CTCAE version 3.0.*
[3] *Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.*
[4] *Based on investigator reported adverse reactions.*
[5] *One Grade 5 adverse reaction of acute capillary leak syndrome occurred in the setting of an IL-2 overdose.*
[6] *Includes preferred terms gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage, hematuria, hemorrhage urinary tract, renal hemorrhage, epistaxis, respiratory tract hemorrhage, disseminated intravascular coagulation, catheter site hemorrhage, hemorrhage and hematoma.*
[7] *Includes preferred terms tachycardia and sinus tachycardia.*

Table 6 compares the per-patient incidence of selected adverse reactions occurring during cycles containing dinutuximab in combination with GM-CSF (Cycles 1, 3, and 5) with cycles containing dinutuximab in combination with IL-2 (Cycles 2 and 4).

Table 6: Comparison of Adverse Events by Treatment Cycle in the Unituxin/RA Group in Study 1

Preferred Term[1,2]	All Grades		Severe	
	GM-CSF N=134 (%)	IL-2[3] N=127 (%)	GM-CSF N=134 (%)	IL-2[3] N=127 (%)
Blood and Lymphatic System Disorders[4]				
Thrombocytopenia	62	61	31	33
Lymphopenia	54	61	33	50
Anemia	42	42	21	24
Neutropenia	25	31	19	28
Metabolism and Nutrition Disorders[4]				
Hyponatremia	36	55	5	21
Hypokalemia	26	39	13	33
Hypoalbuminemia	29	29	3	5
Hypocalcemia	20	21	1	6
General Disorders and administration site conditions				
Pyrexia	(b) (4)	65	10	37
Pain[5]	77	61	43	35
Immune System Disorders				
Infusion reactions	47	54	10	20
Investigations[4]				
Increased alanine aminotransferase	43	48	15	13
Aspartate aminotransferase increased	16	(b) (4)	4	7
Vascular Disorders				
Hypotension	43	54	5	16
Capillary leak syndrome	22	36	11	20
Gastrointestinal Disorders				
Diarrhea	31	37	6	13
Vomiting	33	35	3	2
Skin and Subcutaneous Tissue Disorders				
Urticaria	25	29	7	7

Abbreviations: GM-CSF: granulocyte-macrophage colony-stimulating factor; IL-2: interleukin-2.

1 *Includes preferred terms with a per-patient incidence of at least 25% in the Unituxin and RA group for either IL-2 or GM-CSF containing cycles.*

2 *Adverse drug reactions were graded using CTCAE version 3.0.*

3 *Seven patients who received GM-CSF in Cycle 1 discontinued prior to starting Cycle 2.*

4 *Based on investigator reported adverse reactions.*

5 *Includes preferred terms abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, infusion related reaction, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia.*

Study 2 and Study 3

Study 2 was a single arm, multicenter expanded access trial that enrolled patients with high-risk neuroblastoma (N=783). The reported adverse event profile of dinutuximab in Study 2 was similar to that observed in Study 1.
Study 3 was a multicenter, single arm safety study of dinutuximab in combination with GM-CSF, IL-2 and RA. In Study 3, adverse events of all CTCAE grades and laboratory data were systematically and comprehensively collected. Of 104 patients enrolled and treated in Study 3, 77% of patients completed study therapy. In general , the adverse reaction profile of dinutuximab observed in Study 3 was similar to that observed in Study 1 and Study 2. The following adverse reactions not previously reported in Study 1 were reported in at least 10% of patients in Study 3: nasal congestion (20%) and wheezing (15%).

Table 7 provides the per-patient incidence of laboratory abnormalities in Study 3.

Table 7: Per-Patient Incidence of Selected (≥ 5% Grade 3-4) Laboratory Abnormalities in Study 3

Laboratory Test[1]	***Grade[2]***	
	All Grades %	***Grades 3-4 %***
HEMATOLOGY		
Anemia	*100*	*46*
Neutropenia	*99*	*63*
Thrombocytopenia	*98*	*49*
CHEMISTRY		
Hypoalbuminemia	*100*	*8*
Hypocalcemia	*97*	*7*
Hyponatremia	*93*	*36*
Hyperglycemia	*87*	*6*
Aspartate Aminotransferase Increased	*84*	*8*
Alanine Aminotransferase Increased	*83*	*13*
Hypokalemia	*82*	*41*
Hypophosphatemia	*78*	*6*
URINALYSIS[3]		
Urine protein	*66*	*ND*
Red blood cell casts	*38*	*ND*

[1] Laboratory abnormalities with a per-patient incidence of at least 20% (all grades) and at least a 5% per-patient incidence of severe (Grade 3 or 4) laboratory abnormalities.
[2] Based on CTCAE version 4.0.
[3] Urinalysis results were reported as positive or negative without assessment of grade.

6.2 Immunogenicity

As with all therapeutic proteins, patients treated with Unituxin may develop anti-drug antibodies. In clinical studies, 52 of 284 (18%) patients from Study 2 and 13 of 103 (13%) patients from Study 3 tested positive for anti-dinutuximab binding antibodies. Neutralizing antibodies were detected in 3.6% of patients who were tested for anti-dinutuximab binding antibodies in study 2 and study 3. However, due to the limitations of the assay, the incidence of neutralizing antibodies may not have been reliably determined.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to Unituxin with the incidences of antibodies to other products may be misleading

Section 8: USE IN SPECIFIC POPULATIONS

DOP2 recommended inclusion of additional risks, reorganization and rewording in compliance with the final Pregnancy and Lactation Labeling Rule. At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the USE IN SPECIFIC POPULATIONS section of the package insert:

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, Unituxin may cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (12.1)]. There are no studies in pregnant women and no reproductive studies in animals to inform the drug-associated risk. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester. Advise pregnant women of the potential risk to a fetus. The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2-4% and of miscarriage is 15-20% of clinically recognized pregnancies.

8.2 Lactation

Risk Summary

There is no information available on the presence of dinutuximab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. However, human IgG is present in human milk. Because of the potential for serious

adverse reactions in a breastfed infant, advise a nursing woman to discontinue breastfeeding during treatment with Unituxin.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Unituxin may cause fetal harm [see Use in Specific Populations (8.1)]. Advise females of reproductive potential to use effective contraception during treatment and for two months after the last dose of Unituxin.

8.4 Pediatric Use

The safety and effectiveness of Unituxin as part of first-line multi-agent, multimodality therapy have been established in pediatric patients with high-risk neuroblastoma based on results of an open-label, randomized (1:1) trial conducted in 226 patients aged 11 months to 15 years (median age 3.8 years) (Study 1). Prior to enrollment, patients achieved at least a partial response to prior therapy for high-risk neuroblastoma consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease. Patients randomized to the Unituxin/13-cis-retinoic acid (RA) arm (Unituxin/RA) received up to five cycles of Unituxin in combination with alternating cycles of granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin-2 (IL-2) plus RA, followed by one cycle of RA alone. Patients randomized to the RA arm received up to six cycles of RA monotherapy. Study 1 demonstrated an improvement in event-free survival and overall survival in patients in the Unituxin/RA acid arm compared to those in the RA arm [see Adverse Reactions (6), Clinical Pharmacology (12) and Clinical Studies (14)].

8.5 Geriatric Use

The safety and effectiveness of Unituxin in geriatric patients have not been established.

8.6 Renal Impairment

Unituxin has not been studied in patients with renal impairment.

8.7 Hepatic Impairment

Unituxin has not been studied in patients with hepatic impairment.

Section 14: CLINICAL STUDIES

DOP2 recommended the following changes to Section 14:

- Inclusion of additional information describing the patient population enrolled in Study 301.

- Presentation of the hazard ratios and 95% confidence intervals for event-free survival and overall survival instead of (b) (4).
- Presentation of overall survival data from the 2012 updated analysis instead of (b) (4).
- Omission of (b) (4)
- Addition of a footnote explaining that the p-value calculated in the seventh interim analysis of EFS resulting in cessation of randomization was equal to (b) (4) the pre-specified p-value for this analysis.

At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the CLINICAL STUDIES Section of the package insert:

14 CLINICAL STUDIES

The safety and effectiveness of Unituxin was evaluated in a randomized, open-label, multicenter trial conducted in pediatric patients with high-risk neuroblastoma (Study 1). All patients had received prior therapy consisting of induction combination chemotherapy, maximum feasible surgical resection, myeloablative consolidation chemotherapy followed by autologous stem cell transplant, and radiation therapy to residual soft tissue disease. Patients were randomized between Day 50 and Day 77 post-autologous stem cell transplantation.

Patients were required to have achieved at least a partial response prior to autologous stem cell transplantation, have no evidence of disease progression following completion of front-line multi-modality therapy, adequate pulmonary function (no dyspnea at rest and peripheral arterial oxygen saturation of at least 94% on room air), and adequate renal function (glomerular filtration rate at least 70 mL/min/1.73 m^2). Patients with systemic infections or a requirement for concomitant systemic corticosteroids or immunosuppressant usage were not eligible for enrollment.

Patients randomized to the Unituxin/RA arm received up to five cycles of dinutuximab (clinical trials material) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) (Table 8) or interleukin-2 (IL-2) (Table 9) plus 13-cis-retinoic acid (RA), followed by one cycle of RA alone. Patients randomized to the RA arm received six cycles of RA. Dinutuximab was administered at a dose of 17.5 mg/m^2/day (equivalent to 25/mg/m^2/day of clinical trials material) on four consecutive days. Patients in both treatment arms received six cycles of RA at a dose of 160 mg/m^2/day orally (for patients weighing more than 12 kg) or 5.33 mg/kg/day (for patients weighing less than or equal to 12 kg) in two divided doses for 14 consecutive days.

Table 8: Dosage Regimen in the Unituxin/RA Arm for Cycles 1, 3, and 5

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15-24
GM-CSF[1]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Unituxin[2]				X	X	X	X								
RA[3]											X	X	X	X	X

[1]. GM-CSF: 250 µg/m2/day, administered by either subcutaneous injection (recommended) or IV infusion administered over 2 hours.
[2]. Unituxin: 17.5 mg/m2/day, administered by diluted IV infusion over 10–20 hours.
[3]. RA: for >12 kg body weight, 80 mg/m2 orally twice daily for a total dose of 160 mg/m2/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

Table 9: Dosage Regimen in the Unituxin/RA Arm for Cycles 2 and 4

Cycle Day	1	2	3	4	5	6	7	8	9	10	11	12-14	15-28	29-32
IL-2[1]	X	X	X	X				X	X	X	X			
Unituxin[2]								X	X	X	X			
RA[3]													X	

[1]. IL-2: 3 MIU/m2/day administered by continuous IV infusion over 96 hours on Days 1-4 and 4.5 MIU/m2/day on Days 8-11.
[2]. Unituxin: 17.5 mg/m2/day, administered by diluted IV infusion over 10-20 hours.
[3]. RA: for >12 kg body weight, 80 mg/m2 orally twice daily for a total dose of 160 mg/m2/day; for ≤12 kg body weight, 2.67 mg/kg orally twice daily for a total daily dose of 5.33 mg/kg/day (round dose up to nearest 10 mg).

A total of 226 patients were randomized, 113 patients to each arm. In general, demographic and baseline tumor characteristics were similar across study arms. Across the study population, 60% were male, the median age was 3.8 years and 3% of patients were less than 1.5 years, 82% were White and 7% were Black. The majority (80%) of patients had International Neuroblastoma Staging System Stage 4 disease. Thirty-five percent of patients had a complete response, 43% had a very good partial response, and 23% had a partial response to therapy received prior to autologous stem cell transplant. Forty-six percent of patients had neuroblastoma that was not MYCN-amplified, 36% had tumors with known MYCN-amplification, and MYCN status was unknown or missing in 19% of patients. Forty-three percent of patients had hyperdiploid tumors, 36% had diploid tumors, and DNA ploidy status was unknown or missing in 21% of patients.

The major efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the time from randomization to the first occurrence of relapse, progressive disease, secondary malignancy, or death. Overall survival (OS) was also evaluated. After observing a numerical improvement in EFS based on the seventh interim analysis, the Data Monitoring Committee recommended termination of accrual. Efficacy results are shown in Table 10.

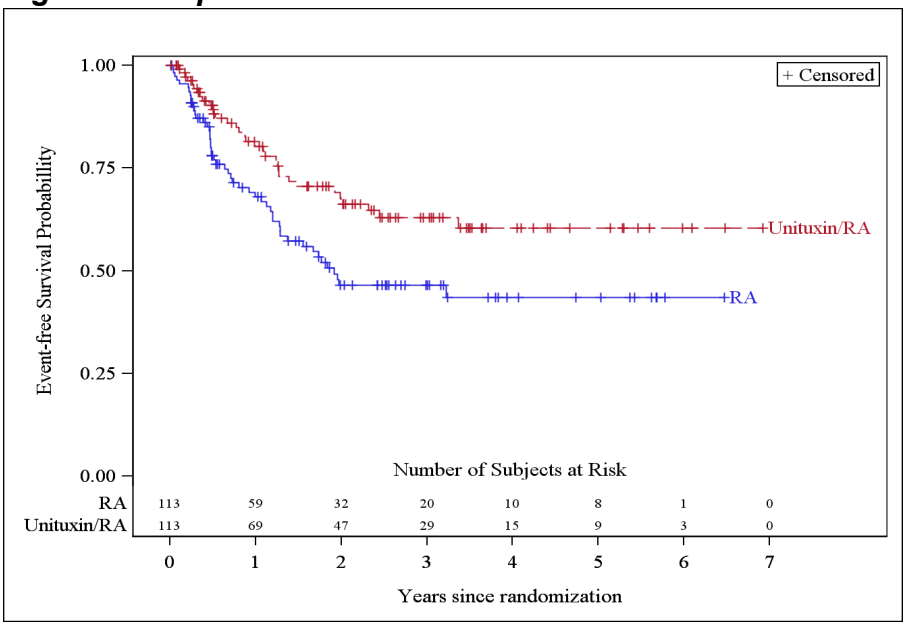
Table 10: Efficacy Results

Efficacy Parameter		***Unituxin/ RA arm n=113***	***RA arm n=113***
EFS	*No. of Events (%)*	*33 (29%)*	*50 (44%)*
	Median (95% CI) (years)	*NR (3.4 ,NR)*	*1.9 (1.3, NR)*
	Hazard Ratio (95% CI)	*0.57 (0.37, 0.89)*	
	p-value (log-rank test)[1]	*0.01*	
OS[2]	*No. of Events (%)*	*31 (27%)*	*48 (42%)*
	Median (95% CI) (years)	*NR (7.5,NR)*	*NR (3.9,NR)*
	Hazard Ratio (95% CI)	*0.58 (0.37,0.91)*	

NR = not reached
[1] *Compared to the allocated alpha of 0.01 pre-specified for the seventh interim analysis of EFS*
[2] Based on an additional three years of follow up after the seventh interim analysis of EFS

The Kaplan-Meier curve of EFS is shown in Figure 1.

Figure 1: Kaplan-Meier Curve of Event-Free Survival



Section 17: PATIENT COUNSELING INFORMATION

DOP2 proposed substantive changes instructing healthcare providers to communicate additional information to patients regarding the risks of dinutuximab and the need to report signs and symptoms of these risks promptly to confirm with the December 2014 Guidance for Industry entitled "Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format." At the time of this review, DOP2 and UTC agreed on inclusion of the following text in the PATIENT COUNSELING INFORMATION section of the package insert:

17 PATIENT COUNSELING INFORMATION

- *Serious Infusion Reactions*
  Inform patients and caregivers of the risk of serious infusion reactions and anaphylaxis and to immediately report any signs or symptoms, such as facial or lip swelling, urticaria, difficulty breathing, lightheadedness or dizziness that occur during or within 24 hours following the infusion [see Warnings and Precautions (5.1)].

- *Pain and peripheral neuropathy*
  Inform patients and caregivers of the risk of severe pain and peripheral sensory and motor neuropathy and to promptly report severe or worsening pain and signs and symptoms of neuropathy such as numbness, tingling, burning, or weakness [see Warnings and Precautions (5.2)].

- *Capillary leak syndrome*
  Inform patients and caregivers of the risk of capillary leak syndrome and to immediately report any signs or symptoms. [see Warnings and Precautions (5.3)].

- *Hypotension*
  Inform patients and caregivers of the risk of hypotension during the infusion and to immediately report any signs or symptoms [see Warnings and Precautions (5.4)].

- *Infection*
  Inform patients and caregivers of the risk of infection following treatment and to immediately report any signs or symptoms [see Warnings and Precautions (5.5)].

- *Neurological Disorders of the Eye*
  Inform patients and caregivers of the risk of neurological disorders of the eye and to promptly report signs or symptoms such as blurred vision, photophobia, ptosis, diplopia, or unequal pupil size [see Warnings and Precautions (5.6)].

- *Bone marrow suppression*
  Inform patients and caregivers of the risk of bone marrow suppression, and to promptly report signs or symptoms of anemia, thrombocytopenia, or infection [see Warnings and Precautions (5.7)].

- *Electrolyte abnormalities*
  Inform patients and caregivers of the risk of electrolyte abnormalities including hypokalemia, hyponatremia, and hypocalcemia, and to report any signs or symptoms such as seizures, heart palpitations, and muscle cramping [see Warnings and Precautions (5.8)].

- *Atypical Hemolytic Uremic Syndrome*
  Inform patients and caregivers of the risk of hemolytic uremic syndrome and to report any signs or symptoms such as fatigue, dizziness, fainting, pallor, edema, decreased urine output, or hematuria [see Warnings and Precautions (5.9)]

- *Embryo-Fetal Toxicity*
  Advise women of reproductive potential of the potential risk to the fetus if administered during pregnancy and the need for use of effective contraception during and for at least two months after completing therapy [see Warnings and Precautions (5.10)].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA B DONOGHUE
03/05/2015

SUZANNE G DEMKO
03/05/2015

CLINICAL REVIEW

Application Type	Biologics License Application
Application Number(s)	125516
Priority or Standard	Priority
Submit Date(s)	April 11, 2014
Received Date(s)	April 11, 2014
PDUFA Goal Date	December 10, 2014
Division / Office	DOP2/OHOP
Reviewer Name(s)	Martha Donoghue
Review Completion Date	September 13, 2014
Established Name	Dinutuximab
(Proposed) Trade Name	Unituxin
Therapeutic Class	Chimeric monoclonal antibody
Applicant	United Therapeutics
Formulation(s)	Injection for intravenous infusion
Dosing Regimen	17.5 mg/m^2/day for four consecutive days for five cycles
Indication(s)	High-risk neuroblastoma
Intended Population(s)	Pediatric patients

Template Version: March 6, 2009

Table of Contents

Table of Tables

Table of Figures

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The clinical review team recommends granting regular approval to Unituxin (dinutuximab) as a new molecular entity and first in class GD-2 binding monoclonal antibody for the following indication:

> Unituxin (dinutuximab) is indicated for the treatment of patients with (b) (4) high-risk neuroblastoma (b) (4)

1.2 Risk Benefit Assessment

High-risk neuroblastoma is a rare cancer that primarily affects young pediatric patients. Historically, patients with high-risk neuroblastoma have a relatively poor prognosis, with roughly half of patients ultimately suffering relapse and dying of their disease. High-risk neuroblastoma remains a serious and life-threatening disease in need of additional effective treatments. There are few FDA-approved treatments for neuroblastoma, and no treatments are approved specifically for the treatment of patients with high-risk neuroblastoma.

The recommendation for approval of BLA 125516 (dinutuximab) is primarily based upon the results of Study DIV-NB-301 ("Study 301"), which demonstrated a clinically meaningful improvement in event-free survival (EFS) and overall survival (OS) in patients with high-risk neuroblastoma who achieved at least a partial response to prior standard multiagent, multimodality therapy for their high-risk disease. Study 301, which consists of the randomized portion of Study ANBL0032, entitled "Phase III Randomized Study of Chimeric Antibody 14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue," was sponsored by the National Cancer Institute's Cancer Therapy and Evaluation Program (CTEP) and conducted by the Children's Oncology Group (COG). Study 301 was an open label, multicenter, international randomized (1:1) active-controlled trial comparing combination therapy with ch14.18 (produced by the National Cancer Institute), a monoclonal antibody directed against the GD2 antigen, to isotretinoin (RA). The primary efficacy outcome measure was event-free survival (EFS) determined by the local investigator, defined as first occurrence of relapse, disease progression, secondary malignancy, or death. Overall survival (OS) was the key secondary efficacy endpoint, but Study 301 was not powered to detect a clinically significant difference in overall survival.

Patients randomized to the treatment arm received five cycles of therapy consisting of ch14.18 in combination with granulocyte macrophage-colony stimulating factor (GM-CSF) or interleukin-2 (IL-2) in alternating cycles plus RA, followed by an additional cycle of RA alone. Patients randomized to the control arm received six cycles of RA as

monotherapy. Ch14.18 was administered at a dose of 25 mg/m^2/day (equivalent to 17.5 mg/m^2/day of dinutuximab produced by the Applicant) intravenously on four consecutive days for a total of five cycles.

The planned sample size for this study was 386 patients, but randomization was terminated by the COG Data Safety Monitoring Committee (DSMC) in February 2009 upon review of the results of a pre-planned interim analysis of event-free survival (EFS) and overall survival (OS) using data collected through January 13, 2009. At the time of this analysis, the intent-to-treat population consisted of 226 patients, 113 randomized to each treatment arm. There was a striking numerical improvement in EFS favoring the ch14.18 combination therapy arm, with a hazard ratio of 0.57 (95% CI: 0.37, 0.89; p=0.0115 using the unstratified log-rank test). The median for EFS was not reached in the treatment arm; however, the median EFS for the control arm was 1.92 years (95% CI: 1.29, NR). The ch14.18 combination arm had a higher 2-year EFS rate (66%, 95% CI: 56%, 76%) compared to the RA monotherapy arm (46%, 95% CI: 36%, 57%).

Consistent with the numerical improvement in EFS, the analysis of OS documented a strong trend toward improvement in overall survival in patients randomized to the ch14.18 combination arm. The hazard ratio for overall survival was 0.52 (95% CI: 0.30, 0.92; nominal p=0.0223 using the unstratified log-rank test). The median for OS was not reached in the treatment arm; however, the median OS for the control arm was 3.88 years. The treatment arm had higher 2-year survival rate compared to the control arm (86.2%, 95% CI: 78.8%, 93.6% vs. 74.5%, 95% CI: 65.2%, 83.9%) and fewer deaths (19 versus 33).

The primary safety risks of dinutuximab are infusion-related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, neuropathy (which can manifest as pain or motor weakness), or neurological disorders of the eye such as impaired pupillary light reflex, photophobia, or visual impairment.

In Study 301, all patients who received ch14.18 combination therapy (N=134, including patients with biopsy-proven residual disease who were non-randomly assigned to the treatment group) received premedication with acetaminophen, hydroxyzine or diphenhydramine, and morphine sulfate prior to the ch14.18 infusion. Severe [≥Grade 3 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)] hypersensitivity reactions occurred in 35 (26%) patients in the ch14.18 combination therapy group compared to one (1%) patient in the RA monotherapy group. In addition, anaphylaxis was reported as a serious adverse event in 9 (7%) patients in the ch14.18 combination therapy group.

Severe capillary leak syndrome occurred in 31 (23%) patients in the ch14.18 combination therapy group, and in no patients in the RA group. Capillary leak syndrome was reported for Cycles 1 through 5, but occurred more commonly during the cycles containing IL-2 compared to the cycles containing GM-CSF. In Study 301, 22

(16%) patients treated with ch14.18 had severe hypotension compared to 0 patients in the RA group. Sepsis was reported in 24 (18%) of patients in the ch14.18 group, compared to 10 (9%) of patients in the RA group. Additionally, severe bacteremia occurred in 17 (13%) of patients in the ch14.18 combination group compared to 5 (5%) of patients in the RA group.

In Study 301, for prevention and management of pain, all patients randomized to the ch14.18 combination arm received acetaminophen and morphine sulfate immediately prior to and during the ch14.18 infusion. Additional pain medications were given as necessary. Despite use of analgesics, the majority (84%) of patients treated with ch14.18 experienced pain compared to 16% of patients in the control group. Severe pain occurred in 51% of patients in the ch14.18 combination treatment group compared to 5% of patients in the RA group.

Additionally, 3% of patients in the ch14.18 combination therapy group experienced severe peripheral neuropathy compared to no patients treated with RA alone. A total of 5% of patients in the ch14.18 combination group experienced neurological disorders of the eye (all mild) compared to 3% of patients in the RA group.

Serious adverse events were common in the ch14.18 investigational treatment group; 51% of patients in the ch14.18 combination therapy group experienced at least one serious adverse event. The most common (per-patient incidence ≥ 5%) serious adverse reactions were infections, pain, hypokalemia, hypotension, anaphylaxis, capillary leak syndrome, catheter-related infection, and fever.

Although the majority of clinical development of ch14.18 occurred in studies using the NCI produced product, the Applicant conducted a study (Study 201) demonstrating that their product, dinutuximab, has a comparable pharmacokinetic profile to the NCI product. Analysis of safety data from Study 201 revealed a toxicity profile for dinutuximab that is similar to the toxicity profile of ch14.18 produced by NCI.

As part of the risk-benefit assessment of the application, the clinical review team considered whether data from the single adequate and well-controlled trial, Study 301, were sufficient to support approval. The efficacy results from the seventh interim analysis of EFS leading up to cessation of randomization by the Data Safety Monitoring Committee were not statistically robust; the observed p-value, 0.0115, is marginally higher than the pre-specified p-value (0.0108) required for cessation of randomization. However, the updated event-free and overall survival data submitted by the Applicant corroborate the efficacy findings of the primary analysis and strengthen the application. Although Study 301 was not powered to detect a statistically significant difference in overall survival, a follow-up analysis of overall survival conducted using data collected through June 30, 2012 again demonstrated a strong trend toward improvement in overall survival in the ch14.18 combination therapy arm (HR:0.58, 95% CI:0.37,0.91).

The clinical review team also recognizes that although Study 301 evaluated ch14.18 in combination with the cytokines GM-CSF and IL-2, their respective contributions to the observed treatment effect have not been well characterized. Nevertheless, in the United States and Canada, dinutuximab is typically administered in conjunction with GM-CSF, IL-2, and RA, using a treatment regimen comparable to that used in Study 301. Furthermore, efficacy results of Study 301 show that patients receiving this combination have improved event-free and overall survival compared to patients who receive RA alone.

FDA regulations, outlined in Subpart E of CFR part 312, which aim to expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that a medical risk-benefit judgment is required when deciding whether to approve a drug or biological product. As part of this risk-benefit analysis, the Agency will take "into consideration the severity of the disease and the absence of satisfactory alternative therapy" (21 CFR 312.84). Therefore, taking into consideration the challenges of studying treatments for high-risk neuroblastoma, including the rarity of the disease and complexity of the current standard treatment regimen, the life-threatening nature of high-risk neuroblastoma, and the absence of satisfactory, approved alternative therapy, the clinical review team concluded that the totality of data in this submission provide sufficient evidence to grant regular approval to dinutuximab for the treatment of patients with newly diagnosed high-risk neuroblastoma who have achieved at least a partial response to initial standard multiagent, multimodality therapy. Study 301 embodies many of the characteristics of a desirable single study. It was a large, multicenter trial that demonstrated consistent results across most patient subsets, and showed a persuasive effect on two clinically meaningful endpoints, event-free survival and overall-survival. Furthermore, demonstration of an overall survival benefit in patients with high risk neuroblastoma, a patient population with limited and suboptimal treatment options for their life threatening disease, renders the conduct of a second confirmatory randomized controlled trial practically or ethically impossible. Lack of feasibility for an additional (confirmatory) trial is underscored by the fact that in the United States, Canada, and Europe, treatment with ch14.18 is *a priori* part of the standard of care for first-line treatment of patients with high risk neuroblastoma.

Patients receiving dinutuximab are at risk for developing serious and potentially life-threatening adverse reactions, such as infusion reactions, capillary leak syndrome, hypotension, anaphylaxis, infection, and neuropathy. Therefore, patients should receive dinutuximab in an inpatient setting in hospitals capable of providing intensive care unit support. Additionally, treatment with dinutuximab should occur only under the oversight of pediatric oncologists who are skilled in the identification and management of these toxicities. During and following treatment with dinutuximab, patients should undergo careful monitoring for signs and symptoms of these adverse reactions to ensure prompt intervention, including dose interruption, dose modification, dose discontinuation, and institution of supportive care when necessary.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

As indicated, dinutuximab will be administered as a part of a multiagent, multimodality regimen that includes intensive induction and consolidation chemotherapy with autologous stem cell rescue, surgery, and radiation therapy. In the United States, patients with high-risk neuroblastoma receive dinutuximab in tertiary care hospitals with access to intensive care support. Patients with newly diagnosed high risk neuroblastoma receive their treatment while under the care of pediatric oncologists who are highly trained in the identification and treatment of serious adverse reactions, including but not limited to sepsis, capillary leak syndrome, and infusion reactions, that can occur in patients who receive this complex treatment regimen. Therefore, the clinical review team does not recommend a postmarket risk evaluation and mitigation strategy at this time. The proposed package insert contains the necessary guidance for prescribing pediatric oncologists to mitigate patient risk.

1.4 Recommendations for Postmarket Requirements and Commitments

At this time, the clinical review team does not recommend any clinical postmarket requirements or commitments for dinutuximab. However, at the time of completion of this clinical review, multidisciplinary review of the BLA is ongoing so this decision is subject to change.

As discussed in Section 1.2, one of the limitations of the BLA, which posed a significant challenge to a determination of the risk:benefit assessment of dinutuximab, is the lack of clinical data to isolate the treatment effect of dinutuximab from that of GM-CSF, and IL-2. Specifically, there is insufficient data to assess whether the contribution of these cytokines to efficacy outweighs the added toxicities resulting from their use. Similarly, assessment of the toxicity profile of dinutuximab was hampered by the relative lack of clinical data from use of dinutuximab as monotherapy, particularly because IL-2 and GM-CSF are administered concurrently with dinutuximab. Therefore, the clinical review team considered whether to recommend a postmarketing requirement for the conduct of a clinical trial to compare the efficacy and safety of dinutuximab plus RA to the safety and efficacy of dinutuximab in combination with IL-2, GM-CSF, and RA. To inform this decision, the clinical reviewer reviewed information in the published literature, including *in vitro* and *in vivo* data supporting the augmentation of complement dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) of ch14.18 by cytokines, and conducted an assessment of ongoing clinical trials and treatment guidelines for patients with newly diagnosed high risk neuroblastoma in the U.S. and internationally. Based on this review, the clinical reviewer determined that conduct of a clinical trial comparing the safety and efficacy of dinutuximab in combination with RA with dinutuximab in combination with RA and cytokines would not

be feasible and would potentially be considered unethical due to lack of equipoise in the U.S. regarding the role of cytokines in combination with dinutuximab.

At the time of this review, clearance of external Special Government Employees (SGEs) for consultation on the BLA is ongoing. If SGE clearance is obtained, the clinical team plans on seeking input from pediatric oncologists to obtain their opinions regarding whether a potential study to better characterize the contribution of cytokines to the efficacy of dinutuximab is warranted and feasible.

2 Introduction and Regulatory Background

Neuroblastomas represent a heterogeneous group of neuroblastic tumors that originate from primitive sympathetic ganglion cells in the adrenal medulla or paraspinal sites and have the capacity to synthesize and secrete catecholamines. One hallmark of neuroblastoma is its diversity; the clinical presentation and prognosis of patients with neuroblastoma are influenced by several factors, including patient age, tumor location and stage, tumor histology, and tumor molecular characteristics.

With approximately 650 new cases diagnosed each year in the United States[1,2], neuroblastoma is the most common extracranial solid tumor occurring in pediatric patients. Although neuroblastoma rarely occurs in adults[3], it primarily affects young children. The median age at diagnosis is 19 months, and 90% of patients with neuroblastoma are diagnosed at less than five years of age[4].

In North America, the treatment plan for children with neuroblastoma is based upon risk assignment according to a schema developed by the Children's Oncology Group (COG). Using this schema, children are determined to have low-risk, intermediate-risk, or high-risk neuroblastoma based upon the following patient and tumor-based characteristics:

- International Neuroblastoma Staging System (INSS) stage
- age
- International Neuroblastoma Pathologic Classification (INPC)
- ploidy (tumor DNA index)
- amplification of the MYCN oncogene

Additional tumor molecular characteristics, such as chromosome 1p and 11q deletions, confer increased risk and also influence treatment plan. Table 1 displays criteria for

1 Howlader N, Noone AM, Krapcho M, et al., eds: SEER Cancer Statistics Review 1975-2009 (Vintage 2009 Populations). Bethesda, MD: National Cancer Institute, 2012.
2 Gurney JG, Ross JA, Wall DA, et al. *J Pediatr Hematol Oncol.* 1997; 19(5):428-32.
3 Esiashvili N, G. M. *Pediatr Blood Cancer*. 2007; 49, 41-46.
4 London WB, Castleberry RP, Matthay KK, et al. *J Clin Oncol*. 2005; 23(27):6459-65.

assigning neuroblastoma as high-risk, according to the COG schema developed from two COG trials (COG-P9641 and COG-A3961).

Table 1: High-Risk Group Assignment Schema[a]

INSS Stage	Age	MYCN Status	INPC Classification	DNA Ploidy[b]
2A/2B[c]	≥365 d-21 y	Amplified	Unfavorable	-
3[d]	<365 d	Amplified	Any	Any
	≥365 d-21 y	Nonamplified	Unfavorable	-
	≥365 d-21 y	Amplified	Any	-
4[e]	<365 d	Amplified	Any	Any
	≥548 d-21 y	Any	Any	-
4S[f]	<365 d	Amplified	Any	Any

a. Adapted from table contained in NCI's Neuroblastoma Treatment (PDQ®), "Treatment Option Overview for Neuroblastoma" at http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8 accessed on August 15, 2014.

b. DNA index (DI) > 1 (hyperdiploid) or < 1 (hypodiploid) is favorable; DI = 1 is unfavorable

c. INSS Stage 2 includes localized tumors with or without complete gross excision or involvement of ipsilateral nonadherent lymph nodes but contralateral lymph nodes negative for microscopic involvement

d. INSS Stage 3 includes unresectable unilateral tumor infiltrating across the midline±regional lymph node involvement;localized unilateral tumors with contralateral regional lymph node involvement;midline tumors with bilateral extension by infiltration or lymph node involvement.

e. INSS Stage 4 includes any primary tumor with dissemination to distant lymph nodes, bone, bone marrow, liver, skin, or other organs, unless meets criteria for Stage 4S.

f. Stage 4S: includes localized primary tumors meeting criteria for Stage 1 or Stage 2 with dissemination limited to skin, liver, and/or bone marrow in children younger than 1 year of age.

The approach to risk stratification in neuroblastoma is evolving, and current COG trials classify neuroblastoma as high-risk if it meets one of the following criteria:

- Stage II, III, IV, or IV-S disease with amplified MYCN
- Stage III disease in patients > 18 months with unfavorable histology
- Stage IV disease in patients 12-18 months with non-amplified MYCN, unfavorable histology, or DNA index of 1
- Stage IV disease in patients > 18 months[5].

The five year survival rate of children with neuroblastoma ranges from 87% for children less than one year of age to 65% in children aged 1 to 14 years. However, the

5 "Determining Treatment and Risk of Relapse", at http://www.childrensoncologygroup.org/index.php/neuroblastoma/197accessed on May 23, 2014.

prognosis is highly variable. Children of any age with localized neuroblastoma and infants 18 months of age and younger with advance neuroblastoma with favorable histology and molecular characteristics have a high likelihood of long term survival. However, older children with advanced-stage disease have a much lower chance of being cured despite treatment with intensive multimodality therapy. Approximately half of patients diagnosed with neuroblastoma have disease that is categorized as high-risk. Patients with high-risk neuroblastoma, including patients greater than 18 months of age with metastases or unresectable disease with high-risk genetic features (including amplification of the MYCN oncogene) have a 40% to 50% chance of long term survival[6].

Patients with low-risk tumors have a greater than 98% chance of survival with treatment limited to observation or tumor resection. Patients with intermediate-risk neuroblastoma typically receive a chemotherapy regimen that varies in duration and intensity depending upon clinical and biological risk factors prior to surgical resection. The survival rate for intermediate risk patients approaches 95%. In contrast, in the United States, the current standard of care for patients with high-risk neuroblastoma consists of intensive multimodality therapy. In the United States, the standard treatment regimen for patients with high-risk neuroblastoma includes the following elements:

- Induction chemotherapy consisting of cisplatin and etoposide alternating with vincristine, cyclophosphamide and doxorubicin
- Maximum feasible surgical resection
- Consolidation chemotherapy consisting of myeloablative chemotherapy (either carboplatin/etoposide/melphalan or busulfan/melphalan) followed by autologous stem cell transplant
- Radiation to the primary tumor site and metaiodobenzylguanidine (MIBG)-positive bony metastatic sites, either before, during or after myeloablative therapy
- For patients who achieve a partial, very good partial, or complete response to therapy, six months of “maintenance therapy” consisting of anti-GD2 antibody chimeric 14.18 combined with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid [isotretinoin (RA)][7].

2.1 Product Information

Dinutuximab is a chimeric monoclonal antibody composed of murine variable heavy and light chains and the human constant region for the heavy chain IgG1 and light chain kappa that binds to the surface disialoganglioside (GD2) antigen. Dinutuximab is produced in the murine myeloma cell line, SP2/0.

6 Gustafson WC and Matthay KK. *Expert Rev Neurother.* 2011;11(10):1411-23.
7 Neuroblastoma Treatment (PDQ®), “Treatment Option Overview for Neuroblastoma” at http://www.cancer.gov/cancertopics/pdq/treatment/neuroblastoma/HealthProfessional/page4#Reference4.8 accessed on May 23, 2014.

Dinutuximab is supplied as a sterile, preservative-free clear/colorless to slightly opalescent solution for intravenous infusion in single-use vials containing 17.5 mg in 5 milliliters (mL) of solution. Each vial contains 3.5 mg/mL of dinutuximab and the following inactive excipients: histidine (20 mM), polysorbate 20 (0.05%), sodium chloride (150mM), and water for injection, USP at a pH of 6.8.

2.2 Tables of Currently Available Treatments for Proposed Indications

There are no treatments specifically approved for the treatment of patients with high-risk neuroblastoma.

Table 2 provides a list of therapies approved by FDA for the treatment of neuroblastoma.

Table 2: Therapies Approved by FDA for the Treatment of Patients with Neuroblastoma

Therapy	Indication
Cyclophosphamide	Neuroblastoma (disseminated disease), alone or used concurrently or sequentially with other antineoplastic drugs
Doxorubicin hydrochloride	Neuroblastoma
Vincristine sulfate	Neuroblastoma, in combination with other oncolytic agents

As described in Section 2 of this clinical review (page 13), in the United States and Canada, the standard approach to treatment of patients with newly diagnosed high risk neuroblastoma comprises intensive, multimodality and multiagent therapy, including induction and consolidation chemotherapy with autologous stem cell rescue, maximum feasible surgical resection, and radiation to the tumor site(s). Patients who achieve at least a partial response to therapy prior to autologous stem cell transplantation also receive a six month treatment regimen consisting of anti-GD2 antibody therapy (i.e., ch14.18) in combination with GM-CSF, IL-2, and RA (hereafter referred to as "ch14.18 combination treatment").

Prior to incorporation of ch14.18 combination treatment into the standard treatment regimen for high risk neuroblastoma, RA monotherapy following autologous stem cell transplantation was considered standard of care based upon results of Study CCG 3891, entitled "Conventional Dose Chemoradiotherapy vs. Ablative Chemoradiotherapy with Autologous Bone Marrow Transplantation for High-Risk Neuroblastoma"[8,9,10]. In this study, 379 patients were randomized to receive either

8 Matthay et al. *New England Journal of Medicine*. 1999; 241(16):1165-1173.
9 Matthay et al. *Journal of Clinical Oncology*. 2009; 27(7):1007-1013.
10 *Journal of Clinical Oncology*. 2009; 32(17) Errata available at

continuation chemotherapy or autologous bone marrow transplant (ABMT); 258 patients were subsequently randomized to receive either RA or no further therapy following completion of either continuation chemotherapy or ABMT. All patients received five 28-day cycles of induction chemotherapy with cisplatin, doxorubicin, etoposide, and cyclophosphamide, plus surgery and radiation therapy for gross residual disease. Patients were eligible for randomization if they did not have progressive disease just prior to the third cycle of chemotherapy. Patients randomized to undergo ABMT received conditioning with carboplatin, etoposide and melphalan and total body irradiation (333 cGy daily for three days prior to transplantation) followed by infusion of purged bone marrow and GM-CSF. Patients randomized to receive continuation chemotherapy received three additional cycles of chemotherapy consisting of cisplatin, etoposide, doxorubicin, ifosfamide, and G-CSF. After transplantation or completion of continuation chemotherapy (Week 34), patients without disease progression were randomized to receive either six cycles of RA (160 mg/m^2/day for 14 consecutive days of a 28-day cycle) or no additional treatment.

According to papers published by Matthay et al., the mean EFS rate (± standard error) three years after the first randomization was superior in the ABMT arm compared to the continuation chemotherapy arm (reported results: 34%±4% vs. 22%±4%, p=0.034). Additionally, the EFS rate three years after the second randomization was improved in patients randomized to the RA group compared to those who did not receive RA (reported results: 46%±6% vs. 29%±5%, p=0.027). In a follow-up analysis, 5-year EFS was superior in the in the ABMT arm (reported results 30%±4% vs. 19±3%, nominal p=0.04). There was a non-statistically significant trend toward improvement in EFS in patients randomized to the RA arm compared to patients who received no further therapy (42%±5% vs. 31%± 5%). There was also a non-statistically significant trend toward improvement in OS in patients randomized to receive ABMT and in those randomized to receive RA.

Reviewer note: EFS is traditionally used as the efficacy endpoint for many randomized trials evaluating treatments for pediatric cancers due to the large sample size that would be typically be required to detect a statistically significant difference in OS and the longer follow-up time that assessment of OS would entail. This study was not powered to detect a statistically significant improvement in overall survival among any of the treatment arms.

2.3 Availability of Proposed Active Ingredient in the United States

Dinutuximab is currently available for investigational use under an investigational new drug (IND) application only.

http://jco.ascopubs.org/content/32/17/1862.full.

In the United States (U.S.), anti-GD2 therapy with investigational agents such as dinutuximab is considered to be an integral part of multiagent, multimodality therapy for the front line treatment of neuroblastoma. Treatment with dinutuximab is available to patients who enroll in the ongoing single arm open label portion of the Children's Oncology Group, Study ANBL0032 (referred to as DIV-NB-302 by the Applicant; see Table 5) under IND 4308 (sponsored by the Cancer Therapy and Evaluation Program, or CTEP). Children with high-risk neuroblastoma who do not meet the eligibility criteria for Study 302 but for whom treatment with dinutuximab is reasonably safe may receive treatment through CTEP's expanded access program for dinutuximab.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no approved monoclonal antibodies that bind to the ganglioside GD2. Infusion reactions are labeled risks for approved monoclonal antibodies directed against other antigens. For example, approved labeling for rituximab and cetuximab (recombinant antibodies that bind to the CD20 antigen and human epidermal growth factor receptor, respectively), contains a box warning conveying the risk of fatal infusion reactions.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 3 summarizes key regulatory interactions, advice, and decisions related to this BLA. The majority of clinical data submitted to support the BLA is derived from clinical trials of chimeric monoclonal antibody 14.18 (ch14.18) conducted by the National Cancer Institute's Clinical Therapy Evaluation Program (CTEP) in conjunction with the Children's Oncology Group (COG). On July 1, 2010, United Therapeutics Corporation (UTC) and the National Cancer Institute (NCI) executed a Cooperative Research and Development Agreement (CRADA) to collaborate on the clinical and commercial development of ch14.18 for the treatment of patients with neuroblastoma following myeloablative therapy and autologous stem cell transplant in combination with granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin-2 (IL-2) and isotretinoin (RA). This CRADA conferred to UTC exclusive access to the clinical study data derived from all studies of ch14.18 sponsored by NCI under IND 4308 and the technical information required to support commercial manufacturing of ch14.18 (hereafter referred to as dinutuximab when specifically discussing the ch14.18 product produced by UTC).

Table 3: Key Regulatory Activities Related to the Development of Dinutuximab

Date	Nature of Regulatory Activity	Issues
12/4/1991	IND submission	• Application for IND 4308 submitted by CTEP
10/2/2002	FDA placed IND 4308 on partial clinical hold	• IND placed on partial hold to prevent treatment of patients under Study ANBL0032 (DIV-NB-301) at the Children's Hospital of Eastern Ontario (CHEO) investigational site, where two patients received an overdose of IL-2 (one overdose caused a death). Formal letter issued 11/1/2002.
4/9/2003	FDA removed partial hold	• Action plan developed by the Special Protocol Review Committee of CHEO was provided that instituted safety precautions to mitigate the risk of medication errors.
4/30/2003	FDA placed IND 4308 on partial clinical hold	• IND placed on partial hold to prevent enrollment of new patients at any site into Study ANBL0032. Deficiencies included inadequate dose modification rules for IL-2 and ch14.18 (ANBL0032 protocol permitted toxicities that would be acceptable for high dose IL-2 therapy, which typically requires intensive care support, but were not considered reasonable for patients receiving low dose IL-2 therapy), lack of on-site training at COG sites, inadequate trial oversight by the principal investigator, and lack of criteria for screening clinical sites for their ability to administer toxic biologic therapies. Additionally, pre-printed orders at the CHEO site appeared to be the cause of the IL-2 overdose; therefore, incorporation of sample orders into the protocol and a requirement that modifications to pre-printed orders be reviewed and submitted by COG was deemed necessary. Formal letter issued 5/9/2003.

Date	Nature of Regulatory Activity	Issues
7/18/2003	FDA removed partial hold	• CTEP adequately responded to deficiencies outlined in the partial hold letter and agreed to revise the dose modification and stopping criteria for Study ANBL0032 to permanently discontinue IL-2 for any Grade IV toxicity and include stopping criteria for hyponatremia and Grade 4 skin toxicity. • The remove hold letter contained a non-hold comment informing CTEP that as designed, Study ANBL0032 will not provide sufficient data to meet the regulatory standards for a licensing study. FDA described the following flaws in study design and requested a response explaining how these flaws will be corrected: – A one-sided log-rank test comparing the two arms with an alpha of 0.05 would not support licensure – Lack of clarity regarding whether there were co-primary endpoints or one primary endpoint. A single primary endpoint of overall survival (OS) was recommended. – The analysis of event-free survival did not address the post-randomization loss of patients due to missing data, toxicity, and refusal of future treatment, and the necessary adjustment in sample size and analyses for these events. – The statistical plan to conduct interim analyses for futility and efficacy every six months following occurrence of 20% of deaths (possibly up to 10 such analyses during the estimated trial course of seven years) presented potential concern and there was lack of clarity on how trial integrity and lack of bias would be maintained in this open label trial over a long period of time. FDA requested clarification regarding the degree to which the Data Monitoring Committee deliberations are closed, how interim efficacy data are reported, and a plan to for alpha adjustment for multiple analyses.

Date	Nature of Regulatory Activity	Issues
9/1/2005	Type C meeting held between FDA and CTEP	• Meeting held to review the progress of Study ANBL0032 and preview the proposed ANBL0532 induction and consolidation regimen and determine whether all patients from this new regimen who meet ANBL0032 response criteria could be included as evaluable patients in the ANBL0032 study. • FDA stated that inclusion of patients treated on the successor high-risk neuroblastoma study, Study ANBL0532, is acceptable provided that Study ANBL0032 achieves the primary efficacy event-free survival (EFS) endpoint and the treatment effect is robust, consistent across subgroups, and not substantially impacted by a single subgroup. • FDA stated that CTEP needs to provide a plan for isolating the effect of IL-2 and GM-CSF in the treatment regimen, and that this is a critical component of an application. CTEP acknowledged this comment and agreed to submit a plan to establish the contribution of cytokines to the treatment effect. • FDA stated that the primary statistical analysis should have a one-sided type 1 error rate no greater than 0.025. • FDA stated that if NCI plans to request accelerated approval based on a claim of improvement in EFS, they needed to provide evidence to support their contention that a change in EFS is predictive of a change in OS.
5/30/2006	FDA issued advice letter and request for information	• FDA informed CTEP that for regulatory purposes, an appropriate primary analysis plan should have a one-sided type 1 error rate at most 0.025, when ignoring the futility boundary. FDA requested clarification regarding how this requirement would be maintained taking into account interim analyses and whether the trial would be continued if early boundaries are crossed. • FDA requested adequate justification for the use of EFS as a surrogate for OS based on analyses of the correlation between EFS with OS.
8/8/2008	FDA reiterated advice and request for information previously communicated on 5/30/2006.	

Date	Nature of Regulatory Activity	Issues
1/15/2009	IND 4308 placed on partial clinical hold	• IND placed on partial clinical hold preventing enrollment of new patients onto Study ANBL0032 (DIV-NB-301) after being informed of six cases of Grade 3/4 allergic reactions linked to ch14.18 lot L0512003 (formal letter issued 1/27/2009).
4/3/2009	FDA removed partial hold	• CTEP adequately addressed the concerns regarding lot L0512003. Based on the information provided, FDA concluded that the apparent increase in severe allergic/hypersensitivity reactions was related to a change in categorization of reporting adverse events, not a true increase in incidence. The remove hold letter included the following non-hold comments and requests for information: – The amended ANBL0032 protocol should include the requirement that lot numbers of IL-2 and GM-CSF be recorded and be revised to ensure collection of information about targeted adverse events including allergic reaction/hypersensitivity, hypotension, urticaria, adult respiratory distress syndrome, dyspnea, cytokine release syndrome/acute infusion reaction, and acute vascular release syndrome. – FDA reminded CTEP that in light of COG's decision to stop randomization (information submitted to FDA on March 5, 2009), it is critical to diligently pursue commercial development of ch14.18, and that the single arm extension portion of the study is only a temporary measure to provide access to ch14.18 to patients. – FDA requested that CTEP submit a new protocol with the specific objective of obtaining comprehensive safety information from a minimum of 100 patients to support a licensing application for ch14.18 plus cytokines within the next six months.
12/20/2010	FDA granted orphan drug status to ch14.18 for the treatment of neuroblastoma	

Date	Nature of Regulatory Activity	Issues
1/27/2011	Type B Pre-IND meeting with United Therapeutics (pIND 110494)	• FDA stated that if UTC provides data to demonstrate that UTC-manufactured ch14.18 (dinutuximab) is comparable to NCI-derived ch14.18, data from Study ANBL0032 can be submitted as the single trial supporting efficacy of ch14.18 in combination with GM-CSF and IL-2 as a component of standard treatment of patients with high-risk neuroblastoma who have minimal residual disease after autologous stem cell transplant. • DOP2 emphasized that UTC was responsible for the content and quality of the application.
3/9/2012	IND application submission	• UTC submitted IND 110494 for dinutuximab.
4/9/2012	Teleconference between DOP2, CMC, and UTC	• Teleconference held to discuss UTC's plans for addressing results that were out of specification for drug product lot P110602 at the 3-month stability testing time point and reach agreement regarding the use of lot S110601 for Study DIV-NB-201. UTC agreed not to use Lot S11601, not the failed lot, in Study DIV-NB-201. UTC agreed to provide 3-month and 6-month stability data for Lot S110601 as a formal IND amendment when it becomes available.
4/11/2012	FDA issued may proceed letter for IND 110494	
12/11/2012	Type C meeting	• UTC, DOP2, and CMC Division of Monoclonal Antibodies met to discuss status of commercial manufacturing for dinutuximab, planned validation efforts, and reach agreement on CMC requirements for the filing of a future BLA.
8/28/2013	Informal teleconference between UTC and DOP2	• Teleconference held to discuss the status of commercial development of dinutuximab and the potential timing of a BLA application.
12/20/2013	Office of Orphan Products Development (OOPD) designated dinutuximab as a drug for a "rare pediatric disease" for the treatment of neuroblastoma	
1/14/2014	Type B pre-BLA CMC meeting	• Multiple issues were discussed, including the need to include polysorbate 20 in the specifications, lower the bioburden specification for the (b) (4) , justify the use of (b) (4) for bioburden studies, and perform hold time studies to determine the reliability of the endotoxin test results.

Date	Nature of Regulatory Activity	Issues
2/19/2014	Type B pre-BLA meeting	• FDA reminded UTC of the need to provide data in the BLA establishing the contribution of each therapeutic component (dinutuximab, IL-2, and GM-CSF). – UTC stated that they will address this requirement in the ISE by referencing published literature and clinical study data. – FDA stated that the adequacy of the information to isolate the effects of ch14.18 will be determined during the BLA review. – FDA stated that consistency of efficacy across key patient subsets is an important factor in determining whether a single adequate and well controlled study provides sufficient evidence to support an effectiveness claim.

2.6 Other Relevant Background Information

The European Union (EU) granted orphan drug status to dinutuximab for the treatment of high-risk neuroblastoma on June 21, 2011. (b) (4) UTC submitted a Marketing Authorization Application for dinutuximab to the EMA on December 5, 2013.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This BLA submission was of adequate quality to allow for filing of the BLA and for the clinical review to be conducted. However, as the clinical review progressed, multiple deficiencies in data capture and quality were identified that were impediments to the conduct of a timely review. Several key examples of these deficiencies are listed below:

- Case report forms captured the anticipated course start and end dates, but did not the actual dates of study drug administration for Study 301 and Study 302. Case report forms also did not capture the last day of study therapy. These omissions made verification of study drug exposure through examination of case report forms impossible.

- Dates for resolution of adverse events were not recorded in the case report forms for Study 301 and Study 302.
- Dose modifications were not captured in the case report forms for Study 301 and 302. Case report forms also did not comprehensively capture the reason for study drug discontinuation. For example, the adverse events leading up to study drug discontinuation were not specified in the case reports forms for five patients who discontinued ch14.18 due to a reason listed as "toxicity" in study 301.
- The datasets submitted to the BLA incorrectly categorized nine patients who dropped out of the study prior to receiving treatment as having been exposed to study therapy in Study 301 (five incorrectly assigned as part of the safety dataset for the RA group and four for the treatment group). Similarly, four patients were included in the safety dataset for Study 302 who dropped out of the study prior to study drug exposure.
- The Children's Oncology Group did not collect protocol deviations for the ANBL0032 study other than those that related to eligibility criteria.
- The BLA submission did not specify where trial documentation is maintained, and who had responsibility for different aspects of trial monitoring and conduct (CTEP versus COG versus United Therapeutics).
- There were data discrepancies resulting from, at least in part, incongruous data cutoffs between information captured in the datasets and those used to create the tables in the clinical study reports in the BLA. This made verification of the Applicants study results cumbersome and time consuming.
- Data regarding serious adverse events, reported through NCI's Adverse Event Expedited Reporting System (AdEERS), were not integrated into the adverse event dataset. Additionally, the clinical study reports originally submitted to the BLA stated that serious adverse events were coded using MedDRA version 10.0 preferred terms. Upon inquiry by FDA, the Applicant discovered that serious adverse event terms submitted to the BLA comprised CTCAE v. 4.0 terms, equivalent to MedDRA SOC terms and lower-level terms, which precluded systematic evaluation of serious adverse events by MedDRA hierarchy.
- The analysis dataset legacy folder for DIV-NB-301 initially submitted to the BLA contained an incorrect data cut to support the efficacy analysis for the June 2012 data cutoff (corrected by the applicant on July 7, 2014 in response to an IR).
- Dataset definition files contained an inadequate level of detail in the variable definitions to facilitate efficient review.
- The reviewer's guide provided by the Applicant did not contain adequate information to explain the dataset structure and the data used to perform the efficacy analyses presented in the clinical study reports. Multiple information requests were required to obtain the information needed to verify the efficacy results presented by the Applicant.
- Key dataset variables were absent or had incomplete entries.

3.2 Compliance with Good Clinical Practices

The Applicant verified that all studies were conducted following standard research design conventions following institutional review board approval at the associated study centers. The DIV-NB-201 study report contains a statement that it is being conducted in accordance with ICH guidelines and GCP procedures. The study reports for studies CCG-0935, -0935A, POG 9347, ANBL0032 (DIV-NB-301 and -302), and ANBL0931 (DIV-NB-303) contained statements that they were conducted in accordance with FDA, NCI, and any institutional requirements for human studies.

The Division of Oncology Products 2 (DOP2) consulted the Office of Scientific Investigation to perform audits of four clinical sites to assess data integrity and verify that the study was performed according to Good Clinical Practices. DOP2, in consultation with OSI, selected clinical sites for inspection based upon analysis of enrollment characteristics and patterns of serious adverse events and protocol violations reported for the sites.

OSI inspected four clinical sites (Table 4) in addition to the Cancer Therapy Evaluation Program (CTEP), the sponsor of the IND for the majority of the clinical trials supporting the BLA. Results of these inspections were pending at the time of completion of this review. Preliminary feedback from the OSI team indicates that in general, the efficacy and safety data from the clinical sites appeared reliable based upon inspection of the available records at each site. Please see the inspection site addendum for a summary of the results of the OSI inspections.

Table 4: Clinical Sites Inspected for Study 301 and Study 302

Site/Clinical Investigator/Location	Number of Subjects
Site 1865:WA061 Douglas Hawkins, MD Seattle Children's Hospital Seattle, WA	21
Site 1946: MO024 Maxine Hetherington, MD Children's Mercy Hospital Kansas City, MO	12
Site 1866:CA009 Leo Mascarenhas, MD Children's Hospital of Los Angeles Los Angeles, CA	35
Site 1873:PA076 Frank Balis, MD Children's Hospital of Philadelphia Philadelphia, PA	56

3.3 Financial Disclosures

The applicant adequately disclosed financial interests and arrangements with clinical investigators, in accordance with FDA's February 2013 Guidance for Clinical Investigators, Industry, and FDA Staff, entitled *Financial Disclosure by Clinical Investigators.* Per the 2013 FDA Guidance, if a public or academic institution conducts a covered clinical study without any support from a commercial sponsor, but the study is later used by an applicant to support its marketing application, the clinical investigator's financial interests in and arrangements with the applicant do not need to be reported because the company was not a sponsor of the covered clinical study.

In Form 3454, the applicant attested that there have been no financial arrangements with any of the listed clinical investigators for Study 301 (the randomized portion of COG Study ANBL0032). In a subsequent submission to the BLA (May 19, 2014), the applicant clarified that this list "reflects all the available information that UTC was able to obtain from NCI…" The applicant also included a letter signed by Sherry Ansher, Associate Chief of the Agreement Coordination Group, Regulatory Affairs Branch of CTEP/NCI, indicating that NCI did not provide an equity interest to its clinical investigators and that NCI did not give ANBL0032 clinical investigators any form of compensation that was affected by trial outcome and did not provide significant

payments of other sorts to the investigators or the investigators' institution (s) exclusive of the costs of conducting ANBL0032, and that investigators did not report any proprietary interest in ch14.18.

The applicant submitted a Form 3454 for Study DIV-NB-201, attesting that they had not entered into a financial arrangement with any of the listed clinical investigators for Study 201. In a subsequent submission to the BLA (May 19, 2014), the applicant clarified that this list comprised all clinical investigators and subinvestigators currently directly involved in the treatment or evaluation of research subjects in Study 201. The applicant also provided a comprehensive list of all the investigators either actively or previously involved in Study 201 who had no disclosable financial interests.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

This section summarizes issues relating to the safety and efficacy of dinutuximab identified by other review disciplines as of August 31, 2014. This summary should be considered partial and preliminary. Please refer to the respective discipline reviews for a full description of the issues and findings identified during the course of the review process.

4.1 Chemistry Manufacturing and Controls

At the time of this review, the Chemistry Manufacturing and Controls (CMC) team had identified the need for several potential postmarketing requirements or commitments. A partial list of the potential postmarketing requirements or commitments that are being considered includes reassessment of the drug substance and drug process specifications based upon additional clinical experience with ongoing trials with material manufactured using the commercial process; to manufacture, qualify, and implement a new reference standard that will be entered into a requalification program; to validate an improved assay for the detection of host cell proteins and update drug substance specifications with the improved assay; to validate (b) (4) assay for the detection of (b) (4) that will be included in drug substance and drug product specifications; to perform end product cell testing on cells from commercial scale manufacturing; to provide additional testing to confirm the monoclonality of the master cell bank; to perform drug product shipping studies; to perform a leachable study of drug product at the end of shelf-life; and to perform commercial scale (b) (4) lifetime studies.

Reviewer note: This list is a partial list and the potential postmarketing commitments or requirements listed above are subject to change. Please refer to the comprehensive review by the CMC team for additional details.

4.2 Clinical Microbiology

The Clinical Microbiology team identified the following issues related to the manufacturing of dinutuximab.

- The microbial retention study was performed with (b) (4) The clinical microbiology team requested that UTC perform another microbial retention study with (b) (4) for the microbial retention study be worst-case compared to production.
- (b) (4)
- Rabbit pyrogen test data required under 21 CFR 610.13(b) was not provided for the drug product. The clinical microbiology team requested that UTC provide rabbit pyrogen test data for three different lots of the drug product to confirm that the product does not contain pyrogenic substances other than bacteria endotoxin.
- There was insufficient information submitted to the BLA regarding the low endotoxin recovery study. The team requested that UTC provide the missing information in order to determine whether additional endotoxin control and testing is needed.
- The hold time validation study for (b) (4) was not yet completed at the time of the BLA submission, so the team requested that data from this study be submitted for review.

Reviewer note: This list is a partial list. Please refer to the comprehensive review by the Clinical Microbiology team for additional details.

4.3 Preclinical Pharmacology/Toxicology

Knowledge of the preclinical pharmacology/toxicology profile of dinutuximab (ch14.18) is primarily based on information from published studies. Prior to issuance of the CRADA between NCI and UTC, the clinical development of ch14.18 was supported by multiple nonclinical *in vitro* and *in vivo* studies conducted by a variety of academic investigators. These studies helped characterize the binding characteristics, mechanism of action, anti-tumor activity, and toxicity of ch14.18. A limited number of nonclinical studies were conducted with UTC-manufactured ch14.18 (i.e., dinutuximab).

These studies comprise tissue cross reactivity (TCR) studies using human, rat, and rabbit tissues; a single dose study in cynomolgus monkeys (SBL354-004) with a combined cardiovascular and respiratory safety pharmacology study (SBL354-005); and a 28-day repeat-dose toxicity study in rats (SBL354-003).

Published findings suggest that the pain associated with ch14.18 administration is due to ch14.18 binding to GD2 antigen on peripheral nerves and/or myelin in muscle tissues[11,12,13,14].

UTC submitted data from a combined cardiovascular and respiratory safety pharmacology study of dinutuximab in cynomolgus monkeys (SBL354-005). In this study, a single 14 mg/kg/dose (~168 mg/m^2) was administered to three conscious, telemetered male monkeys on Day 3, as a 10-hour IV infusion. Increased blood pressure was observed in one animal and increased heart rate was observed in two animals at interval of 5 to 24 hours following dinutuximab administration, when compared with controls. Shortening of the PR interval and QT interval related to the increase in heart rate was also observed in two animals 5, 10, 12 and/or 24 hours after initiation of dosing; however these changes did not affect the QTc interval, respiratory rate, or blood gas parameters.

No specific ch14.18 tissue-distribution studies were submitted to the BLA; however, information from published tissue distribution studies in athymic mice bearing human melanoma xenografts and healthy dogs using radiolabeled 14.G2a (a murine monoclonal antibody against GD2) or ch14.18 was submitted because the binding region of murine and chimeric antibodies is the same. These studies suggest that the anti-GD2 antibody specifically binds to tumor tissue, the liver, and mesenteric lymph nodes. An additional toxicity study in rats also showed that the liver was the target of ch14.18 toxicity, suggesting that ch14.18 degradation originates in the liver.

A formal single-dose toxicology study was not conducted. Limited toxicity parameters, including body weight, food consumption and clinical observations were recorded in the pilot single dose tolerability study (SBL354-004) in cynomolgus monkeys. A single 30-minute 10.5 or 21 mg/kg intravenous infusion of ch14.18 caused vomiting within 30 minutes in monkeys receiving the higher dose and genital swelling occurred at both dose levels.

UTC submitted data from a one month repeat-dose toxicology study in Sprague-Dawley rats (SBL354-003). In this study, rats received either a test vehicle or ch14.18 [5, 15, or 45 mg/kg (~270 mg/m^2)] once daily for four consecutive days each week for a total of four weeks, followed by a 6-week dose-free period. Dose-related findings included

[11] Slart et al. *Pain*. 1997; 69:119-125.
[12] Xiao et al. *Pain.* 1997; 69:145-151.
[13] Sorkin et al. *Brain Research*. 2002; 930:67-74.
[14] Sorkin et al. *Pain*. 2010;149(1):135-142.

liver-specific histopathologic changes (centrilobular congestion, hepatocellular necrosis, pericentral vein/interlobular fibrosis) related to increases in AST and ALT and total cholesterol. Increased liver weight was also noted in the high dose group when compared to control animals. High reticulocyte ratio, increased platelet count, and increased cellularity of hematopoietic cells were also observed in rats receiving ch14.18. The majority of histopathologic changes were mild, and either partially or fully recovered during the 6-week recovery period, with the exception of microscopic hepatic centrilobular congestion and pericentral vein and interlobular fibrosis.

The nonclinical review team concluded that overall, data from published and applicant-conducted nonclinical studies submitted to the BLA were not able to predict the toxicities of ch14.18 observed in clinical trials of ch14.18. Specifically, capillary leak syndrome, hypotension, systemic infection or sepsis, neurological disorders of the eye and hyponatremia observed in clinical trials were not evident in animal studies. The review team noted that one potential reason for the lack of correlation between toxicities observed in animals and toxicities reported in clinical trials could be that animals did not receive IL-2, GM-CSF, or retinoic acid in combination with ch14.18.

The review team also noted that although FDA waived the requirement for embryofetal studies due to the young age of patients affected by high risk neuroblastoma, because dinutuximab is an IgG1 antibody, it may have the potential to cross through the placenta. The extent of the potential risk to the fetus if dinutuximab is administered during pregnancy is unknown.

During the mid-cycle communication to UTC, the nonclinical team commented that additional clarity is needed regarding whether ch14.18 can elicit an effective ADCC response in the presence of effector cells of mouse, rat, dog, or monkey origin. The nonclinical team is also considering negotiating a postmarketing requirement for a GLP-compliant 13-week chronic toxicology study to gain a better understanding of dinutuximab-specific toxicity, especially the potential for recovery from peripheral nerve damage.

4.4 Clinical Pharmacology

The clinical pharmacology team concluded that the results of the population pharmacokinetic (PK) model-based assessment and non-compartmental analysis (NCA) indicate that UTC-manufactured dinutuximab provides comparable PK exposure to the NCI-manufactured ch14.18 used in DIV-NB-301, -302, and -303 studies. The clinical pharmacology team also determined that the BLA was acceptable for approval from a clinical pharmacology perspective, provided that the Applicant and the Agency come to a mutually satisfactory agreement regarding the content of product labeling.

The clinical pharmacology team noted that an exposure/dose-response relationship for efficacy and safety could not be characterized due to the lack of PK data and lack of incorporation of dose exploration in the major clinical studies submitted to the BLA.

A major issues examined by the Clinical Pharmacology review team was whether use of population PK approach was adequate to demonstrate PK comparability between the UTC and NCI-manufactured ch14.18. The review team requested that UTC provide the results of the non-compartmental analysis performed on a subset of patients. The clinical pharmacology review team concluded that the bioequivalency criteria (80-125%) were met based upon analysis of area under the curve.

4.4.1 Mechanism of Action

Dinutuximab binds to the disialoganglioside GD2. The GD2 antigen is expressed on the cell surface of a variety of tumors, including neuroblastomas and most melanomas. In normal fetal and adult tissues, GD2 expression is primarily limited to the central nervous system, peripheral nerves, and skin melanocytes. Binding of dinutuximab to GD2 induces lysis of GD2-expressing cells. Possible mechanisms of cell lysis are antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC).

4.4.2 Pharmacodynamics

In vitro, dinutuximab binds to neuroblastoma cell lines known to express GD2, and has been shown to induce both ADCC and CDC. In the presence of human effector cells including peripheral blood mononuclear cells (PBMC) and granulocytes form normal human donors, ch14.18 was found to mediate the lysis of several neuroblastoma cell lines in a dose-dependent manner. Granulocytes were found to be more effective than PBMCs in mediating dinutuximab-dependent cytotoxicity of neuroblastoma cells with enhanced cell lysis observed with the addition of GM-CSF. Additionally, in xenografts studies in mice, dinutuximab was shown to partially inhibit tumor growth in mice when administered alone or in combination with IL-2. *In vitro* and *in vivo* studies showed that in the presence of IL-2, ch14.18 enhanced lysis of GD-2 expressing cells more efficiently than ch14.18 alone.[15,16,17,18,19].

[15] Kendra K et al. *Journal of Immunology.* 1999; 22(5):423-430.
[16] Mujoo K et al. *Cancer Research.*1987; 47:1098-1104.
[17] Mueller B et al. *The Journal of Immunology*.1990;144:1382-1386.
[18] Barker E et al. *Cancer Research.* 1991; 51:144-149.
[19] Zeng Y et al. *Molecular Immunology.* 2005; 42:1311-1319.

Please see the nonclinical review by Dr. Dubravka Kufrin for a more detailed review of published i*n vitro and in vivo* studies contributing to the current understanding of the mechanism of action and pharmacodynamic properties of dinutuximab.

4.4.3 Pharmacokinetics

The draft clinical pharmacology review contained the following observations:

- The PK profile dinutuximab has been characterized by population PK analysis based on the data from the study DIV-NB-302 (n=6) and DIV-NB-201 (n=28).
- The volume of distribution of dinutuximab at steady state is 5.37 L (CV%= 27%). The systemic clearance is 0.21 L/day (CV %=62%).
- The terminal half-life is estimated to be 10 days.
- No clinically important differences between single dose and multiple dose PK parameters were observed in Study 302.
- No dedicated studies were conducted to evaluate the effect of factors on PK parameters. In addition, a formal exploration of significant covariates was not conducted in the population PK analysis due to data limitations.
- Allometric body weight scaling of PK parameters was included as a pre-determined covariate in the final population PK model. Body weight appears to be significant covariate for clearance based on population PK model
- No dedicated studies and population PK analysis were conducted to evaluate the effect of renal or hepatic impairment on exposure.

Dinutuximab is a protein and the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

4.4.4 EKG Findings

Electrocardiogram (ECG) parameters are currently being evaluated in ongoing studies 302 and 201. However, according to the Applicant, no notable changes in ECG parameters (e.g., HR, PR interval, QRS interval, QT interval, QTcB interval, QTcF interval, and RR interval) were observed using data from 65 patients accumulated through January 2014.

Reviewer note: At the time of this review, results of the FDA QT-Interdisciplinary Review Team's assessment of the ECG data submitted to the BLA are pending.

4.4.5 Immunogenicity Testing

The clinical pharmacology team draft review contained the following information relating to immunogenicity testing:

- Preliminary data from Study 301 using an academic non-validated ELISA assay found that 8 of 118 patients (7%) receiving dinutuximab and RA analyzed tested positive for human anti-chimeric antibodies (HACA).
- Of 414 patients evaluated for HACA using a validated assay in Studies 302, 303, and 201, 83 subjects (20%) tested positive for HACA.
  - 15 patients (4%) tested positive for neutralizing antibody (Nab).
  - Some patients had confirmed HACA responses prior to dosing with dinutuximab in the DIV-NB-302 (8 patients) and DIV-NB-303 (3 patients). The clinical pharmacology reviewer noted that while the mechanism of this positive response prior to exposure is not fully understood, it is expected to be related to cross-reactivity within the assay with underlying murine antigens.
- The impact of HACA on clinical efficacy is not known at this time.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 5 lists the clinical trials conducted in patients with neuroblastoma submitted in support of the BLA. Some studies were submitted as synopses, abbreviated study reports, or interim reports because they are ongoing. Table 6 lists the clinical trials submitted to the BLA that were conducted in adult patients with diseases other than neuroblastoma (primarily melanoma).

Data from DIV-NB-301 (Study 301) provided the primary basis to support the efficacy of dinutuximab in this BLA. The integrated summary of efficacy (ISE) submitted by the Applicant included supportive data from the following additional NCI-sponsored trials of ch14.18: POG-9347, CCG-0935, CCG0935A, and DIV-NB-302. The integrated summary of efficacy also included information regarding the conduct of ongoing studies CHP1002, NANT2011-04, and ANBL1221, which was limited to copies of the study protocols and summaries of the overall study designs. A reference to an ASCO abstract describing preliminary data for CHP1002 was also provided.

Reviewer note: The clinical review of this BLA included formal review of efficacy data from Study 301 only. Time to event endpoints (e.g. EFS and OS) assessed in single arm studies are not interpretable. Data from Study POG-9347 provided supportive evidence of antitumor activity of ch14.18 when used in combination with GM-CSF through assessment of objective response.

The integrated summary of safety (ISS) included data from the following NCI-sponsored studies: POG-9347, CCG-0935, CCG-0935A, DIV-NB-301 (Study 301), DIV-NB-302 (Study 302), and DIV-NB-303 (Study 303). Additionally, the ISS included data from DIV-NB-201 (Study 201), the open label comparative pharmacokinetic and safety study sponsored by the Applicant.

Table 5: Clinical Studies of ch14.18 in Patients with Neuroblastoma

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
CCG-0935 8/95 to 10/97	A Phase I Study of Chimeric Human/Murine Anti-GD2 Monoclonal Antibody (ch14.18) with GM-CSF in Children with Neuroblastoma and Other GD2 Positive Malignancies Immediately Post Autologous Bone Marrow Transplantation	Dose escalation study. Objectives: to determine the maximum tolerated dose and tolerability of escalating doses of ch14.18+GM-CSF (administered for up to six 4-day courses every 28-days) and assess the anti-tumor effects of this regimen. Investigational regimen ch14.18: 20-50 mg/m^2/day IV; GM-CSF: 250 mcg/m^2/day IV or SC Duration of treatment: one to six courses separated by ≥ 28-day intervals	23	Complete. study report submitted Publication: Ozkaynak et. al., 2000.
CCG-0935A 10/97 to 11/01	A Phase I Study of Chimeric Human/Murine Anti-GD2 Monoclonal Antibody (ch14.18) with GM-CSF and Interleukin-2 in Children with Neuroblastoma and Other GD2 Positive Malignancies Immediately Post Autologous BMT or PBSC Rescue	Dose escalation study Objectives: To investigate the tolerability of two doses of ch14.18 + IL-2 given with alternating GM-CSF and the feasibility of use of isotretinoin between ch14.18 courses. Investigational regimen ch14.18: 20 or 40 mg/m^2/day IV IL-2:up to 4.5 MIU/m^2/day X 4 days IV GM-CSF: 250 mcg/m^2/day IV or SC RA: 80 mg/m^2/dose PO BID X 14 days Duration of treatment: three to five courses of ch14.18	25	Complete study report submitted Publication: Gilman et. al., 2009.

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
		separated by 21 to 28-day intervals		
POG-9347 11/16/94 to 9/19/97	Combined Use of Human-Mouse Chimeric anti-GD2 Monoclonal Antibody and GM-CSF in the Treatment of Recurrent Neuroblastoma, a Pediatric Oncology Group Phase II Study	Open label single arm study Objectives: To investigate the activity and tolerability of ch14.18 in combination with GM-CSF. Investigational regimen Ch14.18: 50 mg/m^2/day X 4 days IV over 5 hours GM-CSF: 1 mcg/kg/day X 14 days IV or SC Duration of treatment: 14 days	32	Complete study report submitted Publication: Yu et. al., 1997

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
DIV-NB-301 (randomized portion of COG Study ANBL0032) First subject enrolled on 10/26/2001 Last randomized subject enrolled on 11/3/2008 Data cutoff for primary analyses: 1/13/09 Data cutoff for follow-up analyses: 6/30/12	Phase III Randomized Study of Chimeric Antibody 14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue	Design: Open label randomized study Objectives Determine if ch14.18 in combination with cytokines and RA improves EFS following myeloablative therapy and stem cell rescue compared to RA alone in patients with high-risk neuroblastoma who achieve a pre-ASCT response of CR, VGPR, or PR. Primary endpoint: 2-year EFS Secondary endpoint: 2-year OS Investigational arm Ch14.18: 25 mg/m^2 IV over 5 to 20 hours X 4 days X 5 courses GM-CSF: 250 mcg/m^2/day SC X 14 days during Course 1,3,and 5 IL-2: 3 MIU/m^2/day X 4 days (Week 1 of Courses 2 and 4) and 4.5 MIU/m^2/day X 4 days (Week 2 of Courses 2 and 4) Isotretinoin (RA): 80 mg/m^2/dose PO BID X 14 days X 6 courses Control arm: Isotretinoin (RA): 80 mg/m^2/dose PO BID X 14 days X 6 courses Duration of treatment: five courses of ch14.18 separated by 28-day intervals, followed by one course of isotretinoin	251, including 226 randomized and 25 non-randomly assigned to investigational treatment.	Complete. Study report submitted.

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
DIV-NB-302 (single arm portion of COG Study ANBL0032) Data from 5/6/2009 to 12/31/2013 (study ongoing)	Phase III Randomized Study of Chimeric Antibody 14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue	Design: Open label single arm study continuing investigational therapy in ongoing patients randomized to the investigational arm in Study DIV-NB-301 and enrolling new patients to receive investigational therapy Objectives: Same as DIV-NB-301; Investigational arm: Ch14.18: 25 mg/m^2 IV over 5 to 20 hours X 4 days X 5 courses GM-CSF: 250 mcg/m^2/day SC X 14 days during Course 1,3,and 5 IL-2: 3 MIU/m^2/day X 4 days (Week 1 of Courses 2 and 4) and 4.5 MIU/m^2/day X 4 days (Week 2 of Courses 2 and 4) Isotretinoin (RA): 80 mg/m^2/dose PO BID X 14 days X 6 courses Duration of treatment: five courses of ch14.18 separated by 28-day intervals, followed by one course of isotretinoin	838 (enrolled since the close of randomization on 1/13/2009 through 12/31/2013	Ongoing. Publication: Yu et. al., NEJM 2010

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
DIV-NB-303 (ANBL0931) 1/27/10 to 1/25/12 (last course completed) Follow-up ongoing.	A Comprehensive Safety Trial of Chimeric Antibody 14.18 (ch14.18) with GM-CSF, IL-2 and Isotretinoin in High-Risk Neuroblastoma Patients Following Myeloablative Therapy	Design: Open label single arm study Objectives: evaluate the safety profile of the investigational treatment regimen Investigational therapy: Ch14.18: 25 mg/m^2 IV over 10 to 20 hours X 4 days X 5 courses GM-CSF: 250 mcg/m^2/day SC X 14 days during Course 1,3,and 5 IL-2: 3 MIU/m^2/day X 4 days (Week 1 of Courses 2, and 4) and 4.5 MIU/m^2/day X 4 days (Week 2 of Courses 2 and 4) Isotretinoin (RA): 80 mg/m^2/dose PO BID X 14 days X 6 courses Duration of treatment: five courses of ch14.18 separated by 28-day intervals, followed by one course of isotretinoin	105	Study report submitted
CHP1002 Study Activated	Pharmacokinetics of the chimeric anti-GD2 antibody, ch14,18, in children with high-risk neuroblastoma	Design: open label PK correlative laboratory study Objectives: describe the pharmacokinetics of ch14.18 in children with high-risk neuroblastoma enrolled in ANBL0032 or ANBL0931 Investigational therapy: Same as DIV-NB-303	12	Ongoing Publication: ASCO abstract Desai et al. 2012

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
ANBL1221 Study Activated 2/4/13	A Phase II Randomized Trial of Irinotecan/Temozolomide with Temsirolimus (NSC#683864, IND #61010) or Chimeric 14.18 Antibody (ch14.18) NSC#623408, IND#4308) in Children with Refractory, Relapsed, or Progressive Neuroblastoma	Design: open label randomized study Primary Objective: Identify whether temsirolimus or ch14.18 is the optimal therapeutic agent to consider for further testing in future randomized trial for treatment of newly diagnosed high-risk neuroblastoma Investigational therapy: Regimen A: Temozolomide (100 mg/m^2/dose PO Daily Days 1-5) Irinotecan (50 mg/m^2/dose IV daily, Days 1-5) Temsirolimus 35 mg/m^2/dose IV on Days 1 and 8) Regimen B: Temozolomide (100 mg/m2/dose PO Daily Days 1-5) Irinotecan (50 mg/m2/dose IV daily, Days 1-5) *Ch14.18*: 25 mg/m^2 IV on Days 2-5 GM-CSF 250 mcg/m2/dose SQ Days 6-12	Up to 74	Ongoing PK Comparability Study Report submitted

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
NANT2011-04	A Phase I Study of Lenalidomide and Anti-GD2 Mab Ch14.18 +/- Isotretinoin in Patients with Refractory/Recurrent Neuroblastoma	Design: single arm dose escalation study Primary Objective: Identify the maximum tolerated dose and tolerability of escalating doses of lenalidomide in combination with ch14.18.in patients with refractory, relapsed or progressive neuroblastoma Investigational therapy: Lenalidomide: doses ranging from 18 mg/m^2/dose to 100 mg/m^2/dose PO on Days 1-21 Ch14.18: 25 mg/m^2/dose IV on Days 8-11 Isotretinoin 80 mg/m^2/dose BID PO days 15-28	Up to 62	Ongoing

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
DIV-NB-201	A Comparative Pharmacokinetic and Safety Study of Chimeric Monoclonal Antibody ch14.18 with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interleukin-2 (IL-2), and Isotretinoin in High Risk Neuroblastoma Patients Following Myeloablative Therapy	Design: Multicenter, randomized open-label, two-sequence, cross-over study Primary Objective: To compare the pharmacokinetic profile (primarily) of intravenous ch14.18 products manufactured by UTC and NCI Investigational therapy: Patients received ch14.18 manufactured by United Therapeutics Corporation (UTC) or Science Applications International Corporation (SAIC) Frederick for the national Cancer Institute (NCI) during Courses 1 and 2 followed by ch14.18 form the alternate manufacturer during Courses 3, 4, and 5. Lenalidomide: doses ranging from 18 mg/m^2/dose to 100 mg/m^2/dose PO on Days 1-21. Ch14.18 dose was either 17.5 mg/m^2/day over 10-20 hours X 4 consecutive days per 28-day course (UTC product) or 25 mg/m$^{2/}$day over 10-20 hours X 4 consecutive days per 28-day course (SAIC product) Patients also received IL-2, GM-CSF, and isotretinoin at the same dosage regimen administered in DIV-NB-301, -302 and -303 studies. Duration of treatment: five courses of ch14.18 separated by 28-day intervals, followed by one course of isotretinoin	28	Ongoing

Table 6: Clinical Studies of ch14.18 in Adult Patients with Other Cancers

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
B89-0005 4/16/92 to 8/17/94	A Phase I Study of Chimeric Human/Murine Anti-GD2 Monoclonal Antibody 14.18 in Metastatic Melanoma	Design: Dose escalation study (Part A) Open label single arm study (Part B) Objectives: to determine the maximum tolerated dose and tolerability of escalating doses of ch14.18 (Part A) Part B(to determine the toxicity and antitumor effects of chimeric mouse/human ch14.18 administered either as a weekly bolus dose or a continuous infusion dose in subjects with metastatic melanoma. Investigational regimen Part A: ch14.18: 5, 15, and 45 mg (same day infusion) and 100 mg split to 50 mg/day X 2 days; IV infusion over 1 to 4 hours. Patients received a single dose. Part B: ch14.18: either 24 mg/m^2 or 30 mg/m^2 X 2 days for up to 3 consecutive weeks up to a maximum cumulative dose of 180 mg/m^2 (later amended to a maximum cumulative dose of 120 mg/m^2). Patients receiving cumulative dose of up to 120 mg/m2 could receive ch14.18 as a bolus dose or as a continuous infusion over 5 days	Part A: 13 Part B: 10	Complete. Study report submitted Publication: Saleh et al., 1992.

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
B90-0014 6/3/93 to 3/7/95	Phase I Trial of Melanoma Reactive Chimeric Monoclonal Anti-GD2 Antibody (ch14.18) Plus IL-2 in Adults with Melanoma	Design: Dose escalation study Objectives: to evaluate the toxicity and tolerance of 4 dose levels of ch14.18 combined with IL-2 Investigational regimen ch14.18: dose ranged from 2 to 10 mg/m^2/day for 5 days before, during or following systemic IL-2 treatment. IL-2: 1.5 X 10^6 units/m$^{2/}$day administered as a continuous infusion for 4 days per week for 3 weeks.	24	Abbreviated study report submitted Publication: Albertini et al. 1997
B93-0009 11/8/93 to 10/6/95	Phase Ia/Ib trial of Anti-GD2 Chimeric Monoclonal Antibody 14.18 (ch14.18) and Recombinant Human Granulocyte-Macrophage Colony-Stimulating Factor (rhGM-CSF) in Metastatic Melanoma.	Design: Dose escalation study Primary Objective: determine the maximum tolerated dose of combination of chimeric monoclonal antibody 14.18 (ch14.18) plus rhGM-CSF in subjects with malignant melanoma Investigational regimen ch14.18: dose ranged from 15 to 60 mg/m^2 as a single 4-hour intravenous infusion rhGM-CSF: 250 µg/m$^{2/}$day sq X14 days	16	Study report submitted. Publication: Murray et al., 1996.

Study Number and Dates	Title	Design and Objectives	No. of Patients	Study Status
B94-0002 1/22/95 to 5/15/97	Phase I Trial of Combined Treatment with ch14.18 and R24 Monoclonal Antibodies and Interleukin-2 for Patients with GD2+/GD3+ Tumors	Design: Dose escalation study Primary Objective: determine the maximum tolerated dose ch14.18 and R24 antibodies when administered together with IL-2 Investigational regimen ch14.18: dose ranged from 2-7.5 mg/m^2/day as a daily 4-hour intravenous infusion for 5 consecutive days during Week 2 of treatment (Days 9-13 of each course) R24 (an anti-GD3 monoclonal antibody): dose ranged from 1-10 mg/m^2/day as a daily 18-hour intravenous infusion for 5 consecutive days during Week 2 of treatment (Days 9-13 of each course) IL-2: 1.5 X 10^6 units/m^2/day (26 subjects) or 4.5 X 10^6 units/m^2/day (one subject) administered as a continuous infusion for 4 days per week for 3 weeks.	27	Study report submitted. Publication: Murray et al., 1996

5.2 Review Strategy

The review of efficacy for this application focuses on the results of Study 301, the only completed randomized clinical trial that was submitted to the BLA.

The review of safety for this application focuses on the results of Study 301, which is the only study that provides a comparator arm to help distinguish adverse reactions attributable to treatment with ch14.18 plus cytokines from adverse reactions that occur with RA. Safety data from Study 302, 303, and 201 were also reviewed to determine if there were additional safety concerns that were not uncovered during the review of Study 301. Of note, Study 302 and Study 201 provide limited safety data from the use of dinutuximab [produced by United Therapeutics Corporation (UTC)] because prior to January 21, 2014, all CTEP-sponsored studies submitted to the BLA used the ch14.18 product produced by the Science Applications International Corporation (SAIC) for CTEP. Therefore, safety data from these studies were analyzed to look for differences in the toxicity profile between the UTC and SAIC produced products. Finally, safety data from Studies POG-9347, CCG-0935, CCG-0935A were limited to exploration of safety signals that were not evident from review of the other studies.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study DIV-NB-301

This BLA submission is primarily supported by data from a single study, DIV-NB-301 ("Study 301"), entitled "Phase III Randomized Study of Chimeric Antibody 14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell rescue.

This study was sponsored by the National Cancer Institute's Cancer Therapy and Evaluation Program (CTEP) and conducted by the Children's Oncology Group in 90 sites in the United States, Canada, and Australia. The majority of the 251 patients enrolled were accrued in US sites (218, or 87%), followed by Canada (29, or 11%), and Australia (4, or 2%). The planned sample size for this study was 386 patients, but randomization was terminated by the Study 301 Data Safety Monitoring Committee (DSMC) in February 2009 upon review of the results of a pre-planned interim analysis of event-free survival (EFS) and overall survival (OS) using data collected through January 13, 2009. The first patient enrolled on October 26, 2001, and the last randomized patient enrolled on November 3, 2008. At the time of this analysis, 226 patients comprised the intent-to-treat population, 113 randomized to each treatment arm. Following cessation of randomization, ongoing patients randomized to either arm rolled over into the single arm extension study, DIV-NB-302 ("Study 302"), with patients randomized to the control (RA only) arm switched over to receive the ch14.18 combination regimen. After cessation of randomization in Study 301, additional patients

meeting the eligibility requirements enrolled into Study 302 to receive ch14.18 in combination with cytokines and RA (from 5/9/2009 to present).

The report for Study 301 provided by United Therapeutics summarizes data from three separate data cuts: the primary efficacy analysis performed using data collected through January 13, 2009, an additional efficacy and safety analysis performed using data collected through June 30, 2009, and a follow up analysis of data collected from randomized patients through June 30, 2012.

Reviewer note: United Therapeutics performed the June 30, 2009 analysis to confirm the efficacy results of the analysis of data using the January 13, 2009 cutoff date (as reported by Yu et al.[20] The tabulated datasets for the January 13, 2009 analysis were corrupted.

Table 7 provides the dates the initial protocol and each amendment were finalized and a summary of the key changes incorporated with each protocol amendment. All randomized patients were initially treated under protocol Amendment 9B (or earlier); however, subsequent amendments are described here because subjects may have been affected by subsequent amendments as well.

Table 7: Summary of Protocol Amendments for Study 301

Protocol Milestone	Date	Summary of key changes
Original Protocol	10/29/2001	• Protocol activated
Amendment 1	6/14/2002	• Adverse event tables updated • Changed the recommended GM-CSF start date from between Days 49 and 63 to between Days 56 and 77
Amendment 2	7/16/2003	• Study Co-Chair added • Toxicity information added for IL-2 • Examples of IL-2 dose calculations added • Added pre-ch14.18 dosing criteria prior to each course including ALT < 5X ULN, skin toxicity ≤Grade 1, serum creatinine < 1.5 mg/dL • Added requirement for epinephrine and hydrocortisone medications to be available during ch14.18 administration • Changed pre-RA dosing criteria from serum triglycerides < 300 mg/dL to < 500 mg/dL • Added Grade 4 skin toxicity as a discontinuation criteria for ch14.18
Amendment 3	9/3/2003	• IL-2 instructions were updated to correct the suggested

20 Yu A., Gilman A, Ozkaynak M, et al. *N Engl J Med.* 2010; 363 (14):1324-34.

Protocol Milestone	Date	Summary of key changes
		48 hour supply volume
Amendment 4	3/12/2004	• Expanded eligibility criteria to include non-A3973 subjects who met all other ANBL0032 eligibility criteria • Added an eight month time limit between the date of diagnosis to the date of study enrollment • Added an exclusion criteria for subjects who received more than one myeloablative consolidation and stem cell transplantation • Clarified that a MRD assessment was required prior to study enrolment and that subjects with biopsy proven residual disease post-ASCT could be enrolled but that they had to have been enrolled on Ad973 and were non-randomly assigned to ch14.18 immunotherapy and RA on stratum 07 • Study sample size increased from 322 to 386 subjects to power the study for a one-sided 0.025 test, increasing the maximum anticipated study duration to eight years • Study endpoints revised from including both OS and EFS as a primary endpoint to EFS as the primary endpoint and OS as the first secondary endpoint. • Adverse event reporting requirements updated to CTCAE v3.0.
Amendment 4A	4/13/2004	• Updated information regarding ch14.18
Amendment 4B	5/20/2004	• Changed the eight month time limit between the date of diagnosis to date of study enrollment to no more than nine months from starting induction chemotherapy to date of ASCT
Amendment 5	7/25/2005	• Updated adverse event reporting criteria and procedures for expedited reporting
Amendment 6	11/28/2005	• Added RA pharmacokinetic substudy component to the protocol • Updated risk information for study therapies • Clarified information relating to tandem transplants and permitted timing between starting chemotherapy and ASCT • Clarified that Grade 3 bronchospasm and Grade 4 anaphylaxis were criteria for discontinuation of ch14.18 • Added guidelines for ch14.18 dose modification for hypersensitivity reactions • Modified RA treatment guidelines to permit patients with ≤ Grade 1 hematuria or proteinuria to receive RA • Expanded randomization strata to include arms for patients previously treated on Studies ANBL0532, ANBL00P1, CP594/DFCI34-DAT

Protocol Milestone	Date	Summary of key changes
Amendment 7	11/18/2006	• Removed requirement for participation in ANBL00B1 (a study investigating biomarkers in tumor tissues samples from patients with newly diagnosed neuroblastoma or ganglioneuroblastoma) • Added gabapentin as a suggested therapy for supportive care for neuropathic pain • Modified definition of adequate renal function • Changed the following criteria from off-study criteria to off-treatment criteria: use of other anti-cancer agents, failure to meet criteria for commencement of ch14.18 immunotherapy and RA by Day 100, failure to meet criteria for completion of radiotherapy at least five days prior to starting ch14.18 immunotherapy and RA • Added entry onto another COG therapeutic protocol and withdrawal of consent to off-study criteria • Added treatment per NANT2001-02 as a randomization stratum
Amendment 8	5/12/2008	• Updated information for RA, ch14.18, GM-CSF, IL-2 • Added exclusion criterion for subjects who underwent CD34+ cell selection and pregnancy or lactation • Expanded enrollment timeline from 77 days post ASCT to 85 days post ASCT • Expanded Stratum 07 to include all subjects with biopsy-proven disease post ASCT (this was previously restricted to patients treated in study A3973) • Added RA dose reduction recommendations for creatinine clearance and/or GFR < 50 mL/min/1.73 m^2
Amendment 9B	4/16/2009	• Ended randomization and added rationale for stopping randomization • Permitted cross-over of subjects originally randomized to receive RA alone to receive ch14.18 immunotherapy and RA • Added the following secondary objectives: – To further describe and refine the EFS and OS estimates and baseline characteristics for subjects receiving ch14.18 with cytokines and RA following cessation of the randomized portion of the study – To further describe the safety and toxicity profile of ch14.18+cytokines+RA, focusing on the number of courses delivered per subject and the number of dose reductions or discontinuations (ch14.18 and/or IL-2) and number of deaths due to toxicity • Extended ch14.18 infusion time from five hours to 10 to 20 hours

Protocol Milestone	Date	Summary of key changes
		• Updated information for ch14.18, IL-2 • Removed ASCT with CD34+ cell selection exclusion criterion • Added prior receipt of anti-GD2 therapy as an exclusion criterion • Removed eligibility requirement for room air pulse oximetry >94% • Added eligibility requirement for APC of at least 1000 cells/µl • Added platelet count ≥20,000/µL as a pre-ch14.18 immunotherapy requirement and requirement for aggressive platelet support to maintain platelet count of ≥50,000/µL for patients with CNS involvement • Added additional sections regarding management of hypersensitivity reactions and vascular leak • Added information permitting use of hydrocortisone for hypotension, bronchospasm or angioedema • Added Grade 3 or higher allergic reactions or vascular leak syndrome as exceptions to Adverse Event Expedited Reporting System (AdEERS) reporting • At the DSMC request, changed the statistical test performed for sequential monitoring for early stoppage from Fleming Harrington-O'Brien with a cumulative alpha level of 0.05 (one-sided) to Lan-DeMets with a cumulative alpha level of 0.025 (one-sided) • Changed the anticipated study duration for then on-randomized portion of the study to a maximum of 3.5 years • Updated the analysis plan to account for the close of randomization
Amendment 10	5/26/2010	• Updated safety information for ch14.18, IL-2, RA • Added provision permitting enrollment of subjects who were not initially diagnosed as high-risk but were later converted or relapsed to high-risk neuroblastoma • Modified the off-study criterion to be the 10th anniversary of study entry instead of the 10th anniversary of closure of accrual
Amendment 11A	3/7/11	• Updated GM-CSF toxicity and formulation information • Increased the anticipated enrollment to 1,150 subjects
Amendment 12	7/22/2011	• Updated CTCAE criteria from version 3.0 to version 4
Amendment 13	12/6/2011	• Added ECG substudy to collect cardiac safety data on up to 60 patients • Changed eligibility criterion relating to the permitted

Protocol Milestone	Date	Summary of key changes
		timeline between the start of induction chemotherapy to ASCT from no more than nine months to no more than 12 months • Updated safety information and dose modification instructions • Added INSS response evaluation criteria • Removed the assessment of ADCC and soluble IL-2 receptors • Restricted the assessment of ch14.18 PK and HACA to those subjects participating in the cardiac safety substudy
Amendment 13A	3/15/2012	• Clarified timing of laboratory assessments prior to enrollment • Added evaluation of lactate dehydrogenase
Amendment 14	6/4/2012	• Updated ch14.18 information

Abbreviations: ADCC: antibody-dependent cell-mediated cytotoxicity; APC: absolute phagocyte count; ALT: alanine aminotransferase; ASCT: autologous stem cell transplant; CTCAE: Common Terminology Criteria for Adverse Events; ECG: electrocardiogram; EFS: Event-free survival; GFR: glomerular filtration rate; INSS: International Neuroblastoma Staging System (INSS); MRD: minimal residual disease; OS: overall survival.

5.3.1.1 DIV-NB-301 Objectives

The primary objective of Study 301, (the randomized portion of COG Study ANBL0032) "was to determine if monoclonal antibody ch14.18 in combination with cytokines and isotretinoin (RA) improved event-free survival (EFS) after myeloablative therapy and stem cell rescue as compared to RA alone, in high-risk neuroblastoma subjects who achieved a pre-autologous stem cell transplant (ASCT) response of complete response (CR), very good partial response (VGPR), or partial response (PR). A key secondary objective was to compare overall survival in patients in the two treatment arms.

Reviewer comment: Following the results of Study CCG 3891[21],[22]*, RA was considered to be part of front-line standard of care therapy for patients with high-risk neuroblastoma by the Children's Oncology Group. This study design does not isolate the treatment effect of RA or of any of the specific components in the investigational arm. In addition, this study design complicates the assessment of the toxicity of dinutuximab due to the difficulty of attributing toxicity to dinutuximab, versus IL-2, GM-CSF, retinoic acid, or the combination of the therapies.*

21 Matthay et al. *New England Journal of Medicine*. 1999 ; 241(16):1165-1173.
22 Matthay et al. *Journal of Clinical Oncology*. 2009; 27(7):1007-1013.

5.3.1.2 Key Eligibility Criteria (from Amendment 14 to the COG ANBL0032 protocol, with some modifications for brevity)

- Diagnosis of neuroblastoma that was categorized as high-risk at the time of diagnosis
  - Patients initially diagnosed as non-high-risk but who later converted or relapsed to high-risk neuroblastoma were also eligible
- Age ≤30.99 years at the time of diagnosis of neuroblastoma
- Completion of intensive induction chemotherapy followed by autologous stem cell transplantation (ASCT) and radiation therapy

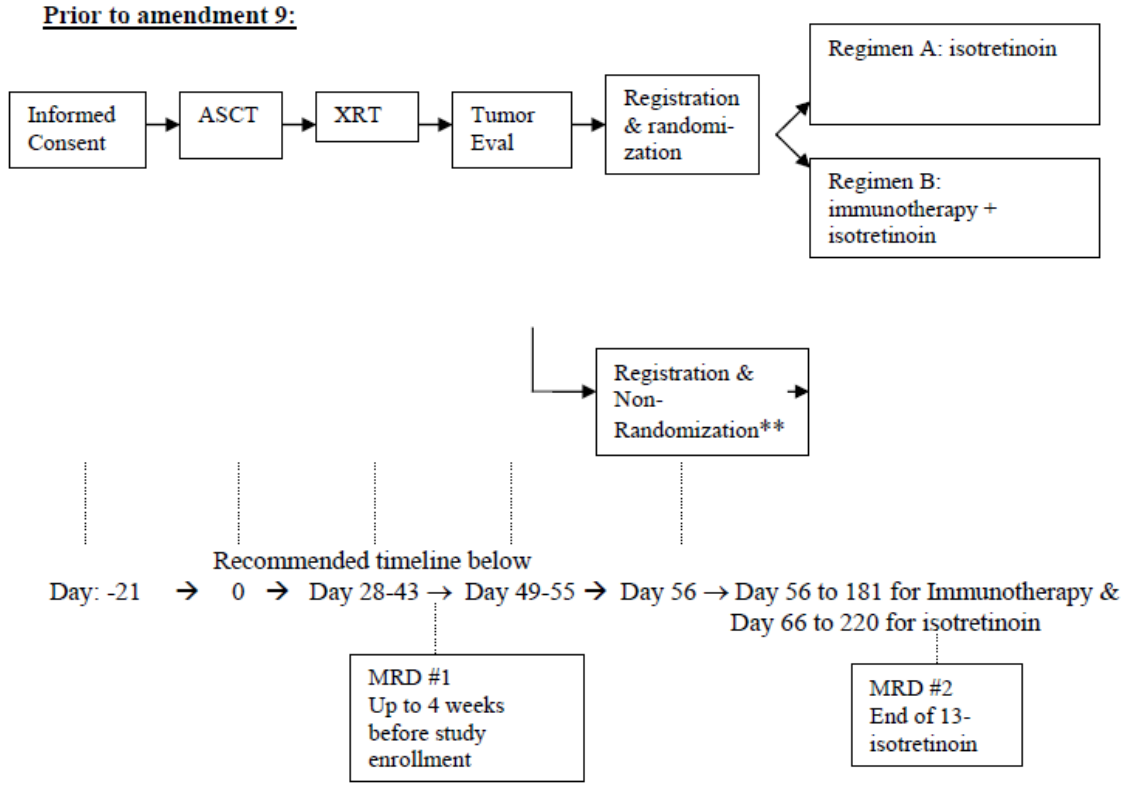
  Reviewer note: the protocol cited multiple neuroblastoma protocols, including Study A3973, POG 9341/9342, CCG 3891, NANT 2001-02, ANBL09P1, ANBL07P1, and ANBL0532, as examples of acceptable prior therapies meeting this eligibility criterion but did not explicitly state that patients had to be treated exactly according to any of these protocols
- Achievement of International Neuroblastoma Response Criteria (INRC)-defined CR, VGPR, or PR for the primary site, soft tissue metastases, and bone metastases at the pre-ASCT evaluation
  - Achievement of bone marrow response defined by the following criteria:
    - ≤ 10% tumor (of total nucleated cellular content) present on any bilateral bone marrow aspirate/biopsy specimen obtained at the pre-ASCT evaluation irrespective of whether tumor was present on the prior bone marrow specimens
- No more than 12 months (8 months prior to protocol Amendment 4B) from the date of initiation of induction chemotherapy for high-risk neuroblastoma to the date of ASCT (or the date of the first stem cell infusion, if a tandem transplant was performed)
- Assessment of residual disease, including computed tomography (CT) or magnetic resonance imaging (MRI) studies, metaidobenzylguanidine (MIBG) scan (or bone or fluroro-2-deoxy-D-glucose positron emission tomography [FDG-PET] scans in patients without MIBG-avid disease), bone marrow aspiration and biopsy, and blood samples
  - Assessment must occur within a maximum of 4 weeks before enrollment
  - Evaluation of irradiated residual tumors was to be performed no earlier than five days after completing radiation therapy in patients with residual disease prior to radiation therapy
  - Patients with biopsy-proven residual disease following ASCT were eligible for ANBL0032 and were non-randomly assigned to Stratum 7 to receive ch14.18+cytokines

- Enrollment preferably between Day 56 and Day 85 after the final autologous stem cell infusion (prior to Amendment 8, enrollment and randomization between Day 50 to Day 77 was required)
  - Enrollment must occur no later than Day 100 following ASCT
  - Enrollment must occur after completion of radiation therapy and post-ASCT tumor assessment
- Lansky or Performance Scale Score ≥ 50% and life expectancy of ≥ 2 months
- Adequate organ function, defined as meeting the following parameters:
  - Total absolute phagocyte count ≥1000/μL
  - Creatinine clearance or radioisotope GFR ≥70mL/min/1.73 m^2 or a serum creatinine within standard age and gender-based limits
  - Total bilirubin 1.5 X the upper limit of normal (ULN) and serum glutamic pyruvic transaminase (SGPT)/alanine aminotransferase (ALT) ≤ 5 X ULN
  - If present, veno-occlusive disease should be stable or improving
  - Shortening fraction ≥30% by echocardiogram or ejection fraction of ≥55% by gated radionuclide study or echocardiogram performed within 4 weeks prior to enrollment.
  - FEV_1 and FVC > 60% of predicted values by pulmonary function test (PFT) performed within 4 weeks prior to enrollment or documented absence of dyspnea at rest and exercise intolerance in children unable to comply with PFTs
  - Patients with a seizure disorder must be on anticonvulsants with well controlled disease and CNS toxicities, if present, must be < Grade 2 severity.
- No prior receipt of anti-GD2 antibody therapy
- Negative pregnancy test for women of childbearing potential
- Agreement to use an effective contraceptive method, for men and women of reproductive potential
- Provision of written informed consent

5.3.1.3 Trial Design and Treatment Plan

Study 301 consists of the open label, randomized portion of COG study ANBL0032. The first subject enrolled in Study 301 on October 26, 2001, and the last subject enrolled on November 3, 2008. Study 301 randomized patients 1:1 to receive either isotretinoin (RA) (160 mg/m^2/day divided into two daily doses on Days 1-14 of six consecutive 28-day cycles) or experimental therapy consisting of ch14.18 in combination with GM-CSF, IL-2, and RA. The study schema for Study 301 (Prior to ANBL0032 Amendment 9, which halted randomization) is depicted below (Figure 1).

Figure 1: Schema for Study 301



MRD assessment:
Bone marrow for immunocytology & RT-PCR, MIBG scan and other radiographical studies.

** **Prior to Amendment # 9:** In the rare cases with persistent tumor post ASCT/ radiotherapy (time point #1), biopsy is required. Those with biopsy proven active disease will be non-randomly assigned to regimen B (Isotretinoin + immunotherapy). Those who do not undergo biopsy will be randomized as all other patients.

Source: Applicant's submission

Abbreviations: ASCT: autologous stem cell transplant; XRT: radiation therapy; MRD: minimal residual disease

Experimental therapy consisted of six 28-day day cycles of therapy according to the following regimen:

- **Cycles 1-5:** Ch14.18 was administered as a continuous intravenous (IV) infusion over 5.75 to 20 hours at a dose of 25 mg/m^2/day for four consecutive days during Courses 1-5, with doses separated by 28-day intervals. Ch14.18 was administered in conjunction with alternating cycles of either GM-CSF or IL-2. Patients received

RA orally at a dose of 160 mg/m^2/day (5.33 mg/kg/day for patients weighing 12 kg or less) divided into two doses for the last 14 days of each cycle.

- **Cycles 1,3,5:** GM-CSF (250 µg/m^2/d on Days 0-13), ch14.18 (25 mg/m^2/day on Days 3-6), and RA (160 mg/m^2/day in two divided doses on Days 10-23).
  - GM-CSF was initiated three days prior to ch14.18 either subcutaneously (SC) or IV over 2 hours.
  - When administered on a day that ch14.18 would also be given, GM-CSF was administered first, followed by a 10 mg/kg bolus of normal saline just prior to initiation of ch14.18.
- **Cycles 2 and 4:** IL-2 (3.0 x 10^6 IU/m^2/day on Days 0-3), IL-2 (4.5 x 10^6 IU/m^2/d on Days 7-10), ch14.18 (25 mg/m^2/day on Days 7-10), and RA (160 mg/m^2/day in two divided doses for on days 14-27).
  - IL-2 was administered as a continuous IV infusion through a dedicated line for four days (96 hours); the Week 1 dose was 3 MIU/m^2/day and the Week 2 dose was 4.5 MIU/m^2/day during Week 2.
  - The first week of IL-2 was typically administered on an outpatient basis via an ambulatory infusion pump. During the second week of each course, IL-2 was administered as an inpatient with the ch14.18 infusion.

- **Cycle 6:** Patients received RA alone [160 mg/m^2/day in two divided doses (5.33 mg/kg/day for patients weighing 12 kg or less)] for 14 days.

Table 8, copied from the Applicant's BLA submission, summarizes the schedule of administration of investigational therapy for patients randomized to the ch14 combination therapy arm.

Table 8: Schedule of Study Drug Administration of ch14.18 Arm of Study 301

SUN	MON	TUES	WED	THURS	FRI	SAT
Pre-ASCT				Prior to study enrollment MRD #1 * @$	0 (Day 56) GM	1 GM
2 GM	3 GM CH	4 GM CH	5 GM CH	6 GM CH $	7 GM	8 GM
9 GM	10 GM	11 GM RA(Day 67)	12 GM RA	13 GM RA	14 RA	15 RA
16 RA	17 RA	18 RA	19 RA	20 RA	21 RA	22 RA
23 RA	24/0 IL-2 RA**	25/1 IL-2	26/2 IL-2	27/3 IL-2	28/4	29/5
30/6	31/7 IL-2 CH	32/8 IL-2 CH	33/9 IL-2 CH	34/10 IL-2 CH	35/11	36/12
37/13	38/14 RA	39/15 RA	40/16 RA	41/17 RA	42/18 RA	43/19 RA
44/20 RA	45/21 RA	46/22 RA	47/23 RA	48/24 RA	49/25 RA	50/26 RA
51/27 RA	52/28	53/29	54/30	55/31	56/32/0 GM	57 GM
58 GM	59 GM CH	60 GM CH	61 GM CH	62 GM CH	63 GM	64 GM
65 GM	66 GM RA	67 GM RA	68 GM RA	69 GM RA	70 RA	71 RA
72 RA	73 RA	74 RA	75 RA	76 RA	77 RA	78 RA
79 RA	80 IL-2 $	81 IL-2	82 IL-2	83 IL-2	84	85
86	87 IL-2 CH	88 IL-2 CH	89 IL-2 CH	90 IL-2 CH $	91	92
93	94 RA	95 RA	96 RA	97 RA	98 RA	99 RA
100 RA	101 RA	102 RA	103 RA	104 RA	105 RA	106 RA
107 RA	108	109	110	111	112 GM	113 GM
114 GM	115 GM CH	116 GM CH	117 GM CH	118 GM CH	119 GM	120 GM
121 GM	122 GM RA	123 GM RA	124 GM RA	125 GM RA (Day 181)	126 RA	127 RA
128 RA	129 RA	130 RA	131 RA	132 RA	133 RA	134 RA
135 RA	136	137	138	139	140	141
142	143	144	145	146	147	148

Table 8 (cont.)

149	150 RA	151 RA	152 RA	153 RA	154 RA	155 RA
156 RA	157 RA	158 RA	159 RA	160 RA	161 RA	162 RA
163 RA$	164 (Day 220)	165	166	167	168	169
170	171	172	173 post-RA MRD #2✶	174	175	176
177	178					

Day 0 is Day 56 post-PBSC infusion, Day in bold parenthesis refers to post-PBSC infusion day.
Ch14.18 at 25 mg/m^2/day x 4 for all 5 courses
GM-CSF at 250 mcg/m^2 for 14 days; Aldesleukin (IL-2) at 3 M IU/m^2/day for first week, 4.5 MIU/m^2/day for 2nd week
RA: Isotretinoin (13-cis-retinoic acid) (80mg/m^2/dose bid) x 14 days every 28 days for a total of 6 cycles.
✶MRD assessment: Bone marrow for immunocytology & RT-PCR, MIBG scan, CT/MRI and bone scan. To be done at 2 time points:
(1) Up to 4 weeks before study enrollment
(2) Within 2 weeks at the completion of protocol therapy (after the last dose of RA)
@ FcR and Kir/Kir-L genotyping: 7 mL blood in preservative-free heparin or green-top tube obtained within 1 week before starting the first GM-CSF injection (on a Monday through Thursday, to avoid Friday shipment). Freshly obtained samples should be sent at room temperature by overnight carrier to Dr. Yu's lab.
$: Blood samples for ch14.18 PK and HACA analysis (for patients participating in the cardiac safety sub-study): 5 mL blood in preservative-free heparin or green-top tube obtained for the 1st and 4th courses of immunotherapy and within two weeks of study Day 163 (after the last dose of RA). Freshly obtained samples should be sent at room temperature by overnight carrier. ECG monitoring (as detailed in Section 5.65) must also be done at each of these time-points.
**cisRA pharmacokinetics: 5 mL blood sample will be obtained from patients on Day 14 of the first course of oral 13 cis retinoic acid, to be shipped to Dr. Reynolds' lab.

Source: Applicant's submission

Prior to initiation of each cycle of ch14.18, the following parameters must have been met:

- ALT ≤ 5 X the upper limit of normal (ULN)
- Skin toxicities ≤ Grade 1 severity
- Absence of serious infection, or infection well-controlled without active disease and negative blood culture
- Serum creatinine < 1.5 mg/dL
- Platelet count ≥ 20,000/µL (with or without transfusion requirement) if central nervous system metastases are not present, ≥50,000/µL otherwise.

Instructions for ch14.18 infusion

Just prior to initiation of the ch14.18 infusion, patients received 10 mg/kg normal saline IV over one hour. Ch14.18 infusions were initiated at a rate of 1.25 mg/m^2/hour for the first half hour, and the infusion rate was increased to 2.5 mg/m^2/hour for the remainder of the infusion, if tolerated. The infusion duration could be extended up to 20 hours to

ameliorate toxicities such as pain, fever, tachycardia, tachypnea, and hypotension that didn't adequately respond to supportive measures. Vital signs were monitored every 15 minutes for the first hour of the infusion, then hourly in stable patients until the completion of the infusion.

Premedication and supportive care guidelines for patients receiving ch14.18

The protocol mandated administration of the following medications for the prevention and mitigation of neuropathic pain and allergic reactions related to ch14.18:

- Hydroxyzine (0.5 mg/kg; max dose 50 mg) or diphenhydramine (0.5-1 mg/kg; max dose 50 mg) IV over 10-15 minutes, starting 20 minutes prior to initiation of the ch14.18 infusion and then continued every 4-6 hours until the end of the ch14.18 infusion in patients that do not have signs/symptoms of over sedation
- Acetaminophen (10 mg/kg; max dose 650 mg) orally given 20 minutes prior to initiation of the ch14.18 infusion, then every 4 hours as needed (during cycles not containing IL-2) or every four hours (during cycles containing IL-2)
- Morphine sulfate loading dose 50 µg/kg immediately prior to ch14.18 administration, then via continuous infusion at a rate of 20-50 µg/kg/hour until 2 hours following completion of the infusion.

Optional supportive care medications for treatment and prevention of fever and pain included ibuprofen, meperidine, lidocaine (in conjunction with morphine), and gabapentin.

Epinephrine and hydrocortisone were required to be available on call in case of life threatening allergic reactions. Grade 1 or 2 hypersensitivity reactions were managed by decreasing the rate of ch14.18 by 50%, with gradual titration back to the planned rate following recovery, in addition to administration of hydroxyzine, diphenhydramine, and meperidine as needed. The ch14.18 and GM-CSF or IL-2 doses were discontinued for Grade 3 or 4 hypersensitivity reactions. The protocol included detailed supportive care guidelines and algorithms for treatment of severe hypersensitivity reactions

Dose modifications for toxicities due to ch14.18+IL-2 or GM-CSF

The following toxicities did not warrant dose modification if they were considered tolerable by the patient, patient's family, and physician:

- Grade 4 pain requiring intravenous narcotics
- Grade 3 nausea, vomiting, or diarrhea
- Grade 3 fever
- Stable or improving Grade 3 skin toxicity

- Grade 3 electrolyte abnormalities that improve within 24 hours
- Grade 3 hepatic toxicity that returned to Grade 1 prior to next scheduled cycle of ch14.18
- Grade 3 neurotoxicity with subjective findings (e.g. tingling, hot or cold hands)
- Grade 4 hematologic toxicity that improved to Grade ≤2 of baseline within one week of completing the IL-2 infusion
- Grade 3 performance status (Karnofsky 30 to < 50%)
- Impaired visual accommodation that corrected with glasses
- Altered taste.

The following toxicities required dose modifications:

- Symptomatic hypotension or systolic blood pressure < 80 mm/hg (for > 12 years old), < 70 mm/hg (age 1-12 years old), < 65 mm/hg (infant), or more than 15% below baseline.
  - Ch14.18 infusion (and IL-2 or IV GM-CSF, if being administered) was held and supportive care instituted.
  - Upon resolution, ch14.18 infusion was resumed at a decreased rate (1.25 mg/m^2/hour). If blood pressure remained stable for two hours, IL-2 and GM-CSF, if held, could be restarted. If cytokine infusion causes hypotension, the cytokine was held until the next day when it was restarted at 50% of the dose. If blood pressure remained stable, ch14.18 infusion rate could be increased to 2.5 mg/m^2/hour.
  - For subsequent days of ch14.18 infusion for that cycle, patients could receive ch14.18 at the rate tolerated without hypotension.
- Grade 3 vascular leak (respiratory compromise or fluid support required)
  - Ch14.18 infusion (and IL-2 or IV GM-CSF, if being administered) was held and supportive care instituted.
  - Upon resolution, ch14.18 was resumed at 50% of the previous rate and, if tolerated, cytokine was resumed at 50% of the previous dose. If tolerated, cytokine dose was increased to the full dose the following day. If IL-2 was not tolerated, then it was discontinued and subsequent ch14.18 cycles used GM-CSF instead of IL-2.
- Grade 4 vascular leak
  - Ch14.18 and cytokines discontinued for that cycle. If occurred during Cycle 2, GM-CSF was substituted for IL-2 during Cycle 4. If occurred

during Cycle 1 or 3, patients could continue ch14.18 without cytokines for the remainder of the study.

- Hypersensitivity reactions
  - Ch14.18, GM-CSF, and IL-2 were discontinued for Grade 3 or 4 hypersensitivity reactions.
  - Resumption of ch14.18 at half the initial rate was permitted in patients who recovered quickly from angioedema without airway compromise or mild bronchospasm without other symptoms.
  - If symptomatic angioedema or asymptomatic bronchospasm recurred upon restarting ch14.18, the infusion was interrupted for that day and could be resumed the next day in an intensive care unit setting with additional premedication with hydrocortisone.
  - The following procedures were instituted if ch14.18 was tolerated upon rechallenge:
    - For Cycles 1, 3, and 5, GM-CSF was administered with a 50% dose reduction starting the next day and through the last dose of ch14,18. If tolerated, GM-CSF could be administered at the full dose after completing the 4^{th} ch14.18 dose.
    - For Cycles 2 and 4, IL-2 was resumed with a 50% dose reduction starting the next morning and continued at this dose for the remainder of the cycle.
    - If angioedema or bronchospasm recurred with addition of either cytokine (IL-2 or GM-CSF), then the cytokine and ch14.18 were stopped. If symptoms resolved, ch14.18 without cytokine could be restarted the following day.
- ≥ Grade 3 infections during ch14.18/cytokine therapy
  - the cycle was aborted for infections of ≥Grade 3 severity and subsequent cycles could begin only after resolution of the infection.
  - If the infection occurred during the first 2 days of cytokine administration prior to administration of ch14.18, then the cycle could be restarted upon resolution of the infection.
- Dilated pupils with sluggish light reflex +/- photophobia
  - The cycle was aborted.
  - If abnormalities remained stable or improve before the next cycle is due, then the full dose cytokine was administered with 50% of the prior ch14.18 dose . If this regimen did not result in worsening ocular toxicity, then the full dose of ch14.18 was administered during the next cycle. Ch14.18 and cytokines were permanently discontinued for worsening ocular toxicity.

GM-CSF was held if the total white cell count was > 50,000/µL and for occurrence of significant hypersensitivity reactions. If GM-CSF toxicities such as fever were observed when used alone or during the ch14.18 infusion, the dose of GM-CSF was reduced by 50% or discontinued while maintaining the full dose of ch14.18.

IL-2 was interrupted for toxicities of Grade 3 severity (except for those toxicities listed as exclusions above). When Grade 3 toxicities recovered to Grade 1 or baseline levels, IL-2 was resumed at 50% of the starting dose. If toxicity of Grade 3 or greater severity recurred with resumption of IL-2 or Grade 4 toxicity occurred, IL-2 was discontinued and patients received GM-CSF for all remaining ch14.18 cycles.

Isotretinoin (13-cis retinoic acid, or RA)

Patients randomized to both treatment arms received six cycles of RA beginning on Day 56-85 following ASCT. RA was administered for 14 consecutive days, followed by 14 days of rest. RA capsules were available in 10, 20, 30, and 40 mg strengths, and doses were rounded up to the nearest 10 mg. For children unable to swallow intact capsules, parents were instructed to administer the contents of the capsule with a high-fat food such as ice cream or peanut butter within one hour of emptying the capsules, or to have their child chew the capsules, preferably with a high fat food.

The protocol specified that the following conditions must be met prior to starting each course of RA:

- ALT ≤ 5 X ULN and total bilirubin < 1.5 X ULN
- ≤ Grade 1 skin toxicity
- Serum triglycerides < 500 mg/dL
- ≤ Grade 1 proteinuria or hematuria
- Serum creatinine < 1.5 mg/dL
- Serum calcium < 11.6 mg/dL

Dose delay and modification for RA toxicities

The protocol contained the following instructions for RA dose delay and reduction for toxicities.

- If criteria for commencing RA were not met by the time the course was supposed to start, the course was delayed by one week.

  - If dose delay > 1 week was necessary for resolution of toxicities, the RA dose was reduced to 125 mg/m^2/day (or to 4 mg/kg/day for patients weighing ≤12 kg).
    - If an additional dose delay > 1 week was necessary for subsequent cycles, then the RA dose was reduced to 100 mg/m^2/day (3.33 mg/kg/day for patients weighting ≤12 kg).
- RA dose was decreased to 125 mg/m^2/day (or to 4 mg/kg/day for patients weighing ≤12 kg) for the occurrence of the following:
  - Grade 3 or 4 toxicity excluding Grade 3 or 4 hematologic toxicities, Grade 3 hepatic toxicities, Grade 3 nausea or vomiting, and Grade 3 fever.
    - An additional dose reduction (to 100 mg/m^2/day or 3.33 mg/kg/day for patients weighting ≤12 kg) was instituted following recovery from recurrent toxicities of ≥ Grade 3 severity.
  - RA dose was decreased to 125 mg/m^2/day (or to 4 mg/kg/day for patients weighing ≤12 kg) for serum triglycerides >500 mg/dL despite institution of lipid-lowering therapies.
  - Cheilitis that did not sufficiently improve with topical therapy to permit sufficient oral intake
- RA dose was reduced by 50% if creatinine clearance and/or GFR was < 50 mL/min/1.73m^2. If hematuria, proteinuria, hypertension, or creatinine worsened, RA was held until parameters returned to baseline.
- RA was interrupted for development of ≥Grade 2 hypertension, hematuria and hypertension.

Concomitant and supportive therapies

The following therapies were prohibited during study participation:

- Other anti-cancer therapies
- Immunosuppressive drugs
  - corticosteroids, unless necessary for acute allergic reaction or other life threatening situation
- pentoxifylline
- non-study prescribed cytokines or growth factors.

The following treatments were permitted within restricted timeframes:

- Use of radiographic contrast materials was not permitted during the IL-2 infusion and for a minimum of at least one week following completion of IL-2
- Intravenous gamma globulin (IVIG) was permitted in the first 100 days post-AST (up to day 51 on the study calendar), but not within 2 weeks of starting and completing a ch14.18 infusion.

Antibiotics, blood products, antiemetics and other general supportive care measures were permitted.

Schedule of Assessments

Table 9, Table 10, and Table 11 provide a summary of the required assessments for patients randomized to the investigational (ch14.18 combination therapy) arm of Study 301.

Table 9: Schedule of Assessments for Study 301 Investigational Arm for Cycles Containing GM-CSF (Cycles 1, 3, and 5)

Days post GM-CSF for Courses 1, 3, 5#	Prior to Immuno therapy	-1, 55, 111 (Thursday)	3, 59, 115	4, 60, 116	5, 61, 117	6, 62, 118	10 (Courses 3 and 5 only) or 11 (Course 1), 66, 122 (Monday)	13, 69, 125	24 (Monday, 1st course only	During 3rd course of RA
		The day before GM-CSF	1st day of ch14.18 GM-CSF	2nd day of ch14.18 GM-CSF	3rd day of ch14.18 GM-CSF	4th day of ch14.18 GM-CSF	GM-CSF Start RA	GM-CSF ends, continue RA		
PE[1]		X	X	X	X	X	X			
CBC/Diff with APC		X	X			X	X			
BUN, creatinine, AST, ALT, albumin, total bili		X				X	X			
Electrolytes		X[7]	X[7]	X[7]	X[7]	X[7]	X			
LDH	X									
Calcium, triglycerides							X			
Urine VMA, HVA	X									
Urinalysis		X					X			
Thyroxine, TSH	X									
ch14.18 PK and HACA[2]		X[2] (Day -1 only)				X[2] (Day 6 only)				
Tumor Survey	X*									X*
MIBG scan, Bone marrow aspirates/ biopsies (2 sites) and MRD testing[3]	X*									Optional
13-cis retinoic acid pharmacokinetics[4]									X	
ECG Assessments		X[5] (Day -1 only)				X[5] (Day 6 only)				
FcR, KIR/ KIR-L genotyping		X[6]								

Days as designated in Immunotherapy Calendars

* Tumor survey, MIBG, bone marrow for mandatory disease staging prior to enrollment. Tumor measurement by pertinent imaging studies (CT, MRI, bone scan if tumor is not MIBG avid). Repeat MIBG later in therapy only if positive at diagnosis. Tumor survey, MIBG and bone marrow are optional during Course 3, performed as necessary for patient care.

1 Physical Exam (including weight, height, vital signs, and performance status [see Appendix I]). Note: performance status and height are only required at the start of each course.

2 ch14.18 PK and HACA (ONLY for patients participating in the optional cardiac safety sub-study): 5 mL blood in preservative-free heparin or green top tube for immunotherapy Course #1: Day 1 (1 day before starting 1st dose of GM CSF, on a Thursday) and Day 6 (at the end of the 4th daily infusion of ch14.18). Freshly obtained samples should be sent at room temperature by overnight carrier.

3 MRD testing (Optional): 3-5 mL heparinized marrow from each site plus 10 mL heparinized peripheral blood to Dr. Seeger's lab (also see Section 5.61). For MRD #1 assessment prior to study enrollment, **please use the ANBL0032 Specimen Shipping Form, complete it and send with the specimen. Please note that consent must be obtained prior to sending the specimen for MRD #1.**

4 cisRA pharmacokinetics (Optional): Send 5 mL blood in sodium heparin to be drawn 4 hours after administration of the 13-cis retinoic acid dose on Day 14 of cis-RA administration in Course #1 to Reynolds' lab. (See section 5.65 for details of specimen submission.)

5 Only for patients participating in the optional cardiac safety sub-study, 12-lead ECGs will be obtained at Course #1: Day -1 (1 day before starting 1st dose of GM-CSF, on a Thursday) and Day 6 (at the end of the 4th daily infusion of ch14.18).

6 FcR and Kir genotyping (optional): 7 mL heparinized blood on Day -1 of Course 1 only; **note**: may be obtained within 1 week before starting the first GM-CSF injection.

7 Include evaluation of phosphorous and magnesium on Day-1 and Days 3-6 of Courses 1, 3 and 5. **Note:** Electrolytes including phosphorous and magnesium will also be evaluated on Day 7 of Courses 1, 3 and 5.

** **In case of Grade 4 hypersensitivity reactions at any time, please order the following lab tests and send the results to Dr. Alice Yu by email (aliceyu@ucsd.edu) and also include the results in AdEERS: Complement levels (C3, C4, CH50 and c1q binding); IgE level, blood levels of tryptase and histamine (to be done locally); In addition, please draw 5 mL heparinized blood and send to the bioanalytical laboratory (see address information in Section 5.63) for HACA determination. The leftover ch14.18 vials should be shipped for inspection per instruction in Section 5.64.**

Source: BLA submission

Table 10: Schedule of Assessments for Study 301 Investigational Arm for Cycles Containing IL-2 (Cycles 2 and 4)

Days **post GM-CSF** for Courses 2 and 4	24, 80 (Monday)	27, 83	31, 87 (Monday)	32, 88	33, 89	34, 90 (Thursday)	38, 94 (Monday)
	1st day of the 1st week IL-2	4th day of the 1st week IL-2	1st day of ch14.18 +IL-2	2nd day of ch14.18 +IL-2	3rd day of ch14.18 +IL-2	4th day of ch14.18 +IL-2	Start RA
PE[1]	X		X	X	X	X	X
CBC/Diff with APC	X	X	X			X	X
BUN, creatinine, albumin, AST, ALT, total bili	X	X	X			X	X
Electrolytes	X	X	X[5]	X[5]	X[5]	X[5]	X
Calcium, triglycerides							X
Urinary VMA and HVA	X[3]						
Urinalysis	X						X
ch14.18 PK and HACA[2]	X (Day 80 only)					X (Day 90 only)	
ECG Assessments[4]	X (Day 80 only)					X (Day 90 only)	

1 Physical Exam (including weight, height, vital signs, and performance status [See Appendix I]). PE is required on Days 1, 2 & 3 only when IL-2 is given in an in-patient setting. Note: performance status and height are only required at the start of each course.

2 ch14.18 PK and HACA (ONLY for patients participating in the optional cardiac safety sub-study): 5 mL blood in preservative-free heparin or green-top tube obtained for the 4th course of immunotherapy, on the first day of the first 4-day/week Interleukin-2 therapy (Day 80, before starting aldesleukin (IL-2) infusion, on a Monday) and at the end of the 4th daily infusion of ch14.18 (Day 90). Freshly obtained samples should be sent at room temperature by overnight carrier.

3 Only prior to 4th course of immunotherapy.

4 Only for patients participating in the optional cardiac safety sub-study, 12-lead ECGs will be obtained for the 4th course of immunotherapy, on the first day of the first 4-day/week Interleukin-2 therapy (Day 80, before starting aldesleukin (IL-2) infusion, on a Monday) and at the end of the 4th daily infusion of ch14.18 (Day 90).

5 Include evaluation of phosphorous and magnesium on the days of ch14.18 infusion. **Note:** Electrolytes including phosphorous and magnesium will also be evaluated on the day after the last ch14.18 infusion of Courses 2 and 4.

**** In case of Grade 4 hypersensitivity reactions at any time, please order the following lab tests and send the results to Dr. Alice Yu by email (aliceyu@ucsd.edu) and also include the results in AdEERS: Complement levels (C3, C4, CH50 and c1q binding); IgE level, blood levels of tryptase and histamine (to be done locally); In addition, please draw 5 mL heparinized blood and send to the bioanalytical laboratory (see address information in Section 5.63) for HACA determination. The leftover ch14.18 vials should be shipped for inspection per instruction in Section 5.64.**

Note: Hypersensitivity reaction will be referred as 'allergic reaction and anaphylaxis' per CTCAE v4.0 followed from October 1st, 2011.

Source: BLA submission

Table 11: Schedule of Assessments for Study 301 Investigational Arm for Cycle 6

Days	During Course 6 (therapy starts on Day 14 of the course) Within 1 week prior to administration	Within 2 weeks after completion of 6th course of RA
PE[1]	X	X
CBC/Diff with APC	X	X
BUN, creatinine, AST, ALT, albumin, total bili	X	X
Electrolytes	X	
Calcium, triglycerides	X	
Urine VMA, HVA		X
Urinalysis	X	X
Thyroxine, TSH		X
ch14.18 PK and HACA[2]		X[2]
Tumor Survey		X*
MIBG scan[4], Bone marrow aspirates/ biopsies (2 sites) and MRD testing[3]		X
ECG Assessments[5]		X

* Tumor survey, MIBG, bone marrow aspirates/biopsies for mandatory disease staging within 2 weeks of completion of the 6th course of RA. Tumor measurement by pertinent imaging studies (CT, MRI, bone scan if tumor is not MIBG avid)

[1] Physical Exam (including weight, height, vital signs, and performance status [see Appendix I])

[2] ch14.18 PK and HACA (ONLY for patients participating in the optional cardiac safety sub-study): 5 mL blood in preservative-free heparin or green-top tube. Freshly obtained samples should be sent at room temperature by overnight carrier (see Section 5.63).

[3] MRD testing (Optional): collection of 3-5 mL heparinized marrow from each site plus 10 mL heparinized peripheral blood shipped to Dr. Seeger's lab (also see Section 5.61). **Please use the ANBL0032 Specimen Shipping Form, complete it and send with the specimen.**

[4] MIBG scans performed only if the tumor is MIBG avid at diagnosis.

[5] Only for patients participating in the optional cardiac safety sub-study, 12-lead ECGs will be obtained within two weeks from study Day 163 (i.e. within 2 weeks from completion of 6th course of RA).

Source: BLA submission

Table 12 displays the schedule of required assessments for patients randomized to the control (RA) arm of Study 301.

Table 12: Schedule of Assessments for Study 301 Control Arm

Days post-ASCT	Prior to RA	66 (Monday)	On Day 14 of cycle #1 of Cis RA	94	122	150	178	206	234
		Start 1st cycle of RA		Start 2nd cycle of RA	Start 3rd cycle of RA	Start 4th cycle of RA	Start 5th cycle of RA	Start 6th cycle of RA	2 weeks after last dose of RA
PE[1]	X			X	X	X	X	X	X
CBC/Diff	X			X	X	X	X	X	X
Chemistry, urinary VMA, HVA[2]	X			X	X	X	X	X	X
Yu's Lab ADCC[3]	X					X			X
Bone marrow aspirates/ biopsies (2 sites)[4]	X*					X** (optional)			X*
Tumor survey[5]	X					X			X
MIBG scan	X*					X (optional)			X*
13-cis retinoic acid pharmacokinetics[6]			X						

* MIBG, bone marrow and blood mandatory for MRD assessment.
** Bone marrow and blood are optional for Day 150 and are only done for patient care. The bone marrow aspirates and biopsies are not for submission to Seeger's lab.
[1] Physical Exam (including weight, height, vital signs, and performance status [see Appendix I]) before each cycle.
[2] Chemistry survey (electrolytes, calcium, BUN, creatinine, triglycerides, AST, ALT, albumin, total bilirubin, LDH) and urinary VMA and HVA before each cycle.
[3] Yu's lab: 15 mL blood in preservative-free heparin or green-top tube obtained before starting 1st and 4th courses of RA and 2 weeks after the last dose of RA (to be drawn Monday through Thursday, avoid Friday). Freshly obtained samples should be sent at room temperature by overnight carrier. See section 5.62.
[4] Only the MRD studies in the two time points marked mandatory have to be sent to Dr. Seeger's lab. 3-5 mL heparinized marrow from each site plus 10 mL heparinized peripheral blood needs to be submitted. (Also see Section 5.61). For MRD #1 assessment prior to enrollment, please print the ANBL0032 Specimen Shipping Form, complete it and send with specimen. Please note that consent must be obtained prior to sending the specimen for MRD #1.
[5] Before starting fourth cycle of RA Therapy and after six cycles of Cis-RA:
-Tumor measurement by pertinent imaging studies (CT, MRI, bone scan if tumor is not MIBG avid, etc).
[6] For patients consenting to pharmacokinetics study, send 5 mL blood in sodium heparin to be drawn 4 hours after administration of the 13-cis retinoic acid dose on Day 14 of cycle #1. (See section 5.7 for details of specimen submission.)

Source: BLA submission

After completion of study therapy, all patients underwent periodic evaluations of tumor status, surveillance for late effects of treatment, and were followed for survival.
Table 13 outlines the schedule of assessments following completion of study therapy for all patients enrolled in Study 301.

Table 13: Schedule of Assessments Following Completion of Study 301 Therapy

Observation	3 Months	6 Months	9 Months	1 year	1.5 year	2 Years	2.5 Years	3 Years	3.5 Years	4 Years	4.5 Years	5 Years	Annually After 5 Years	At Relapse
Physical Exam%	X	X	X	X	X	X	X	X	X	X	X	X	X	
Height, Weight%	X	X	X	X&	X	X&	X	X&	X	X&	X	X&	X&	
CBC with differential and platelets%	X	X	X	X	X	X	X	X	X	X	X	X	X	
MUGA or ECHO, ECG, Pulmonary function tests				X+		X		X		X		X	X	
Bilateral BM Aspirate only#	X													X (Asp & BX) ##
Tumor Imaging$	X	X	X	X	X	X	X	X						X
MIBG# (See Appendix II)	X	X	X	X	X	X	X	X						X
Urine Catecholamines*	X	X	X	X	X	X	X	X	X	X	X	X	X	
TSH, T4				X^										
HRQOL Questionnaire				X†								X		
Chemistry**	X													
Performance Status	X	X	X	X⊗	X	X⊗	X	X⊗	X	X⊗	X	X⊗	X	

% For post-transplant patients perform physical exam and CBC monthly for one year after transplant.
* Perform if positive at diagnosis.
# Bone marrow evaluations, MIBG scans and bone scans every 3 months only if positive at completion of isotretinoin acid therapy. Repeat until at least three consecutive (immunocytologically) negative bone marrows or MIBG scans are documented. If BMA done it is optional to send 5 mL to Dr. Seeger's lab for MRD analysis.
$ Perform as scheduled, then as clinically indicated.
\+ If abnormal, repeat at 2 years and as needed. If child is < 5 years when treated as directed, an additional test should be performed when child becomes age 5.
Send 5 mL sample of bone marrow aspirate to Dr. Seeger's Lab for MRD analysis – label "relapse". This is an optional test.
& Perform sitting height and standing height, if child is ≥ 5 years.
^ Perform if child is ≥ 5 years. If child is < 5 years, delay evaluation until child becomes 5 years of age. If results are abnormal, follow-up with an endocrinologist is recommended and evaluations should be repeated one year later.
† Only patients enrolled on study A3973 will be required to complete the HRQOL questionnaire. Perform if child is ≥ 5 years. If child is < 5 years, delay giving questionnaire until child = 5 years of age. Evaluate HRQOL at 1 and 5 years off-therapy.
⊗ Evaluate yearly until 5 years after completion of therapy.
** Chemistry survey (electrolytes, calcium, BUN, creatinine, albumin, AST, ALT, total bilirubin, LDH) as indicated for good patient care.

Source: BLA submission

Protocol-Specified Study Therapy Discontinuation Criteria

Patients meeting any of the following criteria discontinued protocol-directed therapy:

- Completion of study therapy
- Occurrence of any of the following toxicities (for ch14.18 containing arm; patients remained on RA treatment)
  - Anaphylaxis or symptomatic bronchospasm
  - Grade 3 serum sickness

  - Grade 4 neuropathic pain unresponsive to continuous infusion of narcotics or other measures
  - Grade 3 sensory changes interfering with daily activities > 2 weeks after completing ch14.18 therapy
  - Objective motor weakness
  - Grade 3 visual toxicity
  - Grade 4 hyponatremia despite appropriate fluid management
  - Grade 4 skin toxicity
  - Grade 4 ventricular arrhythmia
  - Grade 4 QTc prolongation
- Refusal to continue treatment
- Physician determination that discontinuation was in the patient's best interest
- Recurrent or progressive disease
- Initiation of non-protocol directed anti-cancer therapy
- Occurrence of Grade 4 QTc prolongation or ventricular arrhythmia

5.3.1.4 Statistical Design and Sample Size

The main efficacy endpoint for Study 301 was event-free survival (EFS), defined as the time from study enrollment until the first occurrence of an EFS event, in the intent to treat (ITT) population. EFS events included relapse, progressive disease, secondary malignancy, or death. The first secondary endpoint was overall survival, defined as the time from study enrollment until death or last patient contact. The ITT population included all eligible patients who were randomized, irrespective of whether or not they received study medication and the treatment they received.

Patients were enrolled and randomized on Day 50 post ASCT, up to Day 85-post ASCT (or up to Day 100 post-ASCT for patients whose enrollment was delayed due to a significant post-transplant complication.)

Randomization was stratified based upon objective response status (CR vs. VGPR vs. PR) using the International Neuroblastoma Staging System (INSS) Response Evaluation Criteria[23] and by the following categories according to the treatment received prior to enrollment in Study 301.

- subject was randomized to receive purged stem cells in study A3973

23 Brodeur GM et al. *J Clin Oncol.* 1993; 11:1466-77.

- subject was randomized to receive unpurged stem cells in study A3973
- subject was not enrolled on but was treated per A3973 with purged stem cells
- subjects was not enrolled on but treated per A3973 with unpurged stem cells
- subject was treated per the POG 9341/9342 or CCG-3891 protocols
- subject was treated with single transplant on or per ANBL02P1, NANT 2001-02, ANBL0532 or ANBL07P1
- subject was treated with Tandem transplant on or per ANBL0532 , 9640, ANBL00P1, CHP594 or DFCI34-DAT
- other treatment

Based upon these stratification factors, patients could be randomized into one of 24 strata. Subjects with post ASCT/radiotherapy (XRT) evaluation who had persistent disease documented by biopsy were not randomized and instead were assigned to receive immunotherapy as part of Stratum 7.

Sample Size
After institution of Amendment 4 to Study 301, a total of 386 patients were planned for randomization in order to provide 80% power to detect a 15% difference (50% vs. 65%) in event-free survival using a one-sided log-rank test with a one-sided p-value of 0.025 for all randomized eligible subjects.

Data Analysis
The statistical plan for Study 301 specified that the primary analysis would be a comparison of EFS rates between treatment arms in the ITT population. The definitive analysis was to be performed after the occurrence of 137 events, after the last enrolled patient had been followed for three years, or when the efficacy monitoring boundary had been reached, whichever occurred first.

Please see Section 6.1.4 of this review of a discussion of the procedures used for interim analyses.

For the primary analysis, a two-sided log-rank test with a significance level of 0.05 was planned to test for a difference between the EFS distributions of the ch14.18 combination therapy arm versus the RA only arm in the ITT population. Two-year survival point EFS estimates (95%confidence interval [CI]) for each treatment group and the inferential statistics (p-value) associated with comparisons of the treatment groups were planned. Time to EFS was to be summarized by treatment group using product-limit estimates calculated by the Kaplan-Meier method, and displayed graphically as Kaplan-Meier curves. Incidence of an event was compared between treatment groups using Fisher's exact test.

In the planned analyses for the randomized portion of the study, other than for the interim monitoring for efficacy or futility using the methods of Lan-DeMets and a cumulative one-sided alpha level of 0.025, no adjustments for multiplicity were made. EFS and OS were planned in sequence; if the two-sided log-rank test comparison for EFS yielded a p value < 0.05, then the OS analysis would be performed.

The protocol also specified that the trial would be stopped or the therapy modified if the stopping rule for unacceptable toxicities was met. Assessment of the frequency of "unacceptable toxicities" was planned to occur twice during the randomized trial: after the first 48 patients completed the ch14.18+RA therapy, and again after a total of 90 patients completed ch14.18+RA treatment. The following toxicities were considered unacceptable:

- Allergic reactions of ≥ Grade 4 severity
- Acute vascular leak syndrome of ≥ Grade 4 severity
- Motor neuropathy of ≥ Grade 3 severity lasting ≥ 2 weeks
- Pain of ≥ Grade 4 severity requiring narcotics/lidocaine that lasts ≥ 4 days after the end of the ch14.18 infusion.

The expected (null) unacceptable true toxicity rate was 20% (10 out of 48 or 18 out of 90). If 12 (25%) of the first 48 patients or 23 (26%) of the first 90 patients in the ch14.18+RA arm had at least one unacceptable toxicity, then the DMC would determine if the treatment regimen should be modified or the study stopped early.

Adverse Event Reporting

Adverse events were graded using NCI Common Terminology Criteria for Adverse Events (CTCAE). CTCAE version 2 was used prior to Amendment 4 (3/12/2004), which updated reporting requirements to CTCAE version 3. CTCAE version 4 was used after institution of Amendment 12 (7/22/2011). Adverse events were coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.1 preferred terms. The Study 301 protocol specified that all adverse events of Grade 3 or greater severity should be reported from the time of initiation of study therapy through 30 days after the last dose of study therapy. Adverse events were to be monitored and recorded from the time of signing of the informed consent document until the patient termination visit, which occurred from 0-30 days after the final dose of study medication.

Adverse events were also evaluated for expedited reporting requirements according to NCI's Adverse Event Expedited Reporting System (AdEERS) database. Events meeting AdEERS reporting requirements were considered to be serious adverse events. AdEERS reporting requirements were based on several factors, including whether the adverse event occurred in association with an investigational or commercial agent, and characteristics of the adverse event, including the severity, relationship to study therapy, whether it was considered to be expected or not, and whether or not it

resulted in hospitalization or prolongation of hospitalization. For the purposes of AdEERS reporting, ch14.18 was considered investigational (Table 14, copied from the study report for DIV-NB-301), and RA, GM-CSF, and IL-2 were considered commercial agents because they were obtained from a commercial source (Table 15, copied from the study report for DIV-NB-301).

Table 14: AdEERS Reporting Criteria for Ch14.18

	Grade 1	Grade 2[3]	Grade 2	Grade 3[3]		Grade 3[3]		Grades 4 & 5[2]	Grades 4[3] & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected	Expected
				with Hospitalization	without Hospital-zation	with Hospitali-zation	without Hospitali-zation		
Unrelated Unlikely	Not Required	Not Required	Not Required	5 Calendar Days	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days
Possible Probable Definite[1]	Not Required	5 Calendar Days	Not Required	5 Calendar Days	5 Calendar Days	5 Calendar Days	Not Required	24-Hour; 5 Calendar Days	5 Calendar Days

Version: March 2005

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:

AdEERS 24-hour notification (via AdEERS for CTEP IND agents; via e-mail to COG AE Coordinator for agents in Non-CTEP IND studies) followed by complete report within 5 calendar days for:

- Grade 4 and Grade 5 unexpected events

AdEERS 5 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization (see exceptions below)
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

[3] Please see exceptions below under section entitled "Additional Instructions or Exceptions" Section 9.5.3.2.3.

Source: BLA submission

Table 15: AdEERS Reporting Criteria for GM-CSF, IL-2, and RA

Attribution	Grade 4		Grade 5
	Unexpected	Expected	
Unrelated or Unlikely			AdEERS
Possible, Probable, Definite	AdEERS		AdEERS

This included all deaths within 30 days of the last dose of treatment with a commercial agent, regardless of attribution. Any death that occurred more than 30 days after the last dose of treatment with a commercial agent which was attributed (possibly, probably, or definitely) to the agent and was not due to cancer recurrence must be reported via AdEERS.

Source: BLA submission

When ch14.18 was administered in combination with another agent, the combination was considered investigational for the purposes of AdEERS reporting. When a commercial agent was administered followed by ch14.18, expedited reporting requirements for adverse events occurring prior to initiation of ch14.18 followed the rules for commercial agents; after initiation of ch14.18, expedited reporting of adverse events followed AdEERS guidelines for investigational agents. Prior to Protocol Amendment 6, expected risks of ch14.18 were included in the protocol, and expected events for GM-CSF, IL-2, and RA were considered those listed in the study protocol or approved package insert. Protocol Amendment 6 incorporated the Comprehensive Adverse Event and Potential Risks (CAEPR) list for ch14.18 (Table 16).

Any adverse events of ≥ Grade 3 severity occurring in association with ch14.18 treatment that precipitated hospitalization or prolongation of hospitalization fulfilled criteria for expedited adverse event reporting via AdEERS, irrespective of attribution and whether or not they were considered "expected" adverse events, with the exception of some protocol-specified exclusions to this rule. Additionally, expedited reporting of any adverse events resulting in permanent or significant disabilities/incapacities, congenital anomalies, or birth defects was required.

The Study 301 protocol also specified that any death that occurred more than 30 days after the last dose of treatment with an investigational agent which could have been attributed to the investigational agent and was not due to the patient's cancer required expedited reporting. Expedited reporting through AdEERS was not required for Grade 4 myelosuppression unless it was considered unexpected by the investigator. The protocol included a requirement for reporting of all cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).

Table 16: CAEPR for ch14.18

Category (Body System)	Adverse Events with Possible Relationship to Chimeric MoAb 14.18 (CTCAE v3.0 Term)	"Agent Specific Adverse Event List" (ASAEL)[1]
ALLERGY/IMMUNOLOGY		
	Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction/hypersensitivity (including drug fever)
	Serum sickness	
BLOOD/BONE MARROW		
	Platelets	Platelets
CARDIAC ARRHYTHMIA		
	Atrial fibrillation	
	Sinus tachycardia	
CARDIAC GENERAL		
	Cardiac ischemia/infarction	
	Cardiopulmonary arrest, cause unknown (non-fatal)	
	Hypertension	
	Hypotension	Hypotension
COAGULATION		
	DIC (disseminated intravascular coagulation)	DIC (disseminated intravascular coagulation)
CONSTITUTIONAL SYMPTOMS		
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)
	Weight loss	
DERMATOLOGY/SKIN		
	Pruritus/itching	Pruritus/itching
	Rash/desquamation	Rash/desquamation
	Urticaria (hives, welts, wheals)	Urticaria (hives, welts, wheals)
GASTROINTESTINAL		
	Anorexia	Anorexia
	Diarrhea	
	Nausea	Nausea
	Vomiting	Vomiting

Category (Body System)	Adverse Events with Possible Relationship to Chimeric MoAb 14.18 (CTCAE v3.0 Term)	"Agent Specific Adverse Event List" (ASAEL)[1]
ALLERGY/IMMUNOLOGY		
	Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction/hypersensitivity (including drug fever)
	Serum sickness	
BLOOD/BONE MARROW		
	Platelets	Platelets
CARDIAC ARRHYTHMIA		
	Atrial fibrillation	
	Sinus tachycardia	
CARDIAC GENERAL		
	Cardiac ischemia/infarction	
	Cardiopulmonary arrest, cause unknown (non-fatal)	
	Hypertension	
	Hypotension	Hypotension
COAGULATION		
	DIC (disseminated intravascular coagulation)	DIC (disseminated intravascular coagulation)
CONSTITUTIONAL SYMPTOMS		
	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)	Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)
	Weight loss	
DERMATOLOGY/SKIN		
	Pruritus/itching	Pruritus/itching
	Rash/desquamation	Rash/desquamation
	Urticaria (hives, welts, wheals)	Urticaria (hives, welts, wheals)
GASTROINTESTINAL		
	Anorexia	Anorexia
	Diarrhea	
	Nausea	Nausea
	Vomiting	Vomiting

METABOLIC/LABORATORY		
	Albumin, serum-low (hypoalbuminemia)	Albumin, serum-low (hypoalbuminemia)
	ALT, SGPT (serum glutamic pyruvic transaminase)	ALT, SGPT (serum glutamic pyruvic transaminase)
	AST, SGOT (serum glutamic oxaloacetic transaminase)	AST, SGOT (serum glutamic oxaloacetic transaminase)
	Creatinine	Creatinine
	Potassium, serum-low (hypokalemia)	
	Sodium, serum-low (hyponatremia)	
NEUROLOGY		
	Neuropathy: cranial (CN III: pupil, upper eyelid, extra ocular movements)	
	Neuropathy: motor	
	Neuropathy: sensory – Dysesthesia, Hyperaesthesia, Paresthesia	Neuropathy: sensory – Dysesthesia, Hyperaesthesia, Paresthesia
	Seizure	
	Somnolence/depressed level of consciousness	
OCULAR/VISUAL		
	Ocular/Visual - Other (Pupil dilation)	
	Ocular/Visual - Other (Optical atrophy)	
	Ocular/Visual - Other (Ptosis)	
PAIN		
	Pain – abdomen NOS (not otherwise specified)	Pain - abdomen NOS
	Pain – back	
	Pain – extremity-limb	
	Pain – joint	
	Pain – neuralgia/peripheral nerve	Pain - neuralgia/peripheral nerve
	Pain – pelvis	
	Pain NOS	
PULMONARY/UPPER RESPIRATORY		
	Bronchospasm, wheezing	
	Dyspnea (shortness of breath)	Dyspnea (shortness of breath)
	Hypoxia	Hypoxia
VASCULAR		
	Acute vascular leak syndrome	Acute vascular leak syndrome

Version 1.0, 17 February 2005 (ch14.18 risk tables were utilized prior to Amendment 6; refer to the original protocol and subsequent protocol amendments located in Appendix 16.1.1 for a copy of the risk tables used prior to the CAEPR).

Source: BLA submission

Adverse events meeting AdEERS reporting criteria were reported using CTCAE version 4.0 terms, which comprise either MedDRA version 10.0 SOCs, lower level terms (LLT) or preferred terms (PT).

5.3.2 Supportive Studies for Efficacy and Safety

The BLA also included data from supportive studies (see Table 5). Three studies, DIV-NB-302 (Study 302), DIV-NB-303 (Study 303), and DIV-NB-201(Study 201), employed the same treatment regimen used in the ch14.18 arm of Study 301. The eligibility criteria for these studies are also virtually identical to the eligibility criteria for Study 301. Study 302 is the extension component of ANBL0032 that enrolled patients to receive ch14.18 after the cessation of randomization, and Study 303 was designed to provide additional safety data to support the development of dinutuximab.

Study 201, the only clinical trial conducted by United Therapeutics Corporation (UTC), is an ongoing trial comparing the pharmacokinetic and safety profiles of ch14.18 manufactured by SAIC for CTEP and dinutuximab (n=28). Study 201 is a multicenter randomized open label two-sequence, crossover study that randomized patients to receive ch14.18 manufactured by UTC (dinutuximab) or ch14.18 manufactured by SAIC during Cycles 1 and 2 followed by ch14.18 from the alternate manufacturer during Cycles 3,4, and 5. Please see refer to the clinical pharmacology review by Jingyu Yu, PhD of the Division of Pharmacometrics for additional details regarding this study.

All patients enrolled in Study 301 and the majority of patients enrolled in Study 302 received ch14.18 produced by SAIC for NCI. As of January 21, 2014, all newly enrolled subjects and subjects continuing to receive study therapy in Study 302 received or were switched to UTC-manufactured dinutuximab. From January 21, 2014 through March 31, 2014, 29 patients received dinutuximab (as opposed to ch14.18 manufactured by SAIC).

6 Review of Efficacy

Efficacy Summary

The BLA submission contained data from a single randomized controlled trial, DIV-NB-301 (Study 301), in support of the following proposed indication:

> UNITUXIN (dinutuximab) is indicated for high-risk neuroblastoma (b) (4) (b) (4) treatment, in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA).

Study 301 was a multicenter international open label randomized (1:1) controlled trial comparing ch14.18 in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2), and 13-cis-retinoic acid [isotretinoin (RA)] to RA alone in 226 patients with newly diagnosed neuroblastoma. Eligible patients had completed intensive induction chemotherapy followed by autologous stem cell transplantation (ASCT) and radiation therapy, and achieved at least a partial response (PR) to the pre-ASCT evaluation. In order to qualify for enrollment, patients were required to have adequate hematologic, hepatic, renal, cardiac, and pulmonary function and not be reliant on systemic corticosteroids or other immunosuppressants.

Randomization was stratified based upon multiple factors, including objective response status (complete response vs. very good partial response vs. partial response) using the International Neuroblastoma Staging System (INSS) Response Evaluation Criteria[24] and according to the treatment regimen received prior to enrollment in Study 301.

The primary efficacy outcome measure was investigator-assessed event-free survival (EFS), defined as the first occurrence of relapse, disease progression, secondary malignancy, or death. Overall survival (OS) was the key secondary endpoint, although the study was not powered to detect a statistical difference in overall survival between the study arms. Of the randomized patients, 63% and 57% of patients in the ch14.18 combination therapy and RA arms, respectively, were male. The majority (97%) of patients in both arms were at least 18 months of age at the time of enrollment (range: 0.9 - 15.3 years), and 88% were enrolled in the United States. The majority of patients in both arms (79% in the ch14.18 combination arm and 81% in the RA arm) had Stage 4 disease according to the International Neuroblastoma Staging System, and had either a very good partial response (VGPR) or partial response (PR) to prior therapy (65% and 66% of patients in the ch14.18 combination and RA arms, respectively).

After observing a numerical improvement in EFS at the time of the seventh interim analysis (in January 2009), the Data Monitoring Committee recommended termination of the trial. At the time of the interim analysis, there were a total of 33 EFS events (29%) in the ch14.18 combination arm compared to 50 (44%) in the RA arm. The median EFS (95% CI) was not reached (3.4 years, NR) in the ch14.18 combination arm and was 1.9 years (1.3 years, NR) in the RA alone arm. The hazard ratio (95% CI) was 0.57 (0.37, 0.89) favoring the ch.14.18 combination arm, and the p-value calculated using the log-rank test was 0.0115 (compared to the allocated alpha of 0.0108) for the seventh interim analysis.

Results of a follow-up analysis of overall survival performed on June 30, 2012 are supportive of the results of the primary EFS analysis. In the analysis of overall survival, there were 31 OS events (27%) in the ch14.18 combination arm and 48 (42%) events in the RA alone arm. Median overall survival was not reached (NR) in either arm (95% CI

24 Brodeur GM et al. *J Clin Oncol.* 1993; 11:1466-77.

for the ch14.18 arm was 7.5 years, NR and 3.9 years, NR for the RA alone arm). The hazard ratio for OS (95% CI) was 0.58 (0.37, 0.91).

6.1 Indication

United Therapeutics proposed the following indication for dinutuximab in the original BLA submission:

> UNITUXIN (dinutuximab) is indicated for high-risk neuroblastoma (b) (4) (b) (4) treatment, in combination with granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin 2 (IL-2), and isotretinoin (RA).

Reviewer comment: GM-CSF, IL-2, and RA have not received FDA approval for the proposed indication. Moreover, Study DIV-NB-301, the randomized study providing the data providing the primary basis for demonstration of the efficacy of dinutuximab, was not designed to isolate the treatment effect of RA (the control arm treatment) or the relative contributions of IL-2, GM-CSF, and ch14.18 to the improvement in event-free survival and overall survival observed in the treatment arm of this trial. Therefore, this reviewer recommends omitting references to use of IL-2, GM-CSF, and RA in the Indications (Section 1) and (b) (4) sections of Unituxin labeling and restricting information regarding the use of these therapies to the Warnings and Precautions (Section 5), Adverse Reactions (Section 6), and Clinical Studies (Section 14) sections of product labeling. Additionally, the use of the term (b) (4) may be misleading because it has an imprecise and variable definition and implies that dinutuximab (b) (4) The majority of patients did not exhibit a complete response (CR) to prior therapy before entering this trial; most had residual disease. Therefore, I recommend deleting the term (b) (4) from the indication statement, and instead describe the level of tumor burden that patients had prior to initiation of therapy on this trial. Finally, I recommend modifying the indication statement to clarify that dinutuximab is approved as (b) (4) Please refer to Sections 1.2 (Risk Benefit Assessment) and 6 (Efficacy Summary) for additional discussion of the assessment of the efficacy of dinutuximab for the treatment of patients with high-risk neuroblastoma.

6.1.1 Methods

This clinical review of the efficacy of dinutuximab focuses on the efficacy results of the single randomized controlled trial of ch14.18, Study DIV-NB-301 (Study 301) submitted to the BLA. For details regarding the FDA statistical analysis of efficacy data submitted to this BLA, please refer to the statistical review conducted by Sirisha Mushti, PhD.

Section 5.3.1 presents a summary of the study design and statistical analysis plan for Study 301. Briefly, Study 301 was a multicenter open label randomized study conducted in patients with newly diagnosed high-risk neuroblastoma who achieved at least a partial response to standard therapy at the pre-ASCT tumor evaluation. A total of 226 patients were randomized 1:1 to receive either standard therapy consisting of six cycles of RA (control arm, n=113) or five cycles of ch14.18 in combination with GM-CSF (Cycles 1,3, and 5) or IL-2 (Cycles 2 and 4) and RA, followed by once cycle of RA alone (investigational arm, n=113). The primary efficacy endpoint of the study was event-free survival (EFS) as determined by the local investigator, and overall survival (OS) was the first secondary efficacy endpoint. Up to 386 patients were originally planned for randomization, but randomization was terminated by the DSMC based upon the results of a planned interim analysis of data accumulated up to January 13, 2009. This BLA includes results of an updated analysis of EFS and OS using data accumulated through June 30, 2012. This clinical review also includes analyses of these data, to determine whether these (more mature) results are consistent with the results of the analyses leading up to early termination of randomization.

6.1.2 Demographics

Table 17 and Table 18 show the baseline demographic and disease characteristics of patients in the intent-to-treat (eligible randomized) population of Study 301.

Table 17: Baseline Demographic Characteristics of Randomized Patients in Study 301

Patient Characteristics	Ch14.18 (n = 113)	RA (n=113)	Total (N=226)
Age at Enrollment (years)			
Mean (sd)	4.3 (2.5)	4.0 (2.1)	4.1 (2.3)
Median (range)	3.9 (0.9 - 15.3)	3.5 (0.9 - 13.3)	3.8 (0.9 - 15.3)
<1.5 years, n (%)	4 (4)	4 (4)	8 (3)
Gender, n (%)			
Male	71 (63)	64 (57)	135 (60)
Female	42 (37)	49 (43)	91 (40)
Race, n (%)			
White	95 (84)	90 (80)	185 (82)
Black	8 (7)	8 (7)	16 (7)
Asian/Pacific Islander	2 (2)	6 (6)	8 (4)
Other/Unknown	8 (7)	9 (8)	17 (8)
Ethnicity			
Not Hispanic or Latino	100 (89)	96 (85)	196 (87)
Hispanic or Latino	11 (10)	11 (10)	22 (10)

Patient Characteristics	Ch14.18 (n = 113)	RA (n=113)	Total (N=226)
Unknown	2 (2)	6 (5)	8 (4)
Country of Enrollment, n (%)			
United States	101 (89)	97 (86)	198 (88)
Canada	11 (10)	13 (12)	24 (11)
Australia	1 (1)	3 (3)	4 (2)

Table 18: Baseline Prognostic Factors of Randomized Patients in Study 301

Patient Characteristics	Ch14.18 (n = 113)	RA (n=113)	Total (N=226)
INSS Stage, n (%)			
Stage 2A	4 (4)	0 (0)	4 (2)
Stage 3	10 (9)	16 (14)	26 (12)
Stage 4	89 (79)	92 (81)	181 (80)
Stage 4s	2 (2)	0 (0)	2 (1)
Unknown	8 (7)	5 (4)	13 (6)
MYCN status, n (%)			
Amplified	36 (32)	45 (40)	81 (36)
Non-amplified	52 (46)	51 (45)	103 (46)
Missing	25 (22)	17 (15)	42 (19)
DNA Ploidy, n (%)			
Diploid	35 (31)	46 (41)	81 (36)
Hyperdiploid	49 (43)	48 (43)	97 (43)
Missing	29 (26)	19 (17)	48 (21)
Tumor Histology, n (%)			
Favorable	4 (4)	5 (4)	9 (4)
Unfavorable	68 (60)	81 (72)	149 (66)
Missing	41 (36)	27 (24)	68 (30)
Pre-ASCT Response, n (%)			
CR	40 (35)	38 (34)	78 (35)
VGPR	47 (42)	49 (43)	96 (43)
PR	26 (23)	26 (23)	52 (23)

Baseline demographic characteristics were generally well balanced between the two treatment arms. The median age of randomized patients was 3.8 years, and there was a slightly higher percentage of boys (60%) compared to girls (40%). The majority of

randomized patients were White (82%), and of non-Hispanic or Latino (87%) ethnicity, and U.S. origin (88%).

Prognostic factors were relatively well balanced between the two treatment groups and reflected the high-risk status of the patients enrolled in the study. The majority of patients had Stage 4 disease (80%), unfavorable tumor histology (66%), and a pre-ASCT response that was either a VGPR (43%) or PR (23%). The control arm had slightly higher percentages of patients with diploid (41% vs. 31%) or MYCN-amplified tumors (40% vs. 32%); however, MYCN status and DNA ploidy were unknown or missing for 19% and 21% or randomized patients, so the relative differences in the incidence of these poor prognostic factors between treatment arms is uncertain.

6.1.3 Subject Disposition

Prior to close of randomization, a total of 251 patients enrolled into Study 301, including 226 randomized patients and 25 patients with biopsy-proven residual disease assigned to receive ch14.18 therapy (Stratum 7). Table 19 summarizes patient disposition for the randomized patients in Study 301.

Table 19: Patient Disposition for Study 301

Disposition Event	Ch14.18 N = 113 n (%)	RA N = 113 n (%)	Total N = 226 n (%)
Ongoing	**81 (72)**	**73 (65)**	**154 (68)**
Discontinued Study	**32 (28)**	**40 (35)**	**72 (32)**
Withdrew consent	6 (5)	5 (4)	11(5)
Enrolled on another study	6 (5)	8 (7)	14 (6)
Death	5 (4)	7 (6)	12 (5)
No information	15 (13)	20 (18)	35 (15)

At the time of the primary analysis, 72 of 226 (32%) randomized patients had discontinued from Study 301. There was no available information describing the reasons for study discontinuation for 35 of 72 (48%) of these patients. Patients who discontinued study therapy prematurely remained in the study and were followed until they met criteria for study discontinuation. The incidence of premature study discontinuation was slightly more common in the RA arm (35%) compared to the ch14.18 arm (28%), despite the fact that a higher percentage of patients prematurely discontinued study therapy in the ch14.18 arm (28%), compared to the RA arm (23%). Section 7.3.3 of this review contains a discussion of the reasons for premature discontinuation of study treatment, including deaths and adverse events.

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for Study 301 was event-free survival (EFS), defined as the time from study enrollment until the first occurrence of relapse, disease progression, secondary malignancy, death, or date of last contact (if no event occurred). EFS was based upon local investigator assessment and the EFS analysis was performed using the randomized eligible (ITT) population. The primary efficacy analysis of Study 301 demonstrated a borderline statistically significant improvement in investigator-assessed EFS in patients who were randomized to receive ch14.18 in combination with GM-CSF, IL-2 and RA, compared to patients who were randomized to receive RA alone.

The original Study 301 protocol specified a plan for multiple interim efficacy analyses beginning after occurrence of 20%, or 23 of the 115 planned EFS events (as described in Section 5.3.1 of this review, Amendment 4 subsequently increased the sample size from 322 to 386 and the planned number of events from 115 to 137). Accordingly, seven consecutive interim efficacy analyses took place from November 2005 (when 29 EFS events were recorded) through January 13, 2009. Please refer to Dr. Mushti's statistical review for details regarding the methods used to calculate the stopping boundaries for the interim efficacy analyses.

The final efficacy analysis was planned to occur after approximately 137 EFS events had occurred, in the absence of a decision to stop the trial early for efficacy or futility based on an interim analysis. Table 20 provides a summary of the results and corresponding stopping boundary for each interim analysis. The p-value for the EFS analysis calculated using the January 13 2009 data cutoff date, 0.0115, was close to the pre-specified alpha boundary of 0.0108 for the seventh interim analysis. Based upon these results, the statistician considered that there was sufficient evidence of superiority of the ch14.18+RA arm to warrant closure of the randomized portion of the study. Upon review of the statistical analyses, the Data Safety Monitoring Committee concurred with the statistician's recommendation and decided to permanently halt the randomized portion of the trial.

Table 20: Summary of Interim Analyses

Monitoring Time point	Cum. No. of Observed Events	% of Expected Events	LD upper boundary z-value (α=0.025)	Corresponding p-value	Observed Upper boundary z-value	Observed p-value
Nov 2005	29	0.212	3.0000		1.963	
June 2006	39	0.285	3.0000		1.905	
Nov 2006	49	0.360	2.9102		2.257	
June 2007	57	0.416	2.8278		2.450	
Dec 2007	62	0.453	2.8001		2.120	
June 2008	70	0.511	2.7002		2.550	

Monitoring Time point	Cum. No. of Observed Events	% of Expected Events	LD upper boundary z-value (α=0.025)	Corresponding p-value	Observed Upper boundary z-value	Observed p-value
Nov 2008*	83	0.606	2.5508	**0.0108**	2.528	**0.0115**

Abbreviations: Cum.: cumulative; No.: number; LD: Lan-DeMets
*Cumulative information observed for Nov 2008 was based on data frozen on January 13, 2009, not November 3, 2008 like the rest of the DSMC report.
Source: Adapted from the FDA statistical review by Dr. Sirisha Mushti

UTC was not able to confirm the results of the 7th interim analysis using the raw dataset originally used by the Children's Oncology Group to generate this analysis because the dataset became corrupted prior to institution of the CRADA between NCI and UTC. Therefore, the Applicant used an available uncorrupted 'soft lock' dataset (data cutoff June 20, 2009) that was temporally closest to the January 13, 2009 dataset to verify the analyses that formed the basis of the decision for early termination of randomization in the trial.

The EFS results calculated using the January 13, 2009 data cutoff date are shown in Table 21, below. There was a striking numerical improvement in EFS favoring the ch14.18+RA arm, with a hazard ratio of 0.57 [95% CI= (0.37, 0.89); p=0.0115 using the unstratified log-rank test]. The median for EFS was not reached in the treatment arm; however, the median EFS for the control arm was 1.92 years. The Kaplan-Meier plot shown below (Figure 2) illustrates that the EFS curves separate early and maintain separation. The treatment arm had higher 2-year EFS rate compared to the control arm (66.3% vs. 46.4%).

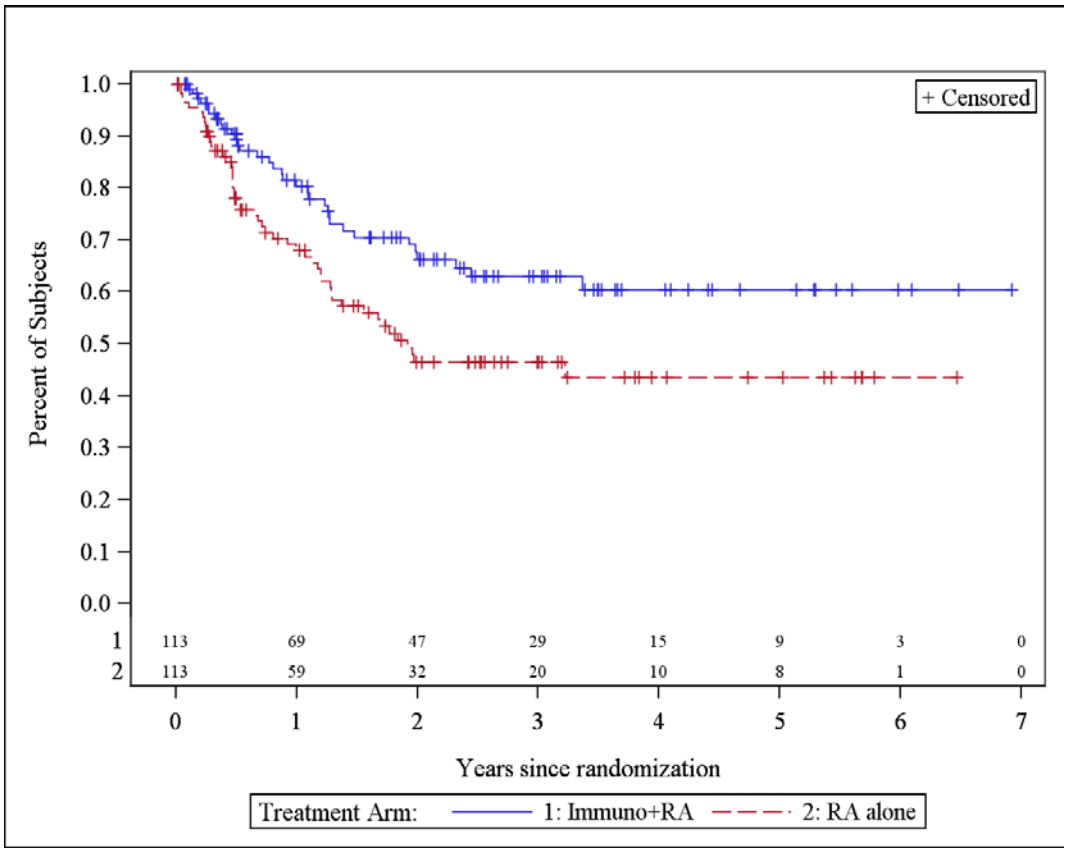
Table 21: Primary Efficacy Analysis of EFS for Study 301*

	Ch14.18 combination n=113	RA alone n=113
No. of EFS events (%)	33 (29.2)	50 (44.25)
2-yr EFS rate (%) (95% CI)	66.29 (56.25, 76.33)	46.44 (35.82, 57.06)
Median EFS (years) (95% CI)	NR(3.36,NR)	1.92 (1.29,NR)
Hazard ratio (95% CI)	0.57 (0.37,0.89)	
p-value[a] (Unstratified log-rank test)	0.0115	

* Using a data cutoff date of January 13, 2009 (corresponding to the seventh interim analysis)
Abbreviations: CI: confidence interval; EFS: event-free survival; No.: number
[a]This p-value approaches but is marginally above the pre-specified p-value of 0.0108 that was required under the statistical plan for stopping randomization for efficacy.

Source: Adapted from the FDA statistical review by Dr. Sirisha Mushti

Figure 2: Kaplan-Meier Estimates of EFS for Study 301* - Primary Analysis



***** Using a data cutoff date of January 13, 2009 (corresponding to the seventh interim analysis)
Source: FDA statistical review by Dr. Sirisha Mushti

The decision to halt randomization was documented in Amendment #9 of the ANBL0032 protocol. After cessation of randomization, all subjects were switched to, continued on, or enrolled onto the treatment arm (ch14.18 + cytokines and RA) immunotherapy and RA) and the control arm (RA alone) closed to accrual.

Reviewer note: as described in Table 5, in the BLA, the Applicant refers to this extension (single arm) portion of Study ANBL0032 as Study DIV-NB-302 (Study 302).

After Study 301 was closed, a total of four subjects who were randomized to the control arm in Study 301 alone arm crossed over to the ch14.18 (treatment) arm; these subjects were censored at the point of crossover for all efficacy analyses.

As previously discussed, because the raw datasets used for the primary efficacy analysis were corrupted, the Applicant performed a confirmatory follow-up analysis of EFS using available raw datasets that had a data cutoff date of June 30, 2009 (Table 22

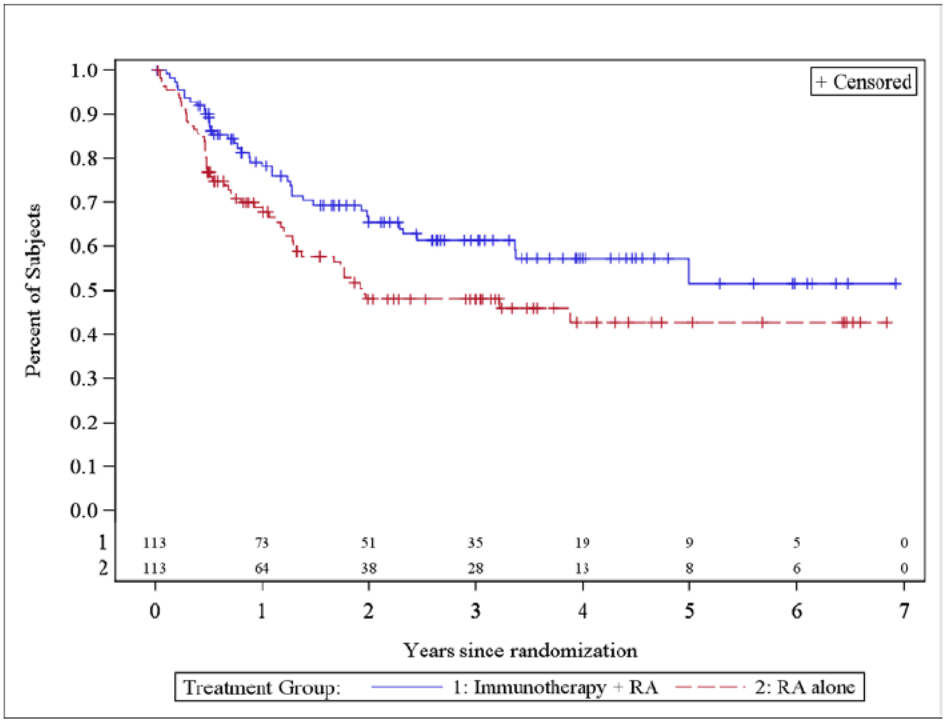
and Figure 3). These results were consistent with the results obtained using the January 13, 2009 data cutoff date (nominal p-value = 0.033).

Table 22: Follow-up EFS Results for Study 301 – June 30, 2009 Analysis

	Ch14.18 combination n=113	RA alone n=113
No. of EFS events (%)	40 (35.4)	54 (47.79)
2-yr survival rates (%) (95% CI)	65.61 (56.06,75.16)	48.08 (37.97,58.19)
Median (years) (95% CI)	NR (3.36,NR)	1.95(1.29,NR)
Hazard ratio (95% CI)	0.64 (0.43,0.97)	
Nominal p-value (Unstratified log-rank test)	0.033	

Abbreviations: CI: confidence interval; EFS: event-free survival; No.: number; NR: not reached
Source: FDA statistical review by Dr. Sirisha Mushti

Figure 3: Kaplan-Meier Estimates of EFS for Study 301 - June 30, 2009 Analysis



Source: FDA statistical review by Dr. Sirisha Mushti

The Applicant conducted a third analysis of EFS in the ITT population after three additional years of follow-up. The EFS results from this follow-up analysis again show a numerical improvement in EFS favoring the ch14.18 combination therapy arm (Table 23 and Figure 4).

Table 23: Follow-up EFS Results for Study 301 – June 30, 2012 Analysis

	Ch14.18 combination n=114[a]	RA alone n=114[b]
No. of EFS events	49 (42.98%)	58 (50.88%)
3-yr survival rates (%) (95% CI)	62.82 (53.9, 71.74)	50.89 (41.58, 60.2)
Median (years) (95% CI)	NR (3.37,NR)	3.22 (1.67,NR)
Unadjusted Hazard Ratio (95% CI)	0.73 (0.50,1.06)	

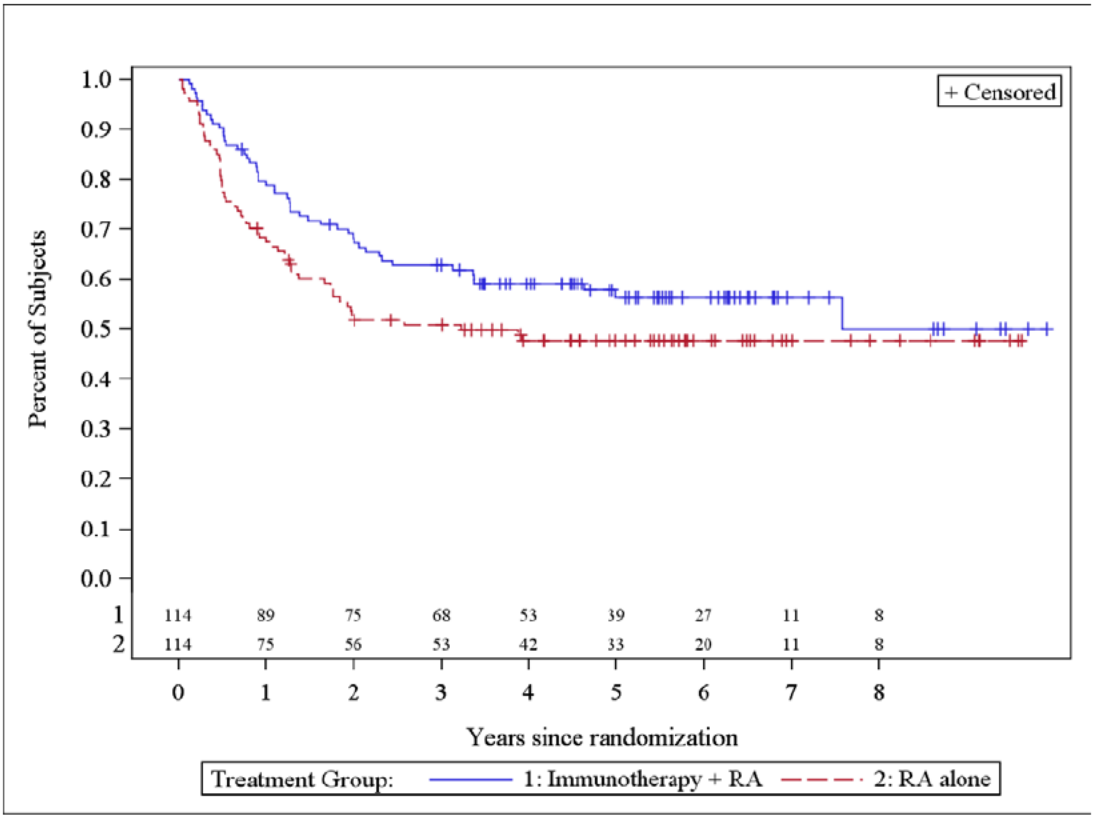
	Ch14.18 combination n=114[a]	RA alone n=114[b]
Nominal p-value (Unstratified log-rank test)	0.099	

[a]The 2012 analyses include one additional patient in the ch14.18 combination ITT population due to the addition of one patient (ID 778828) who was randomized prior to January 2009 but did not have data entered into the database until after June 2009.
[b]The 2012 analyses include one additional net patient in the RA ITT population because one subject (ID 774514) was deemed ineligible during an audit, and two patients (IDs 785522 and 778176) were randomized to the RA arm prior to January 2009 but were not entered into the database until after June 2009.

Abbreviations: CI: confidence interval; EFS: event-free survival; No.: number; NR: not reached

Source: Adapted from FDA statistical review by Dr. Sirisha Mushti

Figure 4: Kaplan-Meier Estimates of EFS for Study 301 - June 30, 2012 Analysis



Source: FDA statistical review by Dr. Sirisha Mushti

6.1.5 Analysis of Secondary Endpoints(s)

The key secondary endpoint of Study 301 was overall survival, defined as the time from study enrollment until the date of death or last contact with the subject if the subject is still living. Table 24 and Figure 5 summarize the OS results for the ITT population (data cutoff date January 13, 2009). Consistent with the numerical improvement in EFS, the analysis of OS documented a strong trend toward improvement in overall survival in patients randomized to the ch14.18 combination arm. The hazard ratio for overall survival was 0.52 [95% CI= (0.30, 0.92); nominal p=0.0223 using the unstratified log-rank test]. The median for OS was not reached in the treatment arm; however, the median OS for the control arm was 3.88 years. The treatment arm had higher 2-year survival rate compared to the control arm (86.2% vs. 74.5%) and fewer deaths (19 vs. 33). The Kaplan-Meier plot shown below (Figure 5) illustrates that the survival curves separate early and maintain separation.

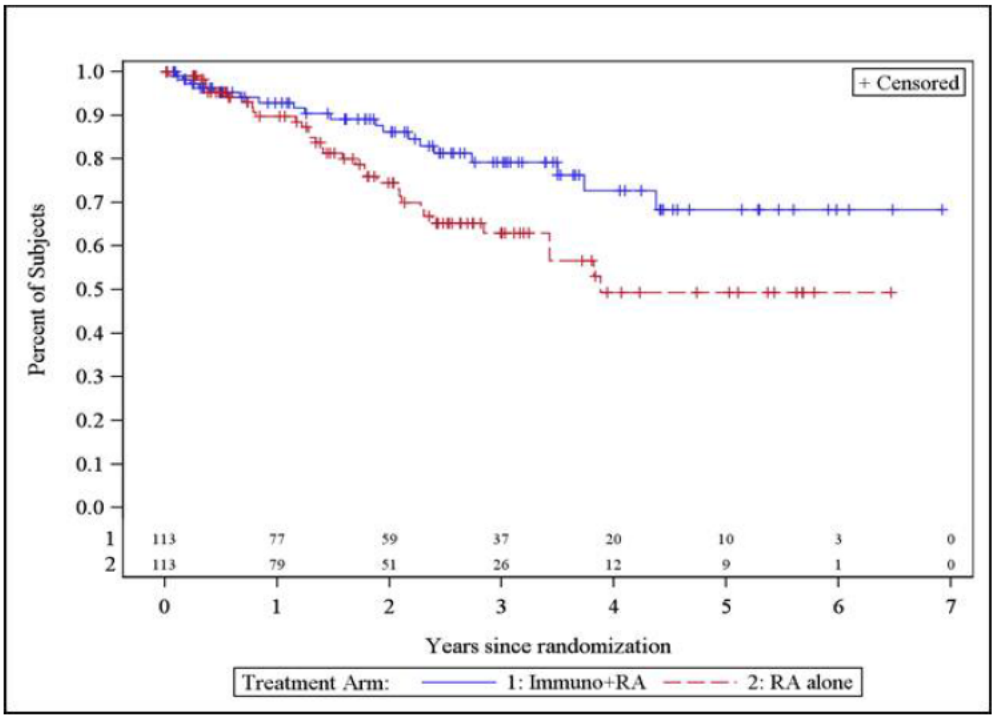
Table 24: Analysis of OS for Study 301*

	Ch14.18 combination n=113	**RA alone n=113**
No. of OS events (%)	19 (16.81)	33 (29.2)
2-yr survival rate (%) (95% CI)	86.17 (78.76,93.58)	74.53 (65.18,83.88)
Median (years) (95% CI)	NR (NR,NR)	3.88 (3.43,NR)
Unadjusted Hazard Ratio (95% CI)	0.52 (0.30,0.92)	
Nominal p-value (Unstratified log-rank test)	0.0223	

* Using a data cutoff date of January 13, 2009 (corresponding to the seventh interim analysis)

Abbreviations: CI: confidence interval; No.: number; NR: not reached; OS: overall survival
Source: Adapted from FDA statistical review by Dr. Sirisha Mushti

Figure 5: Kaplan-Meier Estimates of OS for Study 301*



* Using a data cutoff date of January 13, 2009 (corresponding to the seventh interim analysis)
Source: FDA statistical review by Dr. Sirisha Mushti

Because the raw datasets used for the primary efficacy analysis (January 13, 2009 data cutoff) were corrupted, the Applicant performed a confirmatory follow-up analysis of OS using available raw datasets that had a data cutoff date of June 30, 2009 (Table 25 and Figure 6). These results were consistent with the results obtained using the January 13, 2009 data cutoff date (nominal p-value = 0.0330).

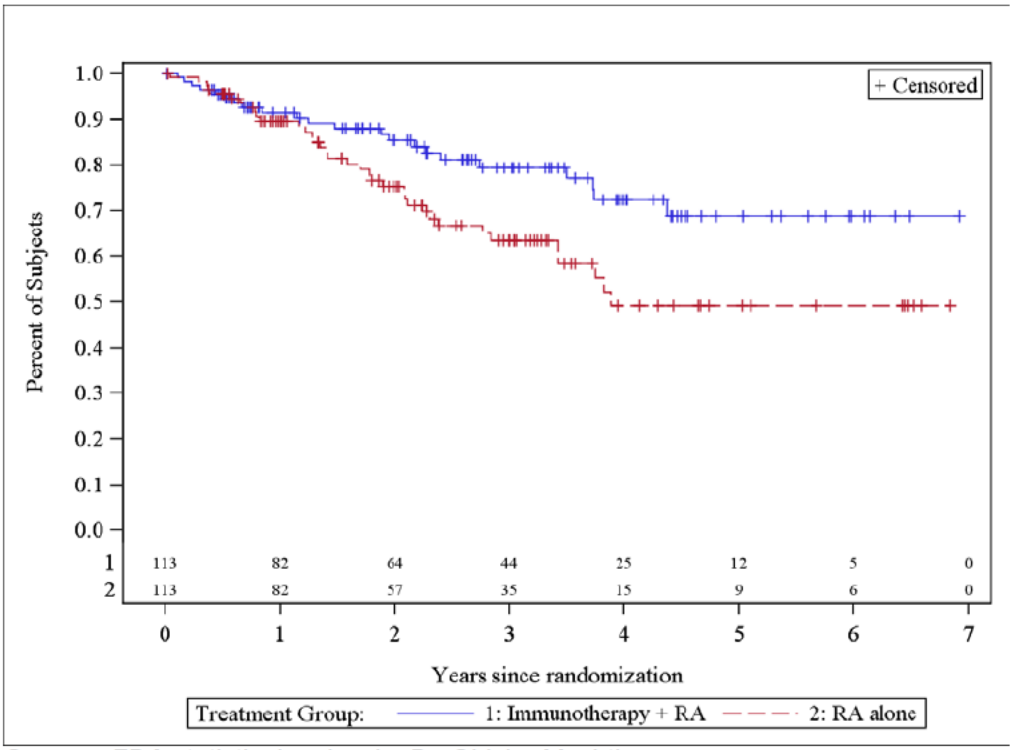
Table 25: Follow-up OS Results for Study 301 – June 30, 2009 Analysis

	Ch14.18 combination n=113	RA alone n=113
No. of OS events (%)	22 (19.47)	36 (31.86)
2-yr survival rate (%) (95% CI)	85.38% (78.19%, 92.57%)	75.3% (66.4%, 84.2%)
Median (years) (95% CI)	NR (NR,NR)	3.88 (3.43,NR)
Unadjusted Hazard Ratio (95% CI)	0.58 (0.37,0.91)	

	Ch14.18 combination n=113	RA alone n=113
Nominal p-value (Unstratified log-rank test)	0.0213	

Abbreviations: CI: confidence interval; No.: number; NR: not reached; OS: overall survival
Source: Adapted from FDA statistical review by Dr. Sirisha Mushti

Figure 6: Kaplan-Meier Estimates of OS for Study 301 - June 30, 2009 Analysis



Source: FDA statistical review by Dr. Sirisha Mushti

The Applicant conducted a third analysis of OS in the ITT population after three additional years of follow-up. The OS results from this follow-up analysis show that the numerical improvement in OS was maintained in the ch14.18 combination therapy arm Table 26 and Figure 7).

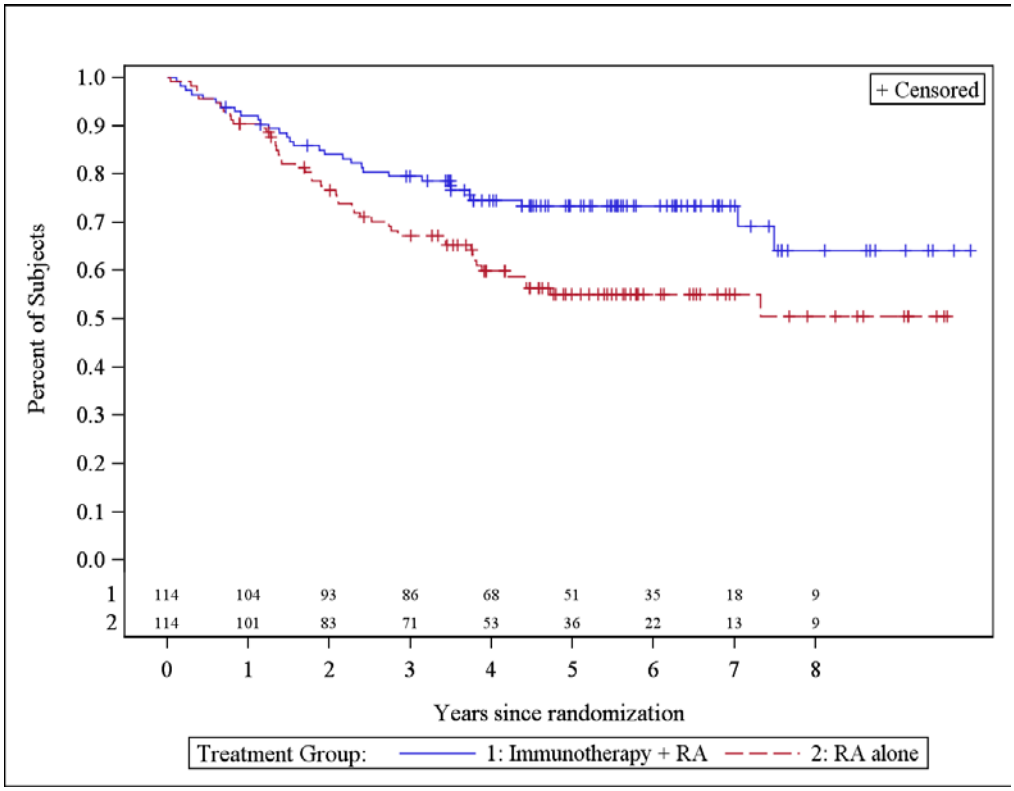
Table 26: Follow-up OS Results for Study 301 – June 30, 2012 Analysis

	Ch14.18 combination n=114[a]	RA alone n=114[b]
No. of OS events (%)	31 (27.19)	48 (42.11)
2-yr survival rate (%) (95% CI)	79.52 (72.05, 86.99)	67.25 (58.45, 76.05)
Median (years) (95% CI)	NR (7.49,NR)	NR (3.88,NR)
Unadjusted Hazard Ratio (95% CI)	0.58 (0.37,0.91)	
Nominal p-value (Unstratified log-rank test)	0.0165	

[a]The 2012 analyses include one additional patient in the ch14.18 combination ITT population due to the addition of one patient (ID 778828) who was randomized prior to January 2009 but did not have data entered into the database until after June 2009.
[b]The 2012 analyses include one additional net patient in the RA ITT population because one subject (ID 774514) was deemed ineligible during an audit, and two patients (IDs 785522 and 778176) were randomized to the RA arm prior to January 2009 but were not entered into the database until after June 2009.

Abbreviations: CI: confidence interval; No.: number; NR: not reached; OS: overall survival
Source: Adapted from FDA statistical review by Dr. Sirisha Mushti

Figure 7: Kaplan-Meier Estimates of OS for Study 301 - June 30, 2012 Analysis



Source: FDA statistical review by Dr. Sirisha Mushti

Reviewer note: the p-value results included in the June 30, 2009 and June 30, 2012 EFS analyses and all of the OS analyses are nominal p-values because there was no alpha allocation for these analyses; the entire pre-specified alpha was spent on the seventh (January 13, 2009) interim analyses of EFS. These nominal p-values are included for descriptive purposes only

6.1.6 Other Endpoints

This review did not include an analysis of additional secondary and exploratory endpoints for Study 301 because the Applicant did not propose to include these results in labeling or rely on these endpoints to demonstrate the efficacy of dinutuximab for the proposed patient population.

6.1.7 Subpopulations

FDA analyses of investigator-assessed event-free survival (EFS) by demographic and baseline characteristics are presented in Table 27 and Figure 8. These subgroup analyses show that the treatment effect of ch14.18 combination therapy was consistent

across the majority of patient subgroups; in many cases, the upper bound of the 95% confidence intervals for the hazard ratio (HR) did not cross 1. In subgroups where estimates of the EFS hazard ratio favored the control arm, there were small numbers of patients and wide confidence intervals (e.g., Age Category "unknown" and Race "unknown"). Notably, the upper bound of the hazard ratio for the MYCN amplified subgroup crossed 1; however, there was a large percentage of patients with unknown MYCN status (presumably because these patients met other criteria for high risk neuroblastoma or because the study was conducted over a decade ago).

Table 27: Subgroup Analyses of EFS for Study 301*

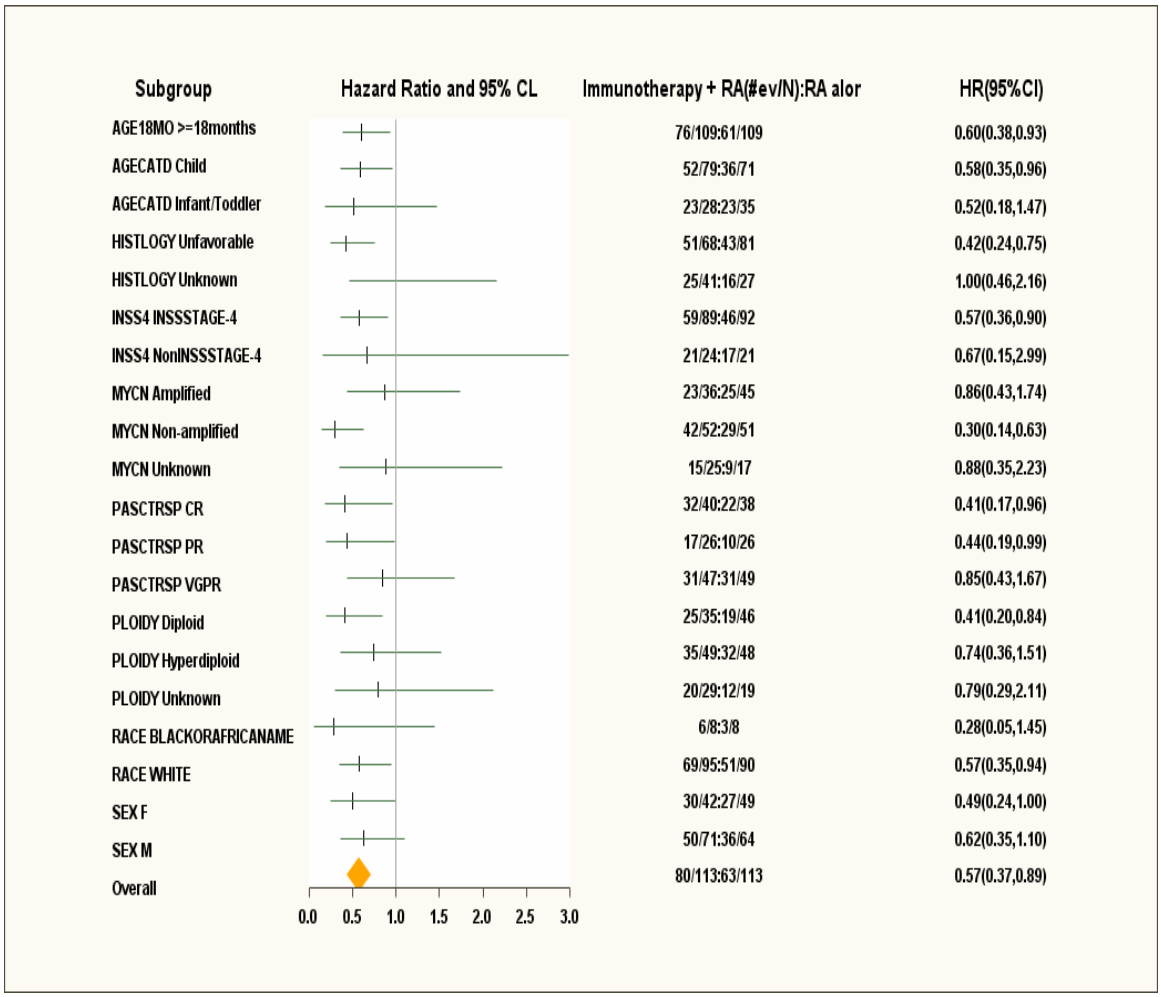
Baseline Demographic or Disease Characteristic	Subgroup	Event Count	Sample size #events/n		Hazard Ratio (95% CI)
			Ch14.18 Comb.	RA	
Age group	<18months	8	4/4	2/4	-
	>=18months	218	76/109	61/109	0.60 (0.38,0.93)
Age Category	Adolescent (12-18 years)	5	4/4	0/1	-
	Child (2 to < 12 years)	150	52/79	36/71	0.58 (0.35,0.96)
	Infant/Toddler (< 2 years)	63	23/28	23/35	0.52 (0.18,1.47)
	Unknown	8	1/2	4/6	2.83 (0.17,47.15
Histology	Favorable	9	4/4	4/5	-
	Unfavorable	149	51/68	43/81	0.42 (0.24,0.75)
	Unknown	68	25/41	16/27	1.00 (0.46,2.16)
INSS Stage	Stage-4	181	59/89	46/92	0.57 (0.36,0.90)
	Other than Stage-4	45	21/24	17/21	0.67(0.15,2.99)
MYCN Amplification	Amplified	81	23/36	25/45	0.86 (0.43,1.74)
	Non-Amplified	103	42/52	29/51	0.30 (0.14,0.63)
	Unknown	42	15/25	9/17	0.88 (0.35,2.23)
Post-ASCT Response	CR	78	32/40	22/38	0.41 (0.17,0.96)
	PR	52	17/26	10/26	0.44 (0.19,0.99)

Baseline Demographic or Disease Characteristic	Subgroup	Event Count	Sample size #events/n		Hazard Ratio (95% CI)
			Ch14.18 Comb.	RA	
	VGPR	96	31/47	31/49	0.85 (0.43,1.67)
DNA Ploidy	Diploid	81	25/35	19/46	0.41 (0.20,0.84)
	Hyper Diploid	97	35/49	32/48	0.74 (0.36,1.51)
	Unknown	48	20/29	12/19	0.79 (0.29,2.11)
Race	Asian	6	1/2	2/4	0.54 (0.04,6.64)
	Black/African American	16	6/8	3/8	0.28 (0.05,1.45)
	Multiple	3	1/1	1/2	-
	Native Hawaiian or other Pacific Islander	2	0/0	1/2	-
	Other	1	1/1	0/0	-
	Unknown	13	2/6	5/7	2.54 (0.46,14.02)
	White	185	69/95	51/90	0.57 (0.35,0.94)
Sex	Female	91	30/42	27/49	0.49 (0.24,1.00)
	Male	135	50/71	36/64	0.62 (0.35,1.10)
Overall		226	80/113	63/113	0.57(0.37,0.89)

*Analysis based on January 13, 2009 data cutoff date.
Source: Adapted from FDA statistical review by Dr. Sirisha Mushti

Forest plots of the hazard ratio estimates based on EFS and the corresponding 95% confidence intervals for each subgroup summarized in Table 27 are presented below (Figure 8).

Figure 8: Forest Plot for the subgroup analysis of EFS*



*Analysis based on January 13, 2009 data cutoff date
Source: FDA statistical review by Dr. Sirisha Mushti

Analyses of OS across demographic and tumor-based subgroups are presented in Table 28 and Figure 9 below.

For OS, the hazard ratio estimates were less than one for most of the subgroups, illustrating the consistency of the treatment effect of dinutuximab across relevant demographic and tumor molecular subgroups. However, the results of subgroup analyses should be interpreted with caution; the small numbers of patients in many of the subgroups resulted in wide confidence intervals in many cases.

Table 28: Subgroup analysis results for OS*

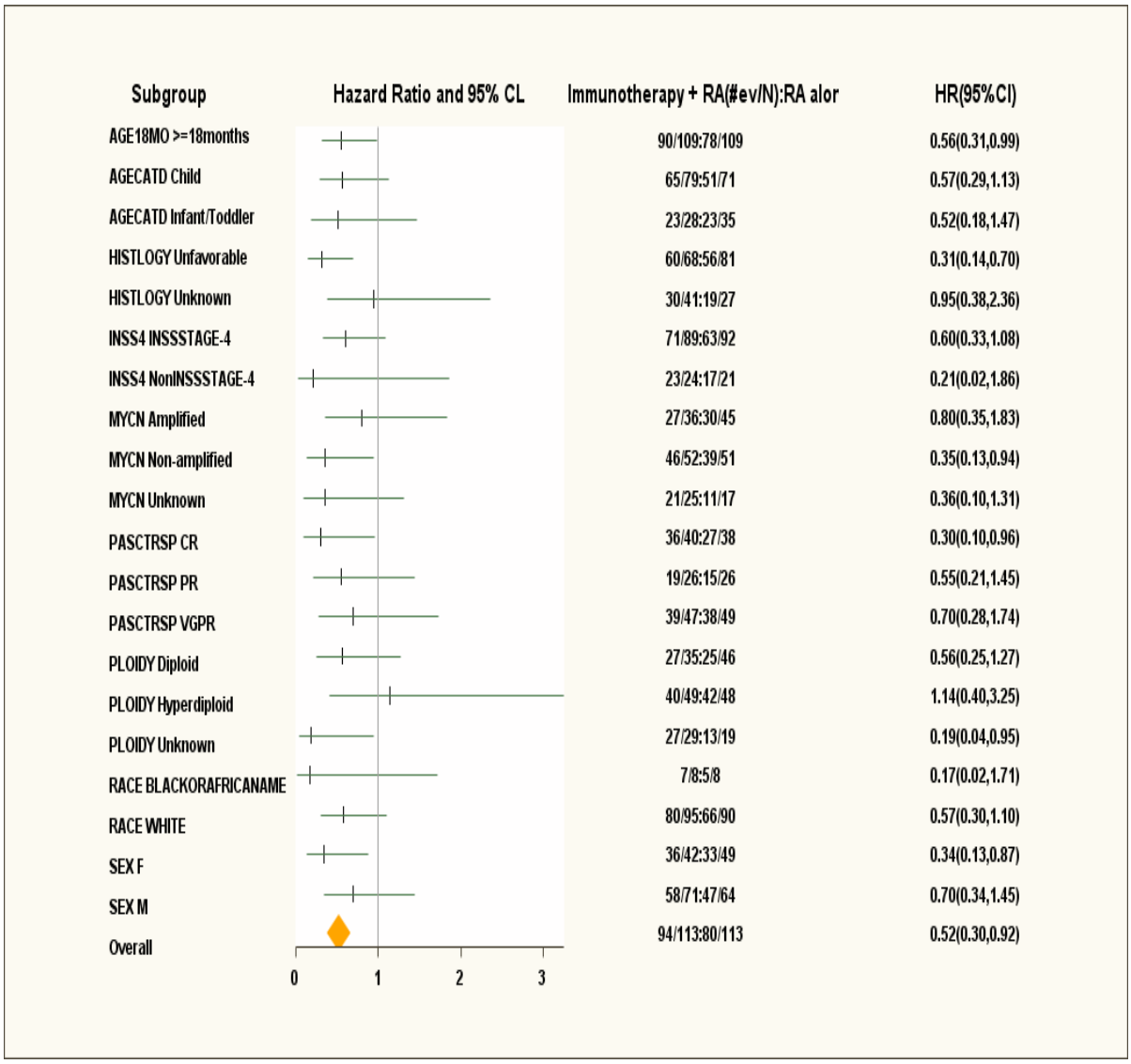
Baseline Demographic or Disease Characteristic	Subgroup	Event Count	Sample size #events/n		Hazard Ratio (95% CI)
			Ch14.18 Comb.	RA	
Age group	<18months	8	4/4	2/4	-
	>=18months	218	90/109	78/109	0.56 (0.31,0.99)
Age Category	Adolescent (12-18 years)	5	4/4	0/1	-
	Child	150	65/79	51/71	0.57 (0.29,1.13)
	Infant/Toddler	63	23/28	23/35	0.52 (0.18,1.47)
	Unknown	8	2/2	6/6	-
Histology	Favorable	9	4/4	5/5	-
	Unfavorable	149	60/68	56/81	0.31 (0.14,0.70)
	Unknown	68	30/41	19/27	0.95 (0.38,2.36)
INSS Stage	Stage-4	181	71/89	63/92	0.60 (0.33,1.08)
	Other than Stage-4	45	23/24	17/21	0.21 (0.02,1.86)
MYCN Amplification	Amplified	81	27/36	30/45	0.80 (0.35,1.83)
	Non-Amplified	103	46/52	39/51	0.35 (0.13,0.94)
	Unknown	42	21/25	11/17	0.36 (0.10,1.31)
Post-ASCT Response	CR	78	36/40	27/38	0.30 (0.10,0.96)
	PR	52	19/26	15/26	0.55 (0.21,1.45)
	VGPR	96	39/47	38/49	0.70 (0.28,1.74)
DNA Ploidy	Diploid	81	27/35	25/46	0.56 (0.25,1.27)
	Hyper Diploid	97	40/49	42/48	1.14 (0.40,3.25)
	Unknown	48	27/29	13/19	0.19 (0.04,0.95)
Race	Asian	6	1/2	2/4	-
	Black/African American	16	7/8	5/8	0.17 (0.02,1.71)
	Multiple	3	1/1	1/2	-

Baseline Demographic or Disease Characteristic	Subgroup	Event Count	Sample size #events/n		Hazard Ratio (95% CI)
			Ch14.18 Comb.	RA	
	Native Hawaiian or other Pacific Islander	2	0/0	1/2	-
	Other	1	1/1	0/0	-
	Unknown	13	4/6	5/7	1.35 (0.19,9.73)
	White	185	80/95	66/90	0.57 (0.30,1.10)
Sex	Female	91	36/42	33/49	0.34 (0.13,0.87)
	Male	135	58/71	47/64	0.70 (0.34,1.45)
Overall		226	94/113	80/113	0.52 (0.30,0.92)

*Analysis based on January 13, 2009 data cutoff date
Source: FDA statistical review by Dr. Sirisha Mushti

There did not appear to be any clinically relevant or statistically meaningful differences in the hazard ratios of EFS and OS for males and females, or pediatric patients categorized as infants (< 2 years of age), children (2 to < 12 years of age), or adolescents (12 to < 18 years of age). Because of the very small numbers of non-White patients, it is not known whether there are any clinically relevant differences in the efficacy of dinutuximab across racial subgroups.

Figure 9: Forest Plot for the Subgroup Analysis of OS*



*Analysis based on January 13, 2009 data cutoff date
Source: FDA statistical review by Dr. Sirisha Mushti

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

There is scant clinical data regarding the clinical activity of dinutuximab administered at a dosage regimen that is different from the proposed dosage regimen for this BLA. Neither the Applicant nor NCI conducted dose-response trials. The FDA Pharmacometrics reviewer concluded that an exposure/dose-response relationship for efficacy and safety could not be characterized due to the lack of PK data and lack of incorporation of dose exploration in the major clinical studies submitted to the BLA.

The proposed dose of dinutuximab, 17.5 mg/m^2/day administered for four consecutive days for a total of five cycles (equivalent to 25 mg/m^2/day of ch14.18 to a difference in methodology of calculating the extinction coefficient for the two products), was identified as the maximum tolerated dose in Study CCG-0935A when used in combination with in IL-2, GM-CSF, and RA in patients with newly diagnosed high-risk neuroblastoma. The results of Study CCG-0945A formed the foundation for the treatment regimen used in subsequent studies of ch14.198 (Studies 301, 302, 303 and 201).

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Please refer to the analyses of event-free survival and overall survival in Sections 6.1.4 and 6.1.5, respectively, for a review of the persistency of efficacy effects.

6.1.10 Additional Efficacy Issues/Analyses

During clinical review of this application, the clinical review team considered whether data from the single adequate and well-controlled trial supporting efficacy of dinutuximab, Study 301, provided adequate scientific and legal basis for approval. In the Guidance for Industry, entitled "*Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*" published in May 1998, FDA described the circumstances in which the Agency would consider data from a single adequate and well-controlled study to provide a sufficient scientific and legal basis for approval. The guidance states that "reliance on only a single study will generally be limited to situations in which a trial has demonstrated a clinically meaningful effect on mortality, irreversible morbidity, or prevention of a disease with potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible." The guidance further described the following desirable characteristics that would support adequacy of a single study:

- Large multicenter study in which no single site provided an unusually large fraction of patients and no single site or investigator was disproportionately responsible for the effect on efficacy
- Consistency across relevant study subsets
- Multiple studies in a single study

- Statistically persuasive evidence of an effect on more than one relevant, prospectively identified endpoint
- Statistically very persuasive finding.

The guidance acknowledged that reliance on persuasive results from a single, internally consistent, multicenter study has limitations, stating that "even a strong result can represent an isolated or biased result." The guidance emphasized that it was important to consider "inadequacies and inconsistencies in the data" in the determination of whether a single trial is adequate to support approval.

The efficacy review of this BLA included examination of the potential limitations of Study 301 as a single trial to support the efficacy of dinutuximab for the proposed indication. One potential limitation is the use of the primary endpoint of EFS, as assessed by the investigator, because this endpoint may be subject to bias in an open label trial. However, the potential for bias in the assessment of EFS was reduced because Study 301 is a large trial in which no site enrolled a large number of patients, which limits the individual contribution of any one study site to the EFS results. Additionally, analyses of EFS across multiple time points (January 2009, June 2009, and June 2012) show that the treatment effect of dinutuximab was consistent and durable. Furthermore, in an Oncologic Drugs Advisory Committee Meeting held on July 24, 2012, FDA presented an analysis of 28 trials which reported progression-free survival (PFS) results assessed by investigators and blinded independent central review; in this analysis, there was a high degree of correlation, irrespective of investigator blinding, between investigator and blinded independent central review assessments of PFS[25].

The results of Study 301, while clinically meaningful, are not statistically robust. As described in Section 6.1.4 of this review, randomization was terminated after the results of the seventh interim analysis showed an improvement in EFS favoring the ch14.18 combination arm, with a hazard ratio of 0.57 (95% CI: 0.37, 0.89; p=0.0115 using the unstratified log-rank test). The observed p-value, 0.0115, approached but is slightly higher than the pre-specified nominal alpha of 0.0108; therefore, the results of the seventh interim analysis did not technically meet the criteria for stopping the trial early for efficacy. However, the updated event-free and overall survival data submitted by the Applicant (using data collected through June 30, 2009 and June 30, 2012) corroborate the efficacy findings and strengthen the application.

[25]Sridhara, R, 2012, FDA Presentation: Assessing Bias in the Determination of Disease Progression in Non-Hematologic Malignancies, Oncologic Drugs Advisory Committee Meeting, July 24, 2012. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/OncologicDrugsAdvisoryCommittee/UCM315078.pdf

One of the other shortcomings of the BLA, which posed a significant challenge to the risk:benefit assessment of dinutuximab, is the lack of clinical data to isolate the treatment effect of dinutuximab from that of GM-CSF and IL-2. During interactions with CTEP and UTC throughout the development of ch14.18 and dinutuximab, the FDA emphasized the importance of characterizing the contributions of each component of ch14.18 combination therapy (GM-CSF, IL-2, and ch14.18/dinutuximab) to the overall treatment effect observed in patients with high risk neuroblastoma (please see Table 3 for details regarding regulatory interactions). Ultimately, the BLA contained insufficient clinical data to assess the relative contributions of GM-CSF and IL-2 to the observed efficacy. Similarly, assessment of the toxicity profile of dinutuximab was hampered by the relative lack of clinical data from use of dinutuximab as monotherapy, particularly because IL-2 and GM-CSF are administered concurrently with dinutuximab in Studies 301, 302, 303, and 201.

The BLA did include information from published literature to support the rationale for use of ch14.18 in combination with IL-2 and GM-CSF for the treatment of patients with high risk neuroblastoma. The Applicant cited data from published *in vitro* and *in vivo* studies showing that ch14.18 exhibits antitumor activity against melanoma and neuroblastoma cells[26,27], and that this antitumor activity is potentially mediated by complement dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC)[28,29,30]. The Applicant also referenced published studies indicating that ADCC increases with increasing concentrations of ch14.18 and that ADCC is enhanced by soluble cytokines such as GM-CSF and IL-2, supporting the rationale for combining ch14.18 therapy with cytokines to augment CDC and ADCC[31]. Published literature also describes stimulation of ADCC of tumor cells by GM-CSF through stimulation of neutrophil, eosinophil, monocyte, and macrophage proliferation and differentiation[32]. Additionally, published *in vitro* and *in vivo* studies describe stimulation of ADCC and CDC by IL-2 through stimulation of T cells, B cells, natural killer cells, and lymphokine-activated killer (LAK) cells[33,34].

Prior to initiation of Study 301, monotherapy trials provided data indicating that ch14.18 exerts antitumor activity in patient with refractory neuroblastoma. In a dose escalation trial reported by Yu et al.[35], one partial response and four mixed responses were observed in the evaluable patients who received ch14.18 at doses ranging from 10 to

26 Mueller B et al. *The Journal of Immunology*. 144:1382-1386,1990.
27 Mujoo K et al. *Cancer Research.* 47:1098-1104,1987
28 Albertini MR et al. *Clin Can Res.* 3:1277-1288, 1997.
29 Chen 2000. *Cancer Immunol Immunother* 48:603-612.
30 Hank JA et al. *Cancer Res* 50:5234-4239, 1990.
31 Hank J et al. *J Immunother* 15:29-37, 1994.
32 Kushner, B et al. *Blood* 75:1936-1941, 1989.
33 Honsik CJ et al. *Proc Natl Acad Sci* 83:7893-7897, 1986.
34 Munn DH, Cheung NKV. *Cancer Res* 47:6600, 1987.
35 Yu AL et al. (Abstract) Proc ASCO 10:318,1991.

200 mg/m^2/cycle. In another Phase I trial conducted by Handgretinger et al.[36], two complete responses and two partial responses were reported in nine patients who received ch14.18.

In summary, the rationale for studying the efficacy of ch14.18 in combination with GM-CSF and IL-2 in Study 301 was based on accumulated published nonclinical and clinical data providing evidence that ch14.18 has antitumor activity as monotherapy, and data from *in vitro* and *in vivo* studies indicating that the antitumor activity of ch14.18 in neuroblastoma is likely to be enhanced by the addition of cytokines. At this time, there are no data from controlled trials comparing the efficacy of ch14.18 administered as monotherapy with the efficacy of ch14.18 administered with IL-2 or GM-CSF (or both) in the proposed patient population. In Europe, an ongoing randomized study is evaluating the efficacy of a related ch14.18 antibody administered with or without IL-2 in patients with newly diagnosed neuroblastoma[37].

The review team acknowledges the design limitations of the single randomized, well-controlled trial, Study 301, as well as the potential limitations of relying on the results of this single trial to provide the primary basis for establishing the efficacy of dinutuximab for the proposed patient population. Despite these limitations, the clinical review team ultimately concluded after careful and comprehensive review of the application that Study 301 provided sufficient evidence of efficacy to support approval of the BLA. Study 301 embodies many of the characteristics of a desirable single study described in relevant FDA Guidance. It was a large, multicenter trial that demonstrated consistent results across patient subsets, and showed a persuasive effect on two clinically meaningful endpoints, event-free survival and overall-survival. Furthermore, demonstration of an overall survival benefit in patients with high risk neuroblastoma, a patient population with limited treatment options for their life threatening disease, renders the conduct of a second confirmatory randomized controlled trial practically or ethically impossible. Lack of feasibility for an additional (confirmatory) trial is underscored by the fact that in the United States, Canada, and Europe, treatment with ch14.18 is *a priori* part of the standard of care for first-line treatment of patients with high risk neuroblastoma.

FDA regulations, outlined in Subpart E of CFR part 312, which aim to expedite the development, evaluation, and marketing of promising therapies to treat individuals with life-threatening and severely debilitating illnesses, reflect that a medical risk-benefit judgment is required when deciding whether to approve a drug or biological product. As part of this risk-benefit analysis, the Agency will take "into consideration the severity of the disease and the absence of satisfactory alternative therapy" (21 CFR 312.84). Therefore, taking into consideration the challenges of studying treatments for high-risk

36 Handgretinger R et al. *Eur J Cancer* 31A:261-267, 1995.
37 Information available at http://clinicaltrials.gov/show/NCT01704716.

neuroblastoma, including the rarity of the disease and complexity of the current standard treatment regimen, the life-threatening nature of high-risk neuroblastoma, and the absence of satisfactory, approved alternative therapy, the clinical review team concluded that the totality of data in this submission provide sufficient evidence to grant regular approval to dinutuximab for the treatment of patients with neuroblastoma.

7 Review of Safety

Safety Summary

The primary safety risks of dinutuximab are infusion-related or allergic reactions, capillary leak syndrome, hypotension, systemic infection, neuropathy (which can manifest as pain or motor weakness), or neurological disorders of the eye such as impaired pupillary light reflex, photophobia, or visual impairment.

In Study 301, all patients who received ch14.18 combination therapy (N=134, including patients with biopsy-proven residual disease who were non-randomly assigned to the treatment group) received premedication with acetaminophen, hydroxyzine or diphenhydramine, and morphine sulfate prior to the ch14.18 infusion. Severe [≥Grade 3 using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)] hypersensitivity reactions occurred in 35 (26%) patients in the ch14.18 combination therapy group compared to one (1%) patient in the RA monotherapy group. In addition, anaphylaxis was reported as a serious adverse event in 9 (7%) patients in the ch14.18 combination therapy group.

Severe capillary leak syndrome occurred in 31 (23%) patients in the ch14.18 combination therapy group, and in no patients in the RA group. Capillary leak syndrome was reported for Cycles 1 through 5, but occurred more commonly during the cycles containing IL-2 compared to the cycles containing GM-CSF. In Study 301, 22 (16%) patients treated with ch14.18 had severe hypotension compared to 0 patients in the RA group. Sepsis was reported in 24 (18%) of patients in the ch14.18 group, compared to 10 (9%) of patients in the RA group. Additionally, severe bacteremia occurred in 17 (13%) of patients in the ch14.18 combination group compared to 5 (5%) of patients in the RA group.

In Study 301, for prevention and management of pain, all patients randomized to the ch14.18 combination arm received acetaminophen and morphine sulfate immediately prior to and during the ch14.18 infusion. Additional pain medications were given as necessary. Despite use of analgesics, the majority (84%) of patients treated with ch14.18 experienced pain compared to 16% of patients in the control group. Severe pain occurred in 51% of patients in the ch14.18 combination treatment group compared to 5% of patients in the RA group.

Additionally, 3% of patients in the ch14.18 combination therapy group experienced severe peripheral neuropathy compared to no patients treated with RA alone. A total of 5% of patients in the ch14.18 combination group experienced neurological disorders of the eye (all mild) compared to 3% of patients in the RA group.

Serious adverse events were common in the ch14.18 investigational treatment group; 51% of patients in the ch14.18 combination therapy group experienced at least one serious adverse event. The most common (per-patient incidence ≥ 5%) serious adverse reactions were infections, pain, hypokalemia, hypotension, anaphylaxis, capillary leak syndrome, catheter-related infection, and fever.

Patients receiving dinutuximab are at risk for developing serious and potentially life-threatening adverse reactions, such as infusion reactions, capillary leak syndrome, hypotension, anaphylaxis, infection, and neuropathy. Therefore, patients should receive dinutuximab in an inpatient setting in hospitals capable of providing intensive care unit support. Additionally, treatment with dinutuximab should occur only under the oversight of pediatric oncologists who are skilled in the identification and management of these toxicities. During and following treatment with dinutuximab, patients should undergo careful monitoring for signs and symptoms of these adverse reactions to ensure prompt intervention, including dose interruption, dose modification, dose discontinuation, and institution of supportive care when necessary.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The database used to evaluate safety reflects adverse events collected from 1184 patients with neuroblastoma treated with ch14.18 in 7 clinical trials: Studies DIV-NB-301 and DIV-NB-302 (corresponding to COG study number ANBL0032); Study DIV-NB-303 (corresponding to COG Study number ANBL0931); Study CCG 0935; Study CCG0935A; Study DIV-NB-201; and Study POG-9347. The safety review of this BLA relies primarily upon data collected from 1184 patients with neuroblastoma treated with ch14.18 in Studies 301 and 302 (n=975 combined), 303 (n=104), 201 (n=28), CCG 0935 (n=22), CCG 0935A (n=23), and POG-9347 (n=32). Except for 29 patients who enrolled or were continuing to receive study therapy in Study 302 from January 21, 2014 through March 31, 2014 and 28 patients enrolled in Study 201 (who received both UTC and SAIC-produced products), all patients were treated with SAIC-produced ch14.18 and were not exposed to UTC-produced dinutuximab.

Summary data from four studies of ch14.18 in adult subjects with melanoma (B89-005, B90-0014, B93-0009, and B94-002) were also reviewed to assess the toxicity profile of ch14.18 in adult subjects and to search for additional safety signals not observed to date in (primarily pediatric) patients with neuroblastoma.

The safety assessment included evaluation of analyses of treatment-emergent adverse events, clinical laboratory studies, physical examination findings, vital signs, and electrocardiograms in the exposed study population. For Study 301 and Study 302, adverse events of Grade 3 or greater severity were required to be reported from the start of study therapy through 30 days after the last dose of study therapy. Adverse events not reported through AdEERS were coded using MedDRA version 13.1.

For Study 301, safety analyses were performed on the safety population, defined as all subjects enrolled who received study therapy, including Stratum 7 subjects (those with biopsy-proven residual disease who were non-randomly assigned to receive ch14.18 combination therapy). Physical examinations included examination of height, weight, vital signs and performance status. Although clinical laboratory assessments included hematological and serum chemistry parameters and urinalyses, the clinical laboratory information captured in case report forms for Study 301 and Study 302 were limited to data regarding urine catecholamines, and total white blood cell count and differential Physical examination data, including vital signs and growth parameters, were not captured in case report forms. However, the protocol instructed investigators to record abnormal laboratory and physical examination findings that were Grade 3 or greater in severity to be reported as adverse events.

Reviewer comment: Although investigators in Study 301 were instructed not to report mild adverse events (i.e., adverse events of CTCAE Grade 1 or 2 severity), some investigators reported these adverse events. Therefore, adverse event analyses for Study 301 include a proportion of Grade 1 and 2 treatment-emergent adverse events that were experienced by patients. However, data regarding mild adverse events should be interpreted with caution because data for mild adverse events were not systematically and comprehensively captured.

7.1.2 Categorization of Adverse Events

For Study 301 and 302, adverse events were graded according to the current CTCAE criteria (version 2 prior to Protocol Amendment 4, version 3 prior to Protocol Amendment 12, and version 4 for protocol amendments thereafter). The adverse event database for these studies was converted from CTCAE version 3 to version 4 on October 1, 2011. Adverse events not reported through AdEERS were coded using MedDRA version 13.1.

Reviewer note: due to the database conversion from CTCAE version 3 to CTCAE version 4 in October 2011, some of the preferred terms reported for the safety analysis of the randomized population of Study 301 (June 2009) do not match the preferred term used to characterize the same adverse event for the same patient in the integrated summary of safety, even though the terms were coded to the same version of MedDRA.

For example, the preferred term "venous embolism" was changed to "vascular access complication" in the ISS.

Serious adverse events were reported by CTCAE term and reported verbatim from the AdEERS database for Study DIV-NB-301 and DIV-NB-302 and DIV-NB-303 studies. Adverse events and serious adverse events were coded to MedDRA version 17 for Study DIV-NB-201 (Study 201). Preferred terms for adverse events not reported through AdEERS were coded using MedDRA version 13.1 for all studies.

Review of verbatim terms in the adverse event dataset to determine whether MedDRA preferred terms were appropriately coded revealed no instances of inaccurate coding. In addition, a review of case report forms (CRFs) for 40 patients enrolled in Study 301 and 302 verified that verbatim terms and toxicity grading were characterized appropriately in the CRFs and accurately entered into the database.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Integrated Summary of Safety (ISS) database included adverse event data from 1184 patients with neuroblastoma treated with ch14.18 in seven clinical trials (See Section 7.1.1 and Table 5).

Adverse events were collected and graded using a variety of criteria. Adverse events were collected and graded using the Children's Cancer Group (CCG) toxicity criteria and the CCG Biologics and Toxicity Scales for the CCG-0935 and CCG-0935A studies. The POG-9347 study used the Pediatric Oncology Group (POG) Toxicity and Complications Criteria and Faces Pain Rating Scale for assessment and grading of adverse events. Study 301, 302, 303, and 201 used NCI's CTCAE criteria to collect and grade adverse events (although different versions of the CTCAE criteria were adopted over time in Study 301 and 302). Adverse events were coded using MedDRA preferred terms for all the studies (MedDRA version 13.1 for all studies except for Study 201, which used MedDRA version 17).

Reviewer note: Because of the different criteria used for collection and grading of adverse events, analysis of severity of adverse events was not performed on the ISS data.

Overall, analyses of data from the ISS database reveal a toxicity profile for ch14.18 that is similar to the toxicity profile observed in the treatment group of Study 301 (Table 48).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The clinical studies of ch14.18 and dinutuximab contributing the bulk of the safety data submitted to the BLA limited enrollment to patients with high-risk neuroblastoma who had adequate bone marrow, renal, hepatic, cardiac, and pulmonary function (See Section 5.3.1.2 of this review for details regarding the eligibility criteria for Study 301, which closely resemble the eligibility criteria for Studies 302, 303, and 201). There is a paucity of data to assess the safety of dinutuximab in patients who do not meet these criteria. However, the baseline characteristics required for eligibility in Studies 301, 302, 303, and 201 are appropriate given the risks associated with ch14.18 combination therapy, and product labeling will include recommendations that patients meet thresholds for baseline organ function prior to initiation of therapy and for assessment of organ function throughout dinutuximab treatment.

The safety database, including 1184 patients with neuroblastoma treated with ch14.18 or dinutuximab, contained adequate number of patients for consideration of approval for the treatment of patients with high-risk neuroblastoma, a life-threatening malignancy.

7.2.2 Explorations for Dose Response

An exposure/dose response relationship for efficacy and safety of dinutuximab cannot be characterized because there is insufficient pharmacokinetic data to correlate with efficacy and safety outcomes and due to the lack of incorporation of dose exploration in the major clinical studies submitted to the BLA.

Case report forms for Study 301 and 302 did not include records of each dose of study drug administered, nor did they include information on dose reductions or interruptions. As described in Section 7.3.3, 28% of patients in the ch14.18 combination therapy group and 23% of patients in the RA group prematurely discontinued study treatment in Study 301.

The case report forms for Study 303 recorded information for each dose of ch14.18 administered. The mean (SD) dose of ch14.18 was 24.7 mg/m^2 (11.2 mg/m^2). The median dose administered was 25 mg/m^2 (min: 0.06 mg/m^2, max: 250 mg/m^2). A total of 32 of 104 (31%) subjects received less than 90% of the planned dose of ch14.18 and 82 of 104 (78%) patients required at least one dose interruption.

Reviewer note: the Applicant indicates that the entry for 250 mg/m^2 was a data entry error.

7.2.3 Special Animal and/or In Vitro Testing

Dinutuximab has been shown to bind to neuroblastoma and melanoma cell lines that express GD2 and induce antibody dependent cell mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) *in vitro*. In the presence of human effector cells, including peripheral blood mononuclear cells (PBMC) and granulocytes from normal human donors, dinutuximab mediated the lysis of neuroblastoma cells in several cell lines in a dose-dependent manner. Granulocytes were found to be more effective than PBMCs in mediating dinutuximab-dependent cytotoxicity, and addition of GM-CSF caused enhanced cell lysis. In a xenograft mouse model, alone or in combination with IL-2, dinutuximab partially inhibited neuroblastoma growth.

Non-clinical studies demonstrated that dinutuximab-induced neurotoxicity is likely to be caused by the induction of mechanical allodynia that may be mediated by binding of dinutuximab with GD2 antigen on the surface of peripheral nerve fibers and/or myelin.

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of dinutuximab or to determine the potential effects on male and female fertility.

7.2.4 Routine Clinical Testing

Refer to Sections 7.4.2 (laboratory monitoring) and 7.3.3 (ECG) for discussions on the adequacy of hematologic, chemistry, and ECG monitoring in Studies 301, 302, and 303.

7.2.5 Metabolic, Clearance, and Interaction Workup

No pharmacokinetic drug interaction studies have been conducted with dinutuximab. The pharmacokinetics profile of dinutuximab was evaluated in children with neuroblastoma following single or repeat dose administration (dose range: 10–200 mg/m^2 up to 5 total courses). The pharmacokinetics are consistent with a two compartment model with a mean distribution half life ($t_{1/2\alpha}$) of 3.4 ± 3.1 hours (range: 0.3–9.5 hours) and a mean terminal elimination half life ($t_{1/2\beta}$) of 66.6 ± 27.4 hours. Mean peak serum levels ranged from 9.5–99.0 µg/ml (dose range: 10–200 mg/m^2) with peak concentrations found to correlate significantly with the total administered dose of dinutuximab ($r = 0.776$, $p < 0.001$). In this study, area under the curve (AUC) values were also found to correlate significantly with dinutuximab dose ($r = 0.815$; $p < 0.001$) with AUC values ranging from 49.0–11,628 µg*h/mL. Peak serum concentrations (C_{max}) were generally observed immediately following the end of the infusion.

Following single- or repeat-dose administration of dinutuximab in neuroblastoma patients (dose range: 10–200 mg/m^2) the volume of distribution (Vd) values were variable ranging from 0.8–164.9 L/m^2. The high variability of these values may be influenced by differences in tumor burden and location. Dinutuximab is a protein and

the expected metabolic pathway is degradation to small peptides and individual amino acids by ubiquitous proteolytic enzymes.

Reviewer note: The information above is adapted from the BLA review conducted by Dr. Jinyu Yu, of the Office of Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Dinutuximab, a disialoganglioside, GD-2 binding chimeric monoclonal antibody, is the first biologic in its pharmacologic class to undergo a review for licensure in the United States. There are no approved monoclonal antibodies that bind to the ganglioside GD2. Safety data submitted to this BLA include information regarding the potential for infusion reactions and hypersensitivity reactions, which are labeled risks for approved monoclonal antibodies directed against other antigens.

7.3 Major Safety Results

7.3.1 Deaths

Study DIV-NB-301

Overall survival, defined as the time of study enrollment until death or last patient contact, was the secondary efficacy endpoint for Study DIV-NB-301 (Study 301). After completion of 13-cis-retinoic acid (RA) therapy, all patients were evaluated every 3 months for the first year, then every six months for the next four years, then annually.

At the time of the primary safety analysis (June 30, 2009) 59 deaths had been reported, including 28 deaths in the investigational group (ch14.18 in combination with IL-2, GM-CSF and RA) and 31 deaths in the control group (RA only). Deaths were attributed to disease (90%), multisystem organ failure (5%), other causes (2%, including systemic inflammatory response syndrome due to IL-2 overdose in a patient receiving investigational treatment), or did not have a cause specified (3%).

A total of 5 of the 59 deaths occurred within 30 days of the last dose of investigational treatment: 4 patients in the ch14.18 group and 1 patient in the control group (Table 29).

Table 29: Patient Deaths Occurring within 30 days of Study Therapy – Study 301

Treatment Group	Patient ID	Age (years)	Date of Last Treatment	Date of Death	Cause of Death
RA	757739	2	(b) (6)	(b) (6)	Progressive Disease. Craniospinal leptomeningeal metastases detected (b) (6)
Ch14.18	716002	4	(b) (6)	(b) (6)	Capillary leak syndrome after

Treatment Group	Patient ID	Age (years)	Date of Last Treatment	Date of Death	Cause of Death
					receiving accidental overdose of IL-2 (339.6 IU). IL-2 dosage accidentally calculated in mcg/kg/day instead of mcg/m^2/day.
Ch14.18	719443	2	[redacted]	[redacted]	Disease relapse in adrenal gland, kidney, and pancreas on [redacted]. According to the case report form, patient was taken off protocol therapy that day. Death attributed to progressive disease. *Reviewer note: Database has incorrect date for the last treatment.*
Ch14.18	719992	2			Progressive Disease
Ch14.18	726179	2			Cerebellar relapse detected on [redacted]

According to the Applicant, a search of the COG database uncovered seven additional deaths, including three in the ch14.18 combination group (773124, 749114,719535) and four in the RA group (753264,746457,737090, and 714659). These deaths were included in analyses of EFS and OS, but were not recorded in the case report forms. All but one of these patients successfully completed study therapy; of those patients that completed study therapy, deaths occurred at least 7 months following completion of study therapy. Patient 773124 died [redacted] days after prematurely discontinuing ch14.18 therapy due to progressive disease (Table 30).

Table 30: Listing of Deaths Captured in the COG Database but not in Case Report Forms – Study 301

Treatment Group	Patient ID	Date of Last Treatment	Date of Death	Comment
Ch14.18	773124	[redacted]	[redacted]	Patient discontinued study treatment prematurely due to progressive disease.
Ch14.18	749114			Patient completed study therapy
Ch14.18	719535			Patient completed study therapy
RA	753264			Patient discontinued study treatment prematurely due to progressive disease

Treatment Group	Patient ID	Date of Last Treatment	Date of Death	Comment
RA	746457	(b) (6)		Patient completed study therapy
RA	737090			Patient completed study therapy
RA	714659			Patient completed study therapy

At the time of the follow-up safety analysis (June 30, 2012), of the 244 patients in the safety population, 82 deaths (33%) had been reported [43 of 106 (40%) in the RA group and 39 of 138 (28%) in the ch14.18 combination group]. These deaths were attributed to disease (90%), multi-organ failure (4%), other (2%), infection (1%), or were not given attribution (2%). The two deaths that were attributed to "other" causes were due to systemic inflammatory response syndrome associated with IL-2 overdose (patient 716002, described in Table 29), and airway compression secondary to disease progression (patient 776405).

Reviewer note: A search of the adverse event database for Study 301 uncovered the following two adverse events of Grade 5 severity. These grade 5 adverse events are previously described in Table 29, above.

- *Ch14.18 group:*
  - *Patient 716002 Preferred term: vascular leak (due to IL-2)*
  - *Patient 719443 Preferred term: death (attributed to progressive disease).*

Study DIV-NB-302

Overall survival, defined as the time of study enrollment until death or last patient contact, was a secondary endpoint for Study DIV-NB-302 (Study 302). After completion of 13-cis-retinoic acid (RA) therapy, patients were evaluated every 3 months for the first year, then every six months for the next four years, then annually.

At the time of data cutoff for the safety analysis (12/31/2013) 117 deaths had been reported. Deaths were attributed to disease in 109 patients (93%), other causes in 6 patients (5%), multisystem organ failure in 1 patient (1%), and infection in 1 patient (1%). Of the patients who died due to causes specified as "other", three patients died after suffering an intracranial hemorrhage (patients 799146, 809655, and 803243), and one patient each died due to pulmonary hemorrhage (patient 784907), cardiopulmonary arrest attributed to metastatic neuroblastoma (patient 788820), and respiratory failure attributed to progressive neuroblastoma (patient 819205).

A total of 9 of the 117 reported deaths occurred within 30 days of the last dose of investigational treatment in Study 302 (Table 31).

Table 31: Patient Deaths Occurring Within 30 days of Study Therapy - Study 302.

Patient ID	Age (years)	Date of Last Treatment	Date of Death	Cause of Death
784907	4		(b) (6)	Pulmonary hemorrhage during Course 3. Event occurred in the setting of non-neutropenic gram negative sepsis, pneumonia, Grade 4 thrombocytopenia (was thrombocytopenic at baseline), Grade 4 anemia, Grade 3 hyponatremia, and Grade 3 ALT and Grade 2 AST elevation.
803243	4			CNS hemorrhage that occurred (b) (6) days following initiation of GM-CSF (on (b) (6)). Patient was admitted to the hospital on (b) (6) with a platelet count of 2,000/mcl, and her platelet count remained in the 0-2000/µl from (b) (6) despite treatment with IVIG, IV steroids and 15U of platelets. Workup including antibodies toward Class1 or Class 2 HLA antigens and ADAMTS13 was negative. *Reviewer note: This patient did not receive ch14.18.*
814082	5			Cardiac arrest occurring less than one day after receiving the first two of four scheduled doses of ch14.18 during Course 1. Patient was resuscitated and appropriate support including antibiotics for a potential occult infection but developed acute capillary leak syndrome, and multiple comorbidities including disseminated intravascular coagulation, pleural and pericardial effusions, metabolic acidosis, and cardiac failure and died after suffering multiple additional cardiac arrests. Patient had received 300 mg/m^2 doxorubicin prior to study entry.
815361	4			Death occurred secondary to worsening pneumonia causing

Patient ID	Age (years)	Date of Last Treatment	Date of Death	Cause of Death
				secondary cardiac and renal failure, approximately (b) (6) days following most recent administration of ch14.18 and (b) (6) days following administration of IL-2. Prior to admission on (b) (6), patient had previous incidental finding of pneumonia but was clinically well appearing. Respiratory symptoms worsened following administration of IL-2 on (b) (6). Patient was also lymphopenic.
810008	3	(b) (6)		Progressive disease (b) (6) days after completing course 5. *Reviewer note: case report form indicates that relapse was detected in the brain on* (b) (6).
811199	2			Patient 's death, attributed to progressive disease, occurred (b) (6) days after completing the last dose of RA during Course 2 of therapy ((b) (6) days after the last dose of ch14.18). *Reviewer note: case report form indicates that diffuse relapse was detected* (b) (6).
814271	1			Patient 's death, attributed to progressive disease, occurred (b) (6) days after the last dose of ch14.18 and (b) (6) days after discontinuing study therapy due to PD during Course 2. The patient had an event of capillary leak syndrome which started (b) (6) days prior to death, which resolved. Chemotherapy for relapsed disease initiated on (b) (6) and patient was transferred to hospice on (b) (6).
824181	UNK			Patient died of a cardiac arrest due to increased intracranial pressure secondary to multiple brain metastases(b) (6) days after completing the last dose of

Patient ID	Age (years)	Date of Last Treatment	Date of Death	Cause of Death
				ch14.18 in Cycle 3. Case report form indicates that on (b) (6) CT of the brain was performed to investigate new onset hypertension. This CT showed multiple hyperdense lesions throughout the cerebellum and cerebral hemispheres consistent with metastatic neuroblastoma. Patient discontinued study treatment and received palliative *care prior to death.*
834954	UNK	(b) (6)		Patient discontinued study treatment prematurely due to progressive disease. Right kidney relapse detected via abdominal ultrasound on (b) (6).

Reviewer note: A search of the adverse event database for Study 302 did not uncover any Grade 4 adverse events that are not described in the table above.

Study DIV-NB-303

As of March 31, 2012, two patients had died during the treatment phase of the study. One patient's (793150) death was attributed to hypoxia secondary to progressive disease, approximately (b) (6) days after discontinuing study therapy. This patient discontinued study therapy on (b) (6) after a lung biopsy was positive for relapsed neuroblastoma. Another patient (797565, 6 years of age) died due to cardiac arrest/sudden death after completing the first course of ch14.18/GM-CSF/RA, approximately (b) (6) days after receiving the last dose of GM-CSF, (b) (6) days following administration of the last dose of ch14.18, and (b) (6) days following the last dose of RA. This six year old boy reportedly tolerated the first cycle of treatment without difficulty, but initiation of the second cycle was delayed due to logistical reasons.

Reviewer note: A search of the adverse event database for Study 302 did not uncover any Grade 4 adverse events that are not described in the table above.

Study 201

As of 2/5/2014, all patients enrolled in Study 201 were alive.

Reviewer Conclusions Regarding Deaths in Studies 301, 302, and 301

Deaths within 30 days of ch14.18 were relatively infrequent in light of the severity of the underlying disease and comorbidities of patients enrolled in these studies. The majority

of deaths that occurred within 30 days of receipt of ch14.18 combination treatment (9/15 or 60%) were attributed to progressive disease, and it appears that attribution of deaths to progressive disease were unbiased and accurate. Of the deaths unrelated to disease progression, one death was due to inadvertent IL-2 overdose, and the remaining deaths appeared to be multifactorial in nature and confounded by multiple factors, including concomitant use of GM-CSF or IL-2, prior cytotoxic and myeloablative treatment, and underlying neuroblastoma. There were two deaths related to cardiac arrest: in the first case (Patient 814082), the patient died of cardiac arrest less than 24 hours following the first infusion of ch14.18. This case is potentially compatible with a severe infusion reaction or anaphylaxis, but there are insufficient details regarding the case to conclusively identify the cause of this patient's cardiac arrest. The second case of cardiac arrest (Patient 797565) is not compatible with an infusion reaction or anaphylaxis due to the long latency period from the patient's last treatment but there are insufficient details provided to enable a determination of causality.

7.3.2 Nonfatal Serious Adverse Events

Table 32 provides a summary of the per-patient incidence of serious adverse events for Study 301 reported through 9/30/2012. Serious adverse events were reported through AdEERs for a total of four (4%) patients who received RA (Patients 738592, 747942, 778479, and 779065) and 70 (51%) patients in the ch14.18 combination group. Reported serious adverse events for patients in the RA group were nausea, vomiting, catheter related infection, and eye disorders – other.

Reviewer note: Comparisons of the per-patient incidences of serious adverse events occurring in the ch14.18 combination group with the RA group are not meaningful due to the differences in AdEERS reporting requirements between the treatment groups.

Table 32: Summary of Serious Adverse Events Experienced by at Least Two Patients and Reported Through AdEERS for Study 301

CTCAE reported term	Ch14.18 combination N=138*		RA N=106	
	n	%	n	%
Any AdEERS reportable serious adverse event	**70**	**51**	**4**	**4**
Infections and infestations - other, specify	17	12%	0	0%
Hypokalemia	11	8%	0	0%
Hypotension	11	8%	0	0%
Anaphylaxis	9	7%	0	0%
Capillary leak syndrome	9	7%	0	0%
Catheter related infection	10	7%	2	2%
Fever	9	7%	0	0%

CTCAE reported term	Ch14.18 combination N=138*		RA N=106	
	n	%	n	%
Hypercalcemia	5	4%	0	0%
Pain	5	4%	0	0%
Abdominal pain	4	3%	0	0%
Diarrhea	4	3%	0	0%
Hypoalbuminemia	4	3%	0	0%
Hypocalcemia	4	3%	0	0%
Hypoxia	4	3%	0	0%
Lymphocyte count decreased	4	3%	0	0%
Arthralgia	3	2%	0	0%
General disorders and administration site conditions - other, specify	3	2%	0	0%
Pain in extremity	3	2%	0	0%
Respiratory, thoracic and mediastinal disorders - other, specify	3	2%	0	0%
Acute kidney injury	2	1%	0	0%
Alanine aminotransferase increased	2	1%	0	0%
Allergic reaction	2	1%	0	0%
Anemia	2	1%	0	0%
Anorexia	2	1%	0	0%
Aspartate aminotransferase increased	2	1%	0	0%
Bone pain	2	1%	0	0%
Cardiac disorders - other, specify	2	1%	0	0%
Creatinine increased	2	1%	0	0%
Cytokine release syndrome	2	1%	0	0%
Edema face	2	1%	0	0%
Myalgia	2	1%	0	0%
Neuralgia	2	1%	0	0%
Platelet count decreased	2	1%	0	0%
Rash maculo-papular	2	1%	0	0%
Sinus tachycardia	2	1%	0	0%
Urticaria	2	1%	0	0%

*includes Stratum 7 patients and four crossover patients originally randomized to receive RA.
Data cutoff date: September 30, 2012.

Overall, the most commonly reported serious adverse events by CTCAE term in the ch14.18 combination group included infections and infestations – other (12%),

hypokalemia (8%), hypotension (8%), anaphylaxis (7%), fever (7%), catheter-related infection (7%), and capillary leak syndrome (7%).

Reviewer note: In clinical study report in the original BLA submission, the Applicant indicated that serious adverse events were reported using MedDRA coded preferred terms. Upon review, it appeared that many of the terms included in the preferred term field in the serious adverse event datasets were not consistent with MedDRA preferred terms. The Applicant confirmed that the datasets and serious adverse event reporting in the clinical study reports for Study 301, 302, and 303 used CTCAE v. 4 terms, and not MedDRA preferred terms. Verbatim terms for serious adverse events were not included. Therefore, the clinical team was unable to perform an analysis of serious adverse events across the MedDRA hierarchy.

Integrated Summary of Safety

The analyses of serious adverse events integrated summary of safety (ISS) comprised data reported through AdEERS for Studies 301, 302, and 303, and from the Applicant's database for Study 201. Study 201 employed the standard definition of serious adverse events, which includes adverse events that caused a life-threatening adverse event or had any of the following outcomes: death; inpatient hospitalization; prolongation of existing hospitalization; persistent or significant disability or incapacity; or congenital anomaly or birth defect.

In all four studies, ch14.18 was administered using the same dose and schedule, and in combination with GM-CSF, IL-2, and RA. Serious adverse event data from Studies CCG-0935A and POG-9347 were not included in the ISS database. There were no serious adverse events reported for Study CCG-0935, and serious adverse events from Studies CCG-0935A and POG-9347 were not included due to poor data accessibility.

Table 33 provides a summary of the per-patient incidence (PPI) of serious adverse events reported for Study 301 in comparison to the PPI of serious adverse events in the ISS (PPI ≥ 2%). A total of 651 of 1079 (60%) of patients exposed to ch14.18 combination therapy in the integrated summary of safety experienced at least one serious adverse event. The most commonly reported serious adverse events in patients receiving ch14.18 combination therapy in the ISS were hypotension (16%), fever (13%), capillary leak syndrome (11%), infections and infestations (11%), catheter-related infections (9%), anaphylaxis (9%), and hypokalemia (8%).

Overall, the adverse reaction profile in the ISS was similar to the adverse reaction profile observed in Study 301. Hypotension, capillary leak syndrome, and allergic reaction were reported more frequently in the ISS group compared to patients treated in Study 301 (absolute increase in PPI of at least 5%).

Table 33: Per-Patient Incidence of Serious Adverse Events in Study 301 and in the Integrated Summary of Safety[a]

CTCAE Term	Study 301 N=141[b]		ISS N=1079	
	n	%	n	%
Hypotension	13	9%	168	16%
Fever	10	7%	137	13%
Infections and infestations - other, specify	17	12%	120	11%
Capillary leak syndrome	9	6%	118	11%
Catheter related infection	10	7%	102	9%
Anaphylaxis	11	8%	101	9%
Hypokalemia	11	8%	88	8%
Allergic reaction	2	1%	73	7%
Anemia	3	2%	68	6%
Hyponatremia	1	1%	67	6%
Hypoxia	4	3%	66	6%
Neutrophil count decreased	2	1%	60	6%
Lymphocyte count decreased	5	4%	59	5%
Hypocalcemia	5	4%	48	4%
Urticaria	3	2%	48	4%
Pain	5	4%	44	4%
Diarrhea	4	3%	42	4%
Hypophosphatemia	1	1%	41	4%
Alanine aminotransferase increased	2	1%	39	4%
Platelet count decreased	2	1%	39	4%
White blood cell decreased	1	1%	37	3%
Abdominal pain	4	3%	35	3%
Aspartate aminotransferase increased	2	1%	31	3%
Bronchospasm	1	1%	31	3%
Pain in extremity	3	2%	29	3%
Hypoalbuminemia	6	4%	25	2%
Dyspnea	1	1%	24	2%
Lung infection	1	1%	23	2%
Sepsis	1	1%	23	2%
GGT increased	1	1%	22	2%
Hypercalcemia	5	4%	22	2%
Anorexia	2	1%	20	2%

CTCAE Term	Study 301 N=141[b]		ISS N=1079	
	n	%	n	%
Vomiting	1	1%	20	2%
Dehydration	1	1%	19	2%
Edema face	2	1%	17	2%
Sinus tachycardia	2	1%	17	2%

[a]Reflects data included in the 120-day safety update, with finalized safety data from Study 301, data as of 3/31/2014 for Study 302, data as of 9/30/2012 for Study 303, data as of 5/23/2014 for Study 201.
[b] Safety population includes 134 patients originally included in the safety population in the June 2009 safety analysis+ four crossover patients+ one subject who was randomized prior to June 2009 but had data entered after June 2009 + two subjects enrolled in Stratum 7 who were enrolled prior to January 2009 but had data entered after June 2009.

7.3.3 Dropouts and/or Discontinuations

A higher percentage of patients prematurely discontinued study therapy in the ch14.18 combination therapy group (37 of 134, or 28%), compared to the RA group (24 of 106, or 23%). Table 34 summarizes the reasons for premature discontinuation of therapy reported for Study 301.

Table 34: Status of Completion of Study Therapy in Study 301

	Ch14.18 N=134[a] n (%)	RA N = 106[b] n (%)	Total N = 240 n (%)
Total Completing Therapy	**97 (72)**	**82 (77)**	**179 (75)**
Total number of premature study therapy discontinuations	**37 (28)**	**24 (23)**	**61 (25)**
Withdrew consent	10 (7)	6 (6)	16 (7)
Progressive disease	12 (9)	18 (17)	30 (13)
Toxicity	6 (4)	0 (0)	6 (2)
Unknown/Other	6 (4)	0 (0)	6 (3)
Steroid use	2 (1)	0 (0)	2 (1)
Death	1 (1)	0 (0)	1 (0)

[a] Includes 113 randomized and 25 Stratum 7 patients who received ch14.18 in Study 301
[b] Two patients were excluded from the safety population because no data was recorded in the CRF at the time of the analysis to confirm study drug exposure.

According to the Study 301 case report forms, adverse events were the primary reason for premature discontinuation of study therapy for six patients (714358, 730211, 748582, 752993, and 776003, and 776291). Patient 714358 discontinued study therapy after experiencing Grade 3 fatigue and rash/desquamation following receipt of a dose of IL-2 that was 10 times more than he should have received. Case report forms did not specify which adverse event(s) prompted study therapy discontinuation. Table 35

provides a summary of adverse events occurring close to the time of discontinuation of study therapy for these patients, based upon review of the adverse event database and AdEERS database and narratives submitted to the BLA. Based upon review of the adverse events that occurred prior to study therapy discontinuation, it appears that hypersensitivity reactions or capillary leak syndrome were the primary causes of premature therapy discontinuation for Patients 730211, 748582,776003, 776291. Pain appears to be the primary reason for study discontinuation for Patient 752993.

Table 35: Summary of Adverse Events Experienced Prior to Premature Study Therapy Discontinuation for Study 301 Patients Listed As Discontinuing Therapy Due to Toxicity

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment	Adverse Events
714358	1		(b) (6)	Experienced Grade 3 fatigue and rash/desquamation following overdose of IL-2 during the first cycle of treatment.
730211	5			Patient had Grade 3 drug hypersensitivity, Grade 2 pyrexia, and Grade 1 hyponatremia within one month of the last treatment. The Grade 3 hypersensitivity was reported as a Grade 3 allergic reaction with systemic manifestations and as a serious adverse event through AdEERS. The AdEERS report indicates that he was removed from protocol treatment on (b) (6) , (b) (6) days after this serious adverse event.
748582	5			This patient developed Grade 3 lymphopenia, fluid overload and hypotension within one week of discontinuation of study therapy.
752993	4			Within (b) (6) days of discontinuing study treatment, this patient developed Grade 4 abdominal pain, Grade 4 pain, Grade 2 fluid overload, Grade 3 lymphopenia, Grade 3 pyrexia, and Grade 3 thrombocytopenia. According to the AdEERS report, the adverse events of abdominal pain and joint

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment	Adverse Events
				pain occurred 90 minutes following initiation of the infusion. Pain ultimately resolved within approximately (b) (6) days thereafter.
776003	5	(b) (6)		According to the AdEERS report, this patient developed a Grade 4 allergic reaction/hypersensitivity (including drug fever) with associated Grade 3 hypoxia, Grade 2 hypotension, Grade 2 cytokine release syndrome during Course 4 (IL-2 and ch14.18) approximately 7 hours after initiation of IL-2 and ch14.18. infusion. According to AdEERS, the patient discontinued study therapy on (b) (6) although the disposition database indicates the last day of treatment was (b) (6)
776291	2			This patient developed Grade 4 hypersensitivity and Grade 3 capillary leak syndrome on (b) (6), respectively. Reviewer note: AdEERS report lists treatment discontinuation date as (b) (6).

Table 36 provides a summary of the reported treatment dates and adverse events occurring close to the time of discontinuation of study therapy for patients for whom the reason for premature treatment discontinuation was either missing or was listed as due to “corticosteroid use” or “withdrawal by subject”. The information in this table includes information gleaned from the adverse event database, case report forms, AdEERS database, and AdEERS narratives submitted to the BLA. As reflected by the shaded entries in Table 36, the majority of patients experienced severe or serious adverse events that had a close temporal relationship to the timing of therapy discontinuation. Based upon this analysis, it appears that adverse events were the reason for premature discontinuation of study therapy for most patients, despite the fact that the reasons for premature discontinued were not categorized as being due to toxicity.

Table 36: Adverse Events Prior to Premature Study Therapy Discontinuation for Study 301 Patients With Reported Reasons for Study Therapy Discontinuation Other Than Toxicity, Progressive Disease, or Death

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
Patients with missing reason for premature treatment discontinuation				
772362	15	(b) (6)		On (b) (6) initiated IL-2 and ch14.18 infusion during Cycle 2. Approximately 24 hours later, developed Grade 3 increase in cardiac troponin and N-terminal BNP, hypotension, supraventricular and nodal arrhythmia, sinus tachycardia, left ventricular systolic dysfunction requiring PICU support. Events resolved.
777143	2			Patient developed Grade 2 urticarial rash thought to be related to study therapy on (b) (6) (Cycle 4).
777199	1			Patient developed Grade 3 systemic infection on (b) (6)
777889	4			Patient developed Grade 4 acute capillary leak syndrome on (b) (6) during Cycle 4.
777915	3			During Cycle 2 also had Grade 3 angioedema and mild rash during ch14.18/IL-2 infusion.
777945	5			Grade 3 ALT and AST elevation occurred during Cycle 5, approximately (b) (6) days before the end of therapy.
Patients with "corticosteroid use" listed as the reason for premature treatment discontinuation				
726343	10	(b) (6)		Patient had Grade 3 drug hypersensitivity with dyspnea, shortness of on (b) (6). According to CRF, protocol therapy was discontinued (b) (6).
775732	2			Grade 2 capillary leak syndrome, pain and pyrexia during cycle 3 at around the time of study therapy discontinuation. According to CRF, taken off protocol therapy on (b) (6).
Patients with "withdrawal by subject" listed as the reason for premature treatment discontinuation				
739073	5	(b) (6)		Patient developed Grade 4 hypercalcemia requiring PICU treatment on (b) (6), following Cycle 1 of treatment; also developed staphylococcal bacteremia on (b) (6)
743324	1			Patient developed multiple adverse events, including Grade 3 hypotension and Grade 1 pyrexia, edema, rash, and sinus tachycardia a

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
				few days prior to discontinuing study treatment.
745400	13	(b) (6)		Patient developed Grade 4 abdominal, musculoskeletal, and neck pain on (b) (6). According to CRF, patient was taken off protocol therapy on (b) (6).
760361	3			This patient had multiple adverse events, including Grade 4 anemia, Grade 4 thrombocytopenia ((b) (6)), Grade 3 esophagitis, osteomyelitis, vomiting and fatigue (b) (6).
760611	2			On Day (b) (6) of Cycle 2 ((b) (6)), patient had fevers and rigors requiring Demerol, and "bright red skin with purple extremities" during IL-2 infusion. Removed from protocol therapy on (b) (6) according to ADEERs report.
767692	3			According to ADEERS report, patient was removed from protocol therapy on (b) (6) after experiencing Grade 3 acute vascular leak syndrome, grade 4 lymphopenia, grade 4 hypokalemia, and Grade 3 pain during the first cycle of treatment. According to CRF, the patient was taken off protocol therapy on (b) (6).
772319	3			Patient developed Grade 3 peripheral neuropathy on (b) (6). According to CRF, the patient was off protocol therapy on (b) (6).
772720	3			Patient developed Grade 3 drug hypersensitivity on (b) (6) during Cycle 3. According to CRF, the patient was taken off protocol therapy on (b) (6)
775478	2	(b) (6)		Patient developed Grade 3 ALT elevation, Grade 2 drug hypersensitivity, Grade 3 hyponatremia on (b) (6). According to CRF, off protocol therapy on (b) (6).
783619	3			Patient developed Grade 3 sepsis on , the same day that the patient was taken off protocol therapy according to the CRF.

* Using data from the subject level database, the date of last treatment corresponds to the anticipated last date of the cycle in the case report forms. However, the case report forms and AdEERS reports provided more accurate information regarding the date the patient was off protocol therapy in many cases, as noted in the table.

Study 302 Premature Discontinuation from Study therapy

As of December 31, 2013, a total of 783 subjects were reported to have received at least one dose of study therapy in Study 302 (Table 37).

Table 37: Status of Completion of Study Therapy for Study 302*

Therapy Status	Ch14.18 N=783 n (%)
Completed therapy	**578 (74)**
Therapy Ongoing	**68 (9)**
Prematurely Discontinued	**137 (17)**
Progressive disease	62 (8)
Withdrew consent	30 (4)
Physician decision	22 (3)
Toxicity	15 (2)
Death	4 (<1)
Lost to follow-up	2 (<1)
Use of other anticancer therapy	1 (<1)
Enrollment into another study	1(<1)

*Reflects patients who received at least one dose of study therapy as of December 31, 2013

Of the 783 patients who received at least one dose of ch14.18 combination therapy at the time of the analysis, a total of 578 patients (74%) were reported to have completed study therapy, and 137 patients (17%) prematurely discontinued study therapy. Fifteen patients (2%) were reported to have discontinued study therapy due to toxicity. However, as reflected by the shaded entries in Table 38, it is likely that the majority of patients who discontinued study therapy for reasons listed as "physician decision" or "withdrawal by subject" discontinued study therapy due to adverse events.

Table 38: Summary of Adverse Events Experienced Prior to Premature Study Therapy for Study 302 Patients Reported to Have Discontinued Due to Consent Withdrawal or Physician Decision

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
Withdrew Consent				
782956	5	(b) (6)		AdEERs report indicates that the patient developed Grade 3 fevers on (b) (6) during course 2, day (b) (6) of IL2 and ch14.18. The patient's family opted to discontinue study therapy the next day ((b) (6))
788195	6			According to AdEERs report, Presented to the

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
				emergency room with bilateral dilated and sluggish pupils, papilledema, reduced visual acuity, normal MRI on (b) (6). Received last Cycle 4 dose of IL-2 and ch14.18 on (b) (6). Considered Grade 3 CNII palsy. Accompanied by sensory neuropathy with loss of deep tendon reflexes (Grade 1).
791107	4		(b) (6)	Grade 3 acute vascular leak and fever on (b) (6)
795371	7			According to AdEERs report, parents decided to remove patient from protocol therapy on (b) (6) after occurrence of Grade 3 infection and allergic reaction during Cycle 4 of therapy.
796176	3			Grade 3 anemia and Grade 3 hypersensitivity reaction occurred on (b) (6) and (b) (6), respectively. Parents decided to discontinue therapy on (b) (6) according to the CRF.
796919	3			According to AdEERs report, removed from protocol therapy on (b) (6) following occurrence of Grade 4 acute vascular leak syndrome, pleural effusion, hypokalemia, cardiopulmonary arrest, hypotension during Cycle 4 of therapy.
797863	4			Patient experienced Grade 3 pain starting on (b) (6) (Cycle 1). According to CRF, study therapy was discontinued on (b) (6).
799795	3			According to AdEERS report, experienced Grade 3 pain unresponsive to morphine and gabapentin, falling oxygen saturation, decreased urine output the day of first ch14.18 infusion ((b) (6)). Patient recovered 3 days later. According to CRF, parents decided to discontinue study treatment on (b) (6).
800586	3			Grade 2 hypersensitivity reaction during Cycle 1 on (b) (6)
801399	3			According to AdEERs report, on (b) (6), developed Grade 3 capillary leak syndrome and Grade 4 anaphylaxis during second ch14.18 infusion of Cycle 2
805329	3		(b) (6)	According to AdEERs report, the patient's father decided not to continue study therapy after the patient developed a Grade 4 allergic reaction with hypotension on the first day of the ch14.18 infusion.

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
806595	2		(b) (6)	According to AdEERs, Patient experienced hypotension after each of two doses of GM-CSF on (b) (6) and (b) (6). Removed from protocol treatment on 11/14/2010.
811223	1			Patient experienced Grade 3 pain on (b) (6) during Cycle 3.
811259	2			According to AdEERS, parent decided to remove patient from protocol therapy on (b) (6) due to adverse events that occurred during Cycle 1 and Cycle 2 of therapy (Grade 3 gastritis and fever)
814152	4			Grade 3 apnea and allergic reaction occurring on (b) (6) during the first ch14.18 infusion.
816907				Patient had Grade 3 urinary tract infection on 12/3/2012 and again on (b) (6)
819868				According to AdEERS, family decided not to continue treatment following recurrent episodes of hypotension during ch14.18 infusion requiring pressors (Cycle 1).
820388				According to AdEERS report, family decided to discontinue study treatment on (b) (6) after occurrence of Grade 3 hypotension, stridor, neuralgia; and Grade 2 tachypnea requiring PICU support following initiation of first ch14.18 infusion.
825100				According to AdEERS, IL-2 and ch14.18 were withdrawn following adverse events of Grade 3 capillary leak syndrome and hypotension. Patient also had sluggish pupils and Grade 3 decrease in consciousness.
834631				Patient had Grade 3 pain on (b) (6) during Cycle 3.
Physician Decision				
788808	4		(b) (6)	According to AdEERS, on (b) (6) (Course 1, Day (b) (6)), admitted to hospital in hypertensive crisis (Grade 4 hypertension) and RA was discontinued.
789648	6			Protocol therapy discontinued by physician after patient required hospitalization for Grade 3 renal insufficiency, Grade 4 hypoxia, Grade 3 encephalopathy, Grade 3 seizures, Grade 3 hyperkalemia, Grade 3 hypertension
789885	2			Patient had Grade 3 Escherichia bacteremia in (b) (6).
791085	2			This patient had multiple adverse events during the cycle of therapy leading up to therapy discontinuation, including Grade 4 acute

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
				respiratory distress syndrome, Grade 4 Dyspnea, Grade 4 hypoxia, Grade 4 respiratory acidosis, Grade 4 diarrhea and vomiting, Grade 3 left ventricular dysfunction, Grade 4 hyperglycemia, Grade 3 transaminase elevation.
791436	3		(b) (6)	Patient had Grade 2 aphasia, Grade 3 muscular weakness, Grade 3 staphylococcal bacteremia, respiratory syncytial virus infection, and enterocolitis the month of therapy discontinuation. According to AdEERS, patient had absent deep tendon reflexes in the lower extremities and that the patient's physician removed him from study therapy due to the toxicities.
802702	8			According to AdEERS report, patient discontinued study treatment due to Grade 2 rash/desquamation considered probably related to ch14.18, and possibly related to RA or IL-2.
802927	2			This patient had multiple adverse event in late (b) (6), including Grade 3 capillary leak syndrome, Grade 4 pain, Grade 3 diarrhea and ileus, Grade 3 fever, and Grade 3 creatinine elevation requiring prolonged hospitalization.
808269	10			Patient had Grade 3 anaphylaxis during IL-2 and ch14.18 infusion on (b) (6)
808880	2			AdEERS report describes Grade 4 capillary leak syndrome, Grade 3, hypotension, Grade 4 acute kidney injury, Grade 4 acidosis, Grade 4 DIC, and Grade 3 hyperbilirubinemia and AST elevation occurring mid (b) (6). IL-2 and ch14.18 discontinued (b) (6) and (b) (6), respectively.
811309	7			Patient had Grade 4 acute respiratory distress syndrome, dyspnea, and hypotension, and Grade 2 capillary leak syndrome beginning on (b) (6).
813168	1			Developed Grade 4 capillary leak syndrome, pulmonary edema, cytokine release syndrome, allergic reaction during the first ch14.18 infusion. AdEERS report states that study therapy was withdrawn due to these toxicities.
813913	3		(b) (6)	Patient developed Grade 4 capillary leak syndrome one day following last receipt of ch14.18 and the day of receipt of GM-CSF. Adverse event resolved on (b) (6) but AdEERS report indicates that patient was taken off protocol therapy due to this adverse event.

Patient ID	Age (years)	Treatment Start Date	Date of Last Treatment*	Adverse Events
816142	3		(b) (6)	Patient experienced multiple adverse events between (b) (6) (Grade 3 decreased appetite, anemia, hyperglycemia, and hypoxia, Grade 4 thrombocytopenia, Grade 2 dyspnea).
823127	UNK			According to AdEERs report, patient developed Grade 3 anaphylaxis during the (b) (6) day of the Cycle 3 ch14.18 infusion, and the decision was made to discontinue ch14.18 on (b) (6) due to the severity of the reaction.
824138	UNK			According to AdEERS, removed from protocol therapy because treatment was on hold since (b) (6) due to Grade 3 ileus, Grade 4 hypokalemia, Grade 3 hyponatremia, Grade 4 sepsis during Cycle 2.
824745	UNK			According to AdEERS report, removed from protocol therapy prior to start of Cycle 3 due to "intolerable neuropathic pain" in hands and feet. The report indicated that pain appeared to be improving but had not resolved at the time of submission of report (approximately one week later).
826853	UNK			Patient developed a Grade 4 lung infection requiring pediatric intensive care unit (PICU) support on (b) (6).
829861	UNK			Patient experienced multiple adverse events during the first cycle of treatment, including capillary leak syndrome, cytokine release syndrome, increased GGT, and increase bilirubin.

7.3.4 Significant Adverse Events

The ICH E3 guidance recommends that marked laboratory abnormalities not meeting the definition of serious adverse events also be considered significant adverse events. These laboratory abnormalities are described in Section 7.4.2 of this review.

In addition, the ICH E3 guidance considers other potentially important abnormalities, such as severe adverse events (i.e., ≥ Grade 3 by CTCAE), that do not meet the definition of a severe adverse event potentially significant. A discussion of severe adverse events is included in Section 7.4.1 of this review.

7.3.5 Submission Specific Primary Safety Concerns

During the conduct of Study 301, the Children's Oncology Group considered the following toxicities, designated as "targeted toxicities", to be of special interest: allergic

reaction/hypersensitivity (also termed allergic reaction and anaphylaxis after October 1, 2011 with adoption of CTCAE v.4.0), hypotension, urticaria, adult respiratory distress syndrome (ARDS), dyspnea, cytokine release syndrome/acute infusion reaction, acute vascular leak syndrome (also known as capillary leak syndrome with adoption of CTCAE v.4.0), and peripheral neuropathy.

In Study 301, 120 (89%) patients in the ch14.18 combination therapy group had at least one of these targeted toxicities, compared to 21 (20%) in the RA group.

- One patient in the RA group had Grade 3 acute respiratory distress syndrome (compared to no patients in the ch14.18 combination group)
- Capillary leak syndrome of any severity was reported in 53 (40%) patients in the ch14.18 combination therapy group, compared to 1 (1%) patients in the RA group. A total of 31 (23%) of patients in the ch14.18 combination therapy group had at least one episode of severe capillary leak syndrome.
- 80 (60%) of patients in the ch14.18 combination therapy group had at least one episode of hypotension of any grade; 16% of these cases were severe. A total of 3 (3%) patients in the RA group had hypotension (all of mild severity).
- A total of 81 (60%) of patients in the ch14.18 combination therapy group had at least one episode of “drug hypersensitivity”); 26% of these events were severe. Drug hypersensitivity was reported in 9 (8%) patients in the RA group (1 case was severe).
- Urticaria was reported in 49 (37%) of patients in the ch14.18 combination group (with 13% of patients having severe urticaria), compared to 3 (3%) patients in the RA group.
- Cytokine release syndrome occurred in 3 (2%) patients in the ch14.18 group, compared to no patients in the RA group. One of the cases of cytokine release syndrome was considered severe.
- Dyspnea occurred in 6 (4%) of patients in the ch14.18 group, compared to 1% of patients in the RA group. 2% of cases of dyspnea experienced by patients treated with ch14.18 were severe.
- Peripheral neuropathy occurred in 18 (13%) patients in the ch14.18 combination group, compared to 6 (6%) patients in the control group. 4 (3%) patients in the ch14.18 group had severe peripheral neuropathy. Neuralgia occurred in 15 (12%) patients in the ch14.18 combination group compared to no patients in the RA group.

  Reviewer note: because dates of resolution of adverse events were not captured in the Study 301 database, reversibility of these adverse events cannot be confirmed. However, the Applicant provided an analysis of treatment-emergent peripheral neuropathy reported in Study 303 and 201. According to the

Applicant, there were 15 cases of peripheral neuropathy reported in these studies. Of these 15 cases, 14 resolved, and the remaining case had a duration of approximately 5 days at the time of data cutoff. The median duration of the events that resolved was 10 days (minimum: 4 days, and maximum: 164 days).

Pain-related adverse events are also a safety concern related to ch14.18 therapy. A search of the Study 301 adverse event database was conducted for adverse events with the following preferred terms: abdominal pain, abdominal pain upper, arthralgia, back pain, bladder pain, bone pain, chest pain, facial pain, gingival pain, musculoskeletal chest pain, myalgia, neck pain, neuralgia, oropharyngeal pain, pain, pain in extremity, and proctalgia. Despite premedication analgesics including morphine, pain of any severity occurred in the majority (84%) of patients treated with ch14.18, compared to 16% of patients in the RA group. This search uncovered a total of 68 (51%) patients who experienced pain of Grade 3 severity or greater in the ch14.18 combination arm, compared to 5 patients (5%) in the RA arm.

Reviewer note: because dates of resolution of adverse events were not captured in the Study 301 database, reversibility of these adverse events cannot be confirmed. However, the Applicant provided an analysis of treatment-emergent pain-related adverse events reported in Study 303 and 201. According to the Applicant, there were 1752 treatment-emergent pain-related adverse events reported in these studies; the median duration (min,max) of pain was 1 day (1, 85), and there were 26 ongoing events at the time of data cutoff.

Neurologic disorders of the eye are also a safety concern related to ch14.18 therapy. A search of the Study 301 adverse event database was conducted for adverse events with the following preferred terms: mydriasis, myopia, optic nerve disorder, papilledema, photophobia, photopsia, photosensitivity reaction, fixed pupils, pupillary reflex impaired, pupils unequal, strabismus, blindness vision blurred, visual acuity reduced, and visual impairment. This search uncovered a total of 7 (5%) patients in the ch14.18 combination therapy group who experienced at least one of these adverse events, compared to 3 (3%) patients in the RA group (notably, one patient in the RA group experienced blindness that was considered unrelated to RA). All of the neurologic disorders of the eye experienced by patients in the ch14.18 group were mild.

Reviewer note: because dates of resolution of adverse events were not captured in the Study 301 database, reversibility of neurologic disorders of the eye cannot be confirmed. However, the Applicant provided an analysis of treatment-emergent pain-related adverse events reported in Study 303 and 201. According to the Applicant, there were 27 treatment-emergent neurologic disorders of the eye reported in these studies; the median duration (min,max) was 7 days (1, 222), and there were 7 ongoing events at the time of data cutoff.

Infections, including bacteremia and sepsis, occurred in patients in both treatment groups in Study 301. A search of the Study 301 adverse event database was conducted for adverse events with preferred terms of sepsis or bacteremia. This search uncovered a total of 33 (25%) of patients in the ch14.18 combination group and 13 (12%) of patients in the RA group. Sepsis occurred in 18% of patients in the ch14.18 group, compared to 9% of patients in the RA group. The most common types of bacteremia in the ch14.18 group were Staphylococcal bacteremia (7%) and Klebsiella bacteremia (3%).

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Study 301

According to the safety analysis, a total of 5,760 treatment emergent adverse reactions were reported during Study 301, including 4,734 in the ch14.18 combination therapy group and 1,026 in the RA group. A total of 132 of 134 (98%) patients in the ch14.18 combination group and 89 of 106 (84%) patients in the RA group reported an adverse event. Severe adverse events were more commonly reported in the ch14.18 combination group (96% of patients in the ch14.18 combination therapy group compared to 62% of patients in the RA group)

In this review, common adverse events were evaluated through analyses of the incidence of treatment-emergent adverse events by MedDRA system organ class (SOC), high level group term (HLGT), high level term (HLT).

Table 39 presents the results of an exploratory MedDRA-Based Adverse Event Diagnostic (MAED) analysis of treatment-emergent adverse events by MedDRA System Organ Class (SOC). As expected, there was a dramatically higher per-patient incidence of treatment emergent adverse events in the ch14.18 combination therapy group compared to the RA group across most system organ classes. Shaded entries highlight the SOCs with either low calculated p-values or high odds ratios indicating that the adverse event was more frequent in the ch14.18 combination therapy group.

Table 39: Treatment Emergent Events in Study 301 by System Organ Class

SOC	Ch14.18 Combination (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
General disorders and administration site conditions	486	112	83.58	44	31	29.25	12.317	7E-18
Blood and lymphatic system disorders	716	106	79.1	275	54	50.94	3.646	0.000005
Investigations	716	106	79.1	198	57	53.77	3.254	0.000046
Metabolism and nutrition disorders	797	105	78.36	118	29	27.36	9.614	1E-15
Gastrointestinal disorders	500	100	74.63	93	39	36.79	5.053	0.000000005
Vascular disorders	334	100	74.63	21	9	8.49	31.699	1E-26
Immune system disorders	236	81	60.45	26	9	8.49	16.472	7E-18
Infections and infestations	171	76	56.72	70	47	44.34	1.645	0.069
Skin and subcutaneous tissue disorders	192	67	50	53	24	22.64	3.417	0.000016
Musculoskeletal and connective tissue disorders	137	52	38.81	30	9	8.49	6.835	0.000000039
Respiratory, thoracic and mediastinal disorders	113	52	38.81	23	7	6.6	8.969	0.000000003
Nervous system disorders	87	43	32.09	20	12	11.32	3.701	0.00017
Renal and urinary disorders	81	40	29.85	14	7	6.6	6.018	0.0000034
Cardiac disorders	74	27	20.15	2	2	1.89	13.121	0.0000052
Psychiatric disorders	23	18	13.43	9	4	3.77	3.957	0.012
Hepatobiliary disorders	23	13	9.7	7	5	4.72	2.17	0.217
Eye disorders	16	10	7.46	7	6	5.66	1.344	0.614
Ear and labyrinth disorders	15	9	6.72	8	6	5.66	1.2	0.794
Endocrine disorders	10	9	6.72	2	2	1.89	3.744	0.118
Injury, poisoning and procedural complications	4	3	2.24	0	0	0	5.669	0.257

SOC	Ch14.18 Combination (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
Reproductive system and breast disorders	3	2	1.49	0	0	0	4.019	0.505

*p-values are not adjusted for multiplicity and should be used for ranking purposes only, not for determining statistical significance

The system organ class with the highest per patient incidence of treatment-emergent adverse events was the General Disorders and Administrative Site Conditions SOC (84% in the ch14.18 combination group vs. 29% in the RA group), followed by Blood and Lymphatic System Disorders SOC (79% in the ch14.18 combination group vs. 51% in the RA group. Table 40 lists the most common preferred terms (≥ 5%) within each SOC that is shaded above:

Table 40: Common Preferred Terms (PPI ≥ 5%) Reported for Selected SOCs in Study 301

System Organ Class	Preferred Terms (PPI)
General disorders and administration site conditions	• Pyrexia (72.4%) • Pain (33.6%) • Edema (17.2%) • Chills (8.2%) • Infusion related reaction (7.5%) • Fatigue (6.0%)
Blood and lymphatic system disorders	• Platelet disorder (66.4%) • Lymphopenia (64.2%) • White blood cell disorder (34.3%)
Investigations	• Alanine aminotransferase increased (56.0%) • Decreased Hemoglobin (50.7%) • Abnormall granulocytes (38.8%) • Increased aspartate aminotransferase (27.6%) • Blood creatinine (15.7%) • Blood alkaline phosphatase (6.0%) • Weight increased (10.4%)
Metabolism and nutrition disorders	• Hyponatremia (57.5%) • Hypokalemia 58 (43.3%) • Hypoalbuminaemia (33.6%) • Hypocalcemia (26.9%) • Hypertriglyceridemia (16.4%) • Hypophosphatemia (20.1%) • Hyperglycemia (17.9%) • Decreased appetite (14.9%) • Hypomagnesemia (12.7%)

System Organ Class	Preferred Terms (PPI)
	• Hypercalcemia (8.2%) • Hyperkalemia (7.5%)
Gastrointestinal disorders	• Abdominal pain (56.0%) • Vomiting (45.5%) • Diarrhea (43.3%) • Nausea (10.4%) • Constipation (7.5%) • Gastrointestinal hemorrhage (5.2%)
Vascular disorders	• Hypotension (59.7) • Capillary leak syndrome (39.6%) hypertension (14.2%)
Immune system disorders	• Drug hypersensitivity (60.4%)
Skin and subcutaneous tissue disorders	• Urticaria (36.6%) • Dry skin (14.9%) • Rash (14.2%) • Pruritus (9.7%)
Musculoskeletal and connective tissue disorders	• Pain in extremity (18.7%) • Back pain (11.9%) • Musculoskeletal chest pain (8.2%) arthralgia (6.0%)
Respiratory, thoracic and mediastinal disorders	• Hypoxia (23.9%) • Cough (9.0%)
Nervous system disorders	• Peripheral neuropathy (13.4%) • Neuralgia (11.9%) • Headache (8.2%)
Renal and urinary disorders	• Proteinuria (16.4%) • Urinary retention (8.2%) • Hematuria (5.2%)
Cardiac disorders	• Sinus tachycardia (14.9%) • Tachycardia (9.0%)
Psychiatric disorders	• Altered mood (6%)

Table 41 presents the results from an exploratory MAED analysis of treatment-emergent adverse events by MedDRA HLGT. Shaded entries highlight the HLGTs with either low calculated p-values or high odds ratios indicating that the adverse event was more frequent in the ch14.18 combination therapy group.

Table 41: Treatment Emergent Events in Study 301 by HLGT

HLGT	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
White blood cell disorders	390	99	73.88	133	46	43.4	3.689	0.0000027
Body temperature conditions	276	97	72.39	38	29	27.36	6.961	3E-12
Decreased and nonspecific blood pressure disorders and shock	293	97	72.39	5	3	2.83	90.009	1E-31
Electrolyte and fluid balance conditions	329	95	70.9	48	18	16.98	11.909	2E-17
Gastrointestinal signs and symptoms	309	92	68.66	51	27	25.47	6.409	2E-11
Platelet disorders	318	89	66.42	141	45	42.45	2.681	0.00024
Allergic conditions	233	81	60.45	26	9	8.49	16.472	7E-18
Hepatobiliary investigations	299	80	59.7	93	36	33.96	2.881	0.000091
Hematology investigations (incl blood groups)	321	79	58.96	72	29	27.36	3.814	0.0000011
General system disorders NEC	200	73	54.48	6	4	3.77	30.516	4E-19
Infections - pathogen unspecified	122	65	48.51	58	41	38.68	1.493	0.15
Gastrointestinal motility and defecation conditions	143	64	47.76	28	18	16.98	4.47	0.00000059
Bone, calcium, magnesium and phosphorus metabolism disorders	176	53	39.55	26	9	8.49	7.052	0.00000002
Angioedema and urticaria	110	49	36.57	4	3	2.83	19.792	1E-11
Musculoskeletal and connective tissue disorders NEC	105	47	35.07	14	7	6.6	7.64	0.000000058
Protein and amino acid metabolism disorders NEC	135	45	33.58	4	3	2.83	17.36	3E-10
Respiratory disorders NEC	94	44	32.84	11	6	5.66	8.148	0.00000012
Urinary tract signs and symptoms	72	37	27.61	9	5	4.72	7.705	0.0000019
Cardiac arrhythmias	70	27	20.15	1	1	0.94	26.495	0.00000077

HLGT	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
Bacterial infectious disorders	40	25	18.66	10	10	9.43	2.202	0.064
Neurological disorders NEC	45	21	15.67	2	2	1.89	9.664	0.00024
Renal and urinary tract investigations and urinalyses	35	21	15.67	12	6	5.66	3.097	0.022
Appetite and general nutritional disorders	44	20	14.93	12	5	4.72	3.544	0.011
Vascular hypertensive disorders	33	19	14.18	16	7	6.6	2.337	0.093
Peripheral neuropathies	24	18	13.43	10	6	5.66	2.586	0.053
Physical examination topics	25	16	11.94	0	0	0	29.658	0.000085
Oral soft tissue conditions	17	14	10.45	9	5	4.72	2.357	0.148
Hepatic and hepatobiliary disorders	22	13	9.7	7	5	4.72	2.17	0.217
Gastrointestinal hemorrhages NEC	16	11	8.21	0	0	0	19.834	0.001
Mood disorders and disturbances NEC	14	11	8.21	3	2	1.89	4.65	0.043
Thyroid gland disorders	10	9	6.72	2	2	1.89	3.744	0.118
Joint disorders	13	8	5.97	8	2	1.89	3.302	0.192
Viral infectious disorders	8	8	5.97	2	1	0.94	6.667	0.082
Administration site reactions	9	7	5.22	0	0	0	12.529	0.019

*p-values are not adjusted for multiplicity and should be used for ranking purposes only, not for determining statistical significance

Table 42 lists the most common preferred terms within each HLGT that is shaded above.

Table 42: Common Preferred Terms Reported for Selected HLGTs in Study 301

HLGT	Preferred terms
White blood cell disorders	Lymphopenia, white blood cell disorder, febrile neutropenia (5 patients)
Body temperature conditions	Pyrexia
Decreased and nonspecific blood pressure disorders and shock	Capillary leak syndrome, hypotension
Electrolyte and fluid balance conditions	Hypokalemia, hyponatremia, hyperkalemia, hypernatremia, dehydration, fluid overload
Gastrointestinal signs and symptoms	Abdominal pain, vomiting, nausea, abdominal distension
Platelet disorders	Platelet disorder
Allergic conditions	Drug hypersensitivity, serum sickness (1 patient : 7400100)
Hepatobiliary investigations	Increased alanine aminotransferase, aspartate aminotransferase, gamma glutamyltransferase
Hematology investigations	Granulocytes abnormal, hemoglobin
General system disorders NEC	Pain, edema, infusion related reaction, fatigue, irritability, chills, chest pain, face edema
Gastrointestinal motility and defecation conditions	Diarrhea, constipation
Bone, calcium, magnesium and phosphorous metabolism disorders	Hypocalcemia, hypophosphatemia, hypomagnesemia, hypercalcemia, hypermagnesemia
Angioedema and urticaria	Urticaria
Allergic conditions	Drug hypersensitivity, serum sickness (1 patient)
Peripheral neuropathies	Peripheral neuropathy
Allergic conditions	Drug hypersensitivity, serum sickness (1 patient)
Peripheral neuropathies	Peripheral neuropathy
Allergic conditions	Drug hypersensitivity, serum sickness (1 patient)
Peripheral neuropathies	Peripheral neuropathy
Allergic conditions	Drug hypersensitivity, serum sickness (1 patient)
Musculoskeletal and connective tissue disorders NEC	Pain in extremity, back pain, musculoskeletal chest pain, musculoskeletal pain
Protein and amino acid metabolism disorders NEC	Hypoalbuminemia
Respiratory disorders NEC	Hypoxia, oropharyngeal pain, cough, dyspnea,
Urinary tract signs and symptoms	Proteinuria, urinary retention, hematuria, urinary tract hemorrhage, bladder pain
Cardiac arrhythmias	Sinus tachycardia, tachycardia, ventricular arrhythmia, atrial fibrillation

HLGT	Preferred terms
Neurological disorders NEC	Neuralgia, dysgeusia
Renal and urinary tract investigations and urinalyses	Blood creatinine
Appetite and general nutritional disorders	Decreased appetite
Physical examination topics	Increased weight, decreased weight
Gastrointestinal hemorrhages NEC	Gastrointestinal hemorrhage, upper gastrointestinal hemorrhage, hematemesis, hematochezia, rectal hemorrhage, hematemesis
Mood disorders and disturbances NEC	Altered mood, euphoric mood
Administration site reactions	Injection site reaction, catheter site hemorrhage

Table 43 presents the results from an exploratory MAED analysis of treatment-emergent adverse events by MedDRA HLT. Shaded entries highlight the HLTs with either low calculated p-values or high odds ratios indicating that the adverse event was more frequent in the ch14.18 combination therapy group.

Table 43: Treatment Emergent Events in Study 301 by HLT

HLT	*Ch14.18 (N=134)*			*RA (N=106)*			*Ch14.18 vs. RA*	
	Events	*Subjects*	*Rate (%)*	*Events*	*Subjects*	*Rate (%)*	*Odds Ratio*	*P-value**
Febrile disorders	276	97	72.39	38	29	27.36	6.961	3E-12
Vascular hypotensive disorders	293	97	72.39	5	3	2.83	90.009	1E-31
Platelet disorders NEC	318	89	66.42	141	45	42.45	2.681	0.00024
Leukopenias NEC	272	86	64.18	96	39	36.79	3.078	0.00003
Allergies to foods, food additives, drugs and other chemicals	230	81	60.45	25	9	8.49	16.472	7E-18
Liver function analyses	299	80	59.7	93	36	33.96	2.881	0.000091
Gastrointestinal and abdominal pains (excl oral and throat)	166	77	57.46	14	10	9.43	12.968	2E-15
Sodium imbalance	197	77	57.46	32	13	12.26	9.664	1E-13
Red blood cell analyses	196	68	50.75	47	23	21.7	3.718	0.0000044
Nausea and vomiting symptoms	141	64	47.76	37	21	19.81	3.701	0.0000065
Potassium imbalance	125	61	45.52	14	6	5.66	13.927	6E-13

HLT	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
Diarrhea (excl infective)	127	58	43.28	26	16	15.09	4.293	0.0000026
White blood cell analyses	121	53	39.55	24	18	16.98	3.199	0.00019
Pain and discomfort NEC	100	49	36.57	2	2	1.89	29.976	2E-12
Musculoskeletal and connective tissue pain and discomfort	104	46	34.33	14	7	6.6	7.393	0.00000011
White blood cell abnormal findings NEC	112	46	34.33	37	16	15.09	2.94	0.001
Protein metabolism disorders NEC	135	45	33.58	4	3	2.83	17.36	3E-10
Calcium metabolism disorders	103	43	32.09	17	8	7.55	5.788	0.0000025
Infections NEC	60	36	26.87	26	20	18.87	1.58	0.168
Conditions associated with abnormal gas exchange	58	32	23.88	2	2	1.89	16.314	0.00000032
Urinary abnormalities	50	28	20.9	6	3	2.83	9.069	0.000023
Phosphorus metabolism disorders	42	27	20.15	7	3	2.83	8.664	0.000045
Edema NEC	51	25	18.66	0	0	0	49.603	0.00000017
Sepsis, bacteremia, viremia and fungemia NEC	38	25	18.66	16	10	9.43	2.202	0.064
Elevated triglycerides	55	22	16.42	18	12	11.32	1.539	0.352
Renal function analyses	35	21	15.67	12	6	5.66	3.097	0.022
Supraventricular arrhythmias	46	21	15.67	0	0	0	40.348	0.0000026
Appetite disorders	44	20	14.93	12	5	4.72	3.544	0.011
Dermal and epidermal conditions NEC	36	20	14.93	29	16	15.09	0.987	1
Rashes, eruptions and exanthems NEC	23	20	14.93	17	12	11.32	1.374	0.45
Magnesium metabolism disorders	31	19	14.18	2	2	1.89	8.591	0.00083
Vascular hypertensive disorders NEC	33	19	14.18	16	7	6.6	2.337	0.093
Peripheral neuropathies NEC	24	18	13.43	10	6	5.66	2.586	0.053
Sensory abnormalities NEC	42	18	13.43	0	0	0	33.824	0.000021

HLT	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
Physical examination procedures	25	16	11.94	0	0	0	29.658	0.000085
General signs and symptoms NEC	23	15	11.19	1	1	0.94	13.235	0.001
Pruritus NEC	19	13	9.7	1	1	0.94	11.281	0.004
Bladder and urethral symptoms	15	12	8.96	2	2	1.89	5.115	0.025
Cholestasis and jaundice	21	12	8.96	7	5	4.72	1.987	0.311
Coughing and associated symptoms	18	12	8.96	5	2	1.89	5.115	0.025
Rate and rhythm disorders NEC	18	12	8.96	1	1	0.94	10.328	0.008
Emotional and mood disturbances NEC	14	11	8.21	3	2	1.89	4.65	0.043
Feelings and sensations NEC	16	11	8.21	0	0	0	19.834	0.001
Headaches NEC	13	11	8.21	7	5	4.72	1.807	0.311
Gastrointestinal atonic and hypomotility disorders NEC	15	10	7.46	2	2	1.89	4.194	0.071
Non-site specific gastrointestinal hemorrhages	14	10	7.46	0	0	0	17.964	0.003
Staphylococcal infections	14	10	7.46	0	0	0	17.964	0.003

*p-values are not adjusted for multiplicity and should be used for ranking purposes only, not for determining statistical significance

Table 44 lists the most common preferred terms (experienced by at least 2 patients) within each HLT that is shaded above.

Table 44: Common Preferred Terms Reported for Selected HLTs in Study 301

HLT	Preferred terms
Febrile Disorders	Pyrexia
Vascular Hypotensive Disorders	Capillary Leak Syndrome, hypotension.
Platelet Disorders NEC	Platelet disorder
Leukopenias NEC	Lymphopenia
Allergies To Foods, Food Additives, Drugs And Other Chemicals	Drug hypersensitivity

HLT	Preferred terms
Liver Function Analyses	ALT, AST and GGT Elevations
Gastrointestinal And Abdominal Pains (Excl Oral And Throat)	Abdominal pains, abdominal pain and abdominal pain upper
Sodium Imbalance	Hyponatremia
Red Blood Cell Analyses	Decreased hemoglobin
Nausea And Vomiting Symptoms	Nausea and vomiting
Potassium Imbalance	Hypokalemia
Diarrhea (Excl Infective)	Diarrhea
White Blood Cell Analyses	Granulocytes abnormal, neutrophil count increased, white blood cell count increased, cd4 lymphocytes abnormal
Pain And Discomfort NEC	Pain, chest pain,
Musculoskeletal And Connective Tissue Pain And Discomfort	Pain in extremity, back pain, musculoskeletal chest pain, musculoskeletal pain, neck pain
White Blood Cell Abnormal Findings NEC	White blood cell disorder
Protein Metabolism Disorders NEC	Hypoalbuminemia
Calcium Metabolism Disorders	Hypocalcemia, hypercalcemia
Conditions Associated With Abnormal Gas Exchange	Hypoxia
Urinary Abnormalities	Hematuria, proteinuria
Phosphorus Metabolism Disorders	Hypophosphatemia
Edema NEC	Edema, facial edema
Sepsis, Bacteremia, Viremia And Fungemia NEC	Sepsis, bacteremia
Renal Function Analyses	Blood creatinine (elevated)
Supraventricular Arrhythmias	Sinus tachycardia, atrial fibrillation
Appetite Disorders	Decreased appetite
Magnesium Metabolism Disorders	Hypomagnesemia
Vascular Hypertensive Disorders NEC	Hypertension
Peripheral Neuropathies NEC	Peripheral neuropathy
Sensory Abnormalities NEC	Neuralgia, dysgeusia,
Physical Examination Procedures	Weight increased, weight decreased
General Signs And Symptoms NEC	Infusion related reaction, irritability
Pruritus NEC	Pruritis
Bladder And Urethral Symptoms	Urinary retention, bladder pain
Coughing And Associated Symptoms	Cough
Rate And Rhythm Disorders NEC	Tachycardia
Emotional And Mood Disturbances NEC	Mood altered, euphoric mood
Feelings And Sensations NEC	Chills
Non-Site Specific Gastrointestinal	Gastrointestinal hemorrhage,

HLT	Preferred terms
Hemorrhages	hematochezia, hematemesis, upper gastrointestinal hemorrhage
Staphylococcal Infections	Staphylococcal bacteremia

Table 45 presents the per-patient incidence of treatment-emergent adverse events (TEAEs) that were experienced by at least 5% of patients in the ch14.18 combination therapy group. The most common (≥ 50%) TEAEs in the ch14.18 combination group by preferred term were pyrexia, platelet disorder (i.e., decreased platelets), lymphopenia, drug hypersensitivity, hypotension, hyponatremia, increase alanine aminotransferase, abdominal pain, and low hemoglobin.

Table 45: PPI of Treatment-Emergent Adverse Events by Preferred Term and System Organ Class for Study 301

SOC	PT	Ch14.18 Combination N=134				RA N=106			
		All grades		Severe		All grades		Severe	
		n	%	n	%	n	%	n	%
General disorders and administration site conditions	Pyrexia	97	72	54	40	29	27	6	6
	Pain	45	34	28	21	1	1	0	0
	Edema	23	17	0	0	0	0	0	0
Blood and lymphatic system disorders	Platelet disorder	89	66	52	39	45	42	26	25
	Lymphopenia	86	64	70	52	39	37	21	20
	White blood cell disorder	46	34	26	19	16	15	9	8
Immune system disorders	Drug hypersensitivity	81	60	35	26	9	8	1	1
Vascular disorders	Hypotension	80	60	22	16	3	3	0	0
	Capillary leak syndrome	53	40	31	23	1	1	0	0
	Hypertension	19	14	2	1	7	7	1	1
Metabolism and nutrition disorders	Hyponatremia	77	57	31	23	13	12	4	4
	Hypokalemia	58	43	49	37	4	4	2	2
	Hypoalbuminemia	45	34	9	7	3	3	0	0
	Hypocalcemia	36	27	9	7	0	0	0	0
	Hypophosphatemia	27	20	10	7	3	3	0	0
	Hyperglycemia	24	18	8	6	4	4	1	1
	Hypertriglyceridemia	22	16	1	1	12	11	1	1
	Decreased appetite	20	15	13	10	5	5	4	4

SOC	PT	Ch14.18 Combination N=134				RA N=106			
		All grades		Severe		All grades		Severe	
		n	%	n	%	n	%	n	%
	Hypomagnesemia	17	13	2	1	1	1	0	0
	Hypercalcemia	11	8	7	5	8	8	6	6
Investigations	Alanine aminotransferase increased	75	56	31	23	33	31	3	3
	Decreased Hemoglobin	68	51	45	34	23	22	17	16
	Granulocytes abnormal	52	39	45	34	17	16	14	13
	Aspartate aminotransferase increased	37	28	14	10	7	7	0	0
	Blood creatinine	21	16	2	1	6	6	0	0
	Weight increased	14	10	0	0	0	0	0	0
Gastrointestinal disorders	Abdominal pain	75	56	39	29	9	8	0	0
	Vomiting	61	46	8	6	20	19	3	3
	Diarrhea	58	43	17	13	16	15	1	1
	Nausea	14	10	3	2	3	3	1	1
Skin and subcutaneous tissue disorders	Urticaria	49	37	17	13	3	3	0	0
	Dry skin	20	15	0	0	16	15	0	0
	Rash	19	14	2	1	12	11	2	2
	Pruritus	13	10	0	0	1	1	0	0
Respiratory, thoracic and mediastinal disorders	Hypoxia	32	24	16	12	2	2	1	1
Musculoskeletal and connective tissue disorders	Pain in extremity	25	19	12	9	5	5	2	2
	Back pain	16	12	9	7	1	1	0	0
Infections and infestations	Sepsis	24	18	22	16	10	9	9	8
	Device related infection	23	17	22	16	12	11	12	11
	Localized infection	10	7	8	6	6	6	4	4
	Staphylococcal bacteremia	10	7	10	7	0	0	0	0
Renal and urinary disorders	Proteinuria	22	16	0	0	3	3	1	1

SOC	PT	Ch14.18 Combination N=134				RA N=106			
		All grades		Severe		All grades		Severe	
		n	%	n	%	n	%	n	%
Cardiac disorders	Sinus tachycardia	20	15	2	1	0	0	0	0
Nervous system disorders	Neuropathy peripheral	18	13	4	3	6	6	0	0
	Neuralgia	16	12	11	8	0	0	0	0
Ear and labyrinth disorders	Hearing impaired	8	6	7	5	5	5	3	3

The most common (PPI ≥ 20%) severe adverse reactions reported in the ch14.18 group by preferred term were lymphopenia, pyrexia, platelet disorder, hypokalemia, decreased hemoglobin, granulocyte abnormal, abdominal pain, drug hypersensitivity, hyponatremia, increased alanine aminotransferase, capillary leak syndrome, and pain.

Narrow Standard MedDRA Query

The clinical review also included exploratory safety analyses of Study 301 using a Narrow Standard MedDRA Query analyses performed using the MAED tool.
Table 46 presents the results from an exploratory MAED analysis of treatment-emergent adverse events by MedDRA HLT. Shaded entries highlight the HLTs with either low calculated p-values or high odds ratios indicating that the adverse event was more frequent in the ch14.18 combination therapy group.

Table 46: Analysis of Narrow Based Standardized MedDRA Queries by Treatment Group for Study 301

Narrow SMQ	*Ch14.18 (N=134)*			*RA (N=106)*			*Ch14.18 vs. RA*	
	Events	*Subjects*	*Rate (%)*	*Events*	*Subjects*	*Rate (%)*	*Odds Ratio*	*P-value**
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	454	100	74.63	79	33	31.13	6.506	1E-11
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	451	100	74.63	79	33	31.13	6.506	1E-11

Narrow SMQ	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
(1) Haematopoietic cytopenias	277	87	64.93	96	39	36.79	3.18	0.000017
(2) Leukopenia	277	87	64.93	96	39	36.79	3.18	0.000017
(1) Hepatic disorders	308	80	59.7	100	37	34.91	2.763	0.00016
(2) Drug related hepatic disorders - comprehensive search	308	80	59.7	100	37	34.91	2.763	0.00016
(3) Liver related investigations, signs and symptoms	308	80	59.7	100	37	34.91	2.763	0.00016
(1) Hyponatraemia/SIADH	194	77	57.46	31	13	12.26	9.664	1E-13
(1) Haemodynamic oedema, effusions and fluid overload *	154	69	51.49	3	2	1.89	55.2	9E-20
(1) Angioedema	115	52	38.81	4	3	2.83	21.772	2E-12
(1) Peripheral neuropathy	63	33	24.63	10	6	5.66	5.446	0.000072
(1) Hemorrhages	46	24	17.91	10	6	5.66	3.636	0.005
(1) Hyperglycemia/new onset diabetes mellitus	44	24	17.91	5	4	3.77	5.564	0.00052
(2) Hemorrhage terms (excl laboratory terms) *	44	23	17.16	10	6	5.66	3.453	0.009
(1) Dyslipidaemia *	61	22	16.42	22	12	11.32	1.539	0.352
(1) Hypertension *	33	19	14.18	16	7	6.6	2.337	0.093
(1) Gastrointestinal perforation, ulceration, hemorrhage or obstruction	22	15	11.19	1	1	0.94	13.235	0.001
(1) Oropharyngeal disorders *	22	15	11.19	3	3	2.83	4.328	0.014

Narrow SMQ	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	18	13	9.7	1	1	0.94	11.281	0.004
(3) Cholestasis and jaundice of hepatic origin	21	12	8.96	7	5	4.72	1.987	0.311
(2) Gastrointestinal hemorrhage *	18	12	8.96	0	0	0	21.735	0.001
(1) Biliary disorders	22	12	8.96	7	5	4.72	1.987	0.311
(2) Functional, inflammatory and gallstone related biliary disorders	22	12	8.96	7	5	4.72	1.987	0.311
(3) Biliary system related investigations, signs and symptoms	21	12	8.96	7	5	4.72	1.987	0.311
(3) Site unspecified biliary disorders *	21	12	8.96	7	5	4.72	1.987	0.311
(1) Thyroid dysfunction	10	9	6.72	2	2	1.89	3.744	0.118
(1) Hearing and vestibular disorders	14	8	5.97	7	5	4.72	1.283	0.779
(2) Hearing impairment	14	8	5.97	7	5	4.72	1.283	0.779
(1) Cardiac arrhythmias	10	7	5.22	0	0	0	12.529	0.019
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	10	7	5.22	0	0	0	12.529	0.019
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	454	100	74.63	79	33	31.13	6.506	1E-11

Narrow SMQ	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	451	100	74.63	79	33	31.13	6.506	1E-11
(1) Haematopoietic cytopenias	277	87	64.93	96	39	36.79	3.18	0.000017
(2) Leukopenia	277	87	64.93	96	39	36.79	3.18	0.000017
(1) Hepatic disorders	308	80	59.7	100	37	34.91	2.763	0.00016
(2) Drug related hepatic disorders - comprehensive search	308	80	59.7	100	37	34.91	2.763	0.00016
(3) Liver related investigations, signs and symptoms	308	80	59.7	100	37	34.91	2.763	0.00016
(1) Hyponatramia/SIADH	194	77	57.46	31	13	12.26	9.664	1E-13
(1) Hemodynamic edema, effusions and fluid overload *	154	69	51.49	3	2	1.89	55.2	9E-20
(1) Angioedema	115	52	38.81	4	3	2.83	21.772	2E-12
(1) Peripheral neuropathy	63	33	24.63	10	6	5.66	5.446	0.000072
(1) Haemorrhages	46	24	17.91	10	6	5.66	3.636	0.005
(1) Hyperglycaemia/new onset diabetes mellitus	44	24	17.91	5	4	3.77	5.564	0.00052
(2) Haemorrhage terms (excl laboratory terms) *	44	23	17.16	10	6	5.66	3.453	0.009
(1) Dyslipidaemia *	61	22	16.42	22	12	11.32	1.539	0.352
(1) Hypertension *	33	19	14.18	16	7	6.6	2.337	0.093
(1) Gastrointestinal perforation, ulceration, haemorrhage or obstruction	22	15	11.19	1	1	0.94	13.235	0.001

Narrow SMQ	Ch14.18 (N=134)			RA (N=106)			Ch14.18 vs. RA	
	Events	Subjects	Rate (%)	Events	Subjects	Rate (%)	Odds Ratio	P-value*
(1) Oropharyngeal disorders *	22	15	11.19	3	3	2.83	4.328	0.014
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic *	18	13	9.7	1	1	0.94	11.281	0.004
(3) Cholestasis and jaundice of hepatic origin	21	12	8.96	7	5	4.72	1.987	0.311
(2) Gastrointestinal haemorrhage *	18	12	8.96	0	0	0	21.735	0.001
(1) Biliary disorders	22	12	8.96	7	5	4.72	1.987	0.311
(2) Functional, inflammatory and gallstone related biliary disorders	22	12	8.96	7	5	4.72	1.987	0.311
(3) Biliary system related investigations, signs and symptoms	21	12	8.96	7	5	4.72	1.987	0.311
(3) Site unspecified biliary disorders *	21	12	8.96	7	5	4.72	1.987	0.311
(1) Thyroid dysfunction	10	9	6.72	2	2	1.89	3.744	0.118
(1) Hearing and vestibular disorders	14	8	5.97	7	5	4.72	1.283	0.779
(2) Hearing impairment	14	8	5.97	7	5	4.72	1.283	0.779
(1) Cardiac arrhythmias	10	7	5.22	0	0	0	12.529	0.019
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	10	7	5.22	0	0	0	12.529	0.019

Note: the parentheses refer to the SMQ level. Asterix ("*") after the SMQ name indicates that it is an SMQ with narrow terms only and that a broad SMQ search will yield the same results.

Table 46 lists the most common preferred terms (experienced by at least 2 patients) within each narrow SMQ that is shaded above.

Table 46: Common Preferred Terms Reported for Selected SMQs in Study 301

Narrow SMQ	Preferred terms
(1) Gastrointestinal nonspecific inflammation and dysfunctional conditions	Abdominal pain, Abdominal distension Abdominal pain upper Constipation Diarrhea Nausea Vomiting
(2) Gastrointestinal nonspecific symptoms and therapeutic procedures	Abdominal pain, upper abdominal pain, diarrhea, vomiting, nausea, constipation, abdominal distension
(1) Hematopoietic cytopenias	Lymphopenia, febrile neutropenia (5 patients)
(2) Leukopenia	Lymphopenia, , febrile neutropenia (5 patients)
(1) Hepatic disorders	Increased ALT, increased AST, hyperbilirubinemia
(2) Drug related hepatic disorders - comprehensive search	Increased ALT, increased AST, hyperbilirubinemia
(3) Liver related investigations, signs and symptoms	Increased ALT, increased AST, hyperbilirubinemia
(1) Hyponatremia/SIADH	Hyponatremia
(1) Haemodynamic edema, effusions and fluid overload *	Capillary leak syndrome, edema,
(1) Angioedema	Urticaria, face edema
(1) Peripheral neuropathy	Neuralgia, peripheral neuropathy
(1) Hemorrhages	Hematuria, gastrointestinal hemorrhage, urinary tract hemorrhage, hemorrhage, catheter site hemorrhage, hematochezia, hemorrhage, rectal hemorrhage, occult blood positive, disseminated intravascular coagulation
(1) Hyperglycemia/new onset diabetes mellitus	Hyperglycemia
(2) Hemorrhage terms (excl laboratory terms) *	Hematuria, gastrointestinal hemorrhage, urinary tract hemorrhage, hemorrhage, catheter site hemorrhage, hematochezia, , rectal hemorrhage, occult blood positive, disseminated intravascular coagulation
(1) Gastrointestinal perforation, ulceration, haemorrhage or obstruction	Gastrointestinal hemorrhage, rectal hemorrhage, hematochezia, occult blood positive, hematemesis, upper gastrointestinal hemorrhage
(1) Oropharyngeal disorders	Oropharyngeal pain, stomatitis, oral pain, oral

Narrow SMQ	Preferred terms
	gingivitis, gingival pain, oropharyngeal pain
(2) Oropharyngeal lesions, non-neoplastic, non-infectious and non-allergic	Oropharyngeal pain, oral pain, stomatitis
2) Gastrointestinal haemorrhage	Gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage
(1) Cardiac arrhythmias	Atrial fibrillation, atrial tachycardia, conduction disorder, ventricular arrhythmia
(2) Cardiac arrhythmia terms (incl bradyarrhythmias and tachyarrhythmias)	Ventricular arrhythmia, atrial fibrillation, atrial tachycardia.

The majority of the narrow-based SMQs with high odds ratios and low p-values indicating a potential safety signal with ch14.18 combination treatment were previously identified by the Applicant as adverse events associated with ch14.18 combination therapy, with the exception of hemorrhage, including gastrointestinal hemorrhage, and cardiac arrhythmias. A review of the cases of cardiac arrhythmia revealed that the majority were clearly confounded by associated adverse events such as sepsis or electrolyte abnormalities. All were mild to moderate in severity, except for one case of Grade 4 atrial fibrillation, which occurred in a patient (716002) who received an accidental overdose of IL-2 and ultimately died due to complications relating to systemic inflammatory response syndrome.

Reviewer note: Review of ECG data by the FDA QT-Interdisciplinary review team is pending. Available non-clinical data does not indicate that ch14.18 is likely to be arrhythmogenic.

A search of the Study 301 adverse event database for the following preferred terms was conducted: gastrointestinal hemorrhage, hematochezia, rectal hemorrhage, hematemesis, upper gastrointestinal hemorrhage hematochezia, occult blood positive, renal hemorrhage, and catheter site hemorrhage. This search uncovered a total of 23 (17%) of patients in the ch14.18 group and 5 (5%) in the RA group who experienced at least one event of hemorrhage. The majority of these events were of Grade 1 or 2 severity (Table 47).

Table 47: PPI of Treatment-Emergent Bleeding Events in Study 301

PT	Ch14.18 Combination N=134				RA N=106			
	All grades		Severe		All grades		Severe	
	n	%	n	%	n	%	n	%
Gastrointestinal hemorrhage	7	5%	3	2%	0	0%	0	0%
Hematuria	7	5%	0	0%	0	0%	0	0%
Hemorrhage urinary tract	5	4%	0	0%	1	1%	0	0%
Catheter site hemorrhage	2	1%	0	0%	0	0%	0	0%
Hematochezia	2	1%	1	1%	0	0%	0	0%
Hemorrhage	2	1%	1	1%	0	0%	0	0%
Occult blood positive	2	1%	1	1%	0	0%	0	0%
Rectal hemorrhage	2	1%	1	1%	0	0%	0	0%
Catheter site hemorrhage	2	1%	0	0%	0	0%	0	0%
Hematemesis	1	1%	1	1%	0	0%	0	0%
Hemoglobinuria	1	1%	0	0%	0	0%	0	0%
Respiratory tract hemorrhage	1	1%	1	1%	3	3%	1	1%
Upper gastrointestinal hemorrhage	1	1%	1	1%	0	0%	0	0%
Renal hemorrhage	0	0%	0	0%	1	1%	1	1%

Reviewer note: As described in Table 45, 66% of patients in the ch14.18 combination group experienced at least one adverse event with the preferred term "platelet disorder" (i.e., thrombocytopenia), which would increase the risk for bleeding events. Due to the lack of available data for platelet parameters submitted for Study 301, an analysis to determine whether the bleeding events were associated with thrombocytopenia is not possible. The clinical reviewer therefore recommends that the risk of hemorrhage be included in the dinutuximab package insert.

Integrated Summary of Safety

Table 48 provides a comparison of the PPI of adverse events in patients treated with ch14.18 combination therapy Study 301 with the PPI of adverse events in the Integrated Summary of Safety (ISS) database. Overall, the toxicity profile observed in the ISS database was similar to that observed in Study 301.

Table 48: Treatment Emergent Adverse Events in Patients Treated with Ch14.18 in Study 301 and in the ISS

Preferred Term[a]	Study 301 N=141[b]		All ISS Clinical Trials[c] N=1184	
	n	%	n	%
Hypotension	89	63%	774	65%
Pyrexia	103	73%	645	54%
Hypersensitivity	80	57%	634	54%
Urticaria	63	45%	563	48%
Capillary leak syndrome	59	42%	529	45%
Anemia	76	54%	484	41%
Hypokalemia	61	43%	453	38%
Pain	73	52%	453	38%
Platelet count decreased	93	66%	420	35%
Hyponatremia	80	57%	395	33%
Alanine aminotransferase increased	76	54%	376	32%
Abdominal pain	81	57%	361	30%
Lymphocyte count decreased	95	67%	361	30%
Neutrophil count decreased	59	42%	325	27%
Aspartate aminotransferase increased	38	27%	281	24%
Diarrhea	62	44%	271	23%
Hypoalbuminemia	48	34%	270	23%
White blood cell count decreased	53	38%	249	21%
Hypocalcaemia	36	26%	241	20%
Vomiting	61	43%	235	20%
Hypoxia	37	26%	207	17%
Anaphylactic reaction	37	26%	184	16%
Pain in extremity	24	17%	183	15%
Device related infection	25	18%	181	15%
Hypophosphatemia	29	21%	178	15%
Cough	14	10%	170	14%
Hypertriglyceridemia	24	17%	162	14%
Pruritus	15	11%	141	12%
Hyperglycemia	26	18%	139	12%
Nausea	14	10%	137	12%
Sinus tachycardia	22	16%	135	11%
Dyspnea	8	6%	133	11%

Preferred Term[a]	Study 301 N=141[b]		All ISS Clinical Trials[c] N=1184	
	n	%	n	%
Decreased appetite	21	15%	131	11%
Dry skin	23	16%	131	11%
Face edema	17	12%	125	11%
Hypertension	19	13%	123	10%

[a] MedDRA version 13.1 was used for coding adverse events for all studies except for Study 201, which used MedDRA version 17.
[b] Safety population includes 134 patients originally included in the safety population in the June 2009 safety analysis+ four crossover patients+ one subject who was randomized prior to June 2009 but had data entered after June 2009 + two subjects enrolled in Stratum 7 who were enrolled prior to January 2009 but had data entered after June 2009.
[c]Data from Study 301 are complete. Study 302 data was collected through March 31, 2014; data from Study 201 are complete (collected through May 23, 2014); data from Study 303 use a data cutoff date of March 30, 2012.

7.4.2 Laboratory Findings

Although hematologic parameters, serum chemistries, and urinalyses were routinely monitored closely during study therapy in Study 301, laboratory data collected in case report forms and submitted to the BLA were limited to white blood cell parameters and urine catecholamines. However, investigators were instructed to record clinically relevant (CTCAE Grade 3 or higher) laboratory abnormalities as adverse events in the adverse event database. In the absence of disease progression, urine catecholamine levels were generally stable over time.

Table 49 presents the per-patient incidence of laboratory-related adverse events included in the adverse event database for Study 301.

Table 49: PPI Incidence of Laboratory-Related Adverse Events for Study 301

PT	Ch14.18 Combination N=134				RA N=106			
	All grades		Severe		All grades		Severe	
	n	%	n	%	n	%	n	%
Platelet disorder	89	66%	52	39%	45	42%	26	25%
Lymphopenia	86	64%	70	52%	39	37%	21	20%
Hyponatremia	77	57%	31	23%	13	12%	4	4%
Alanine aminotransferase increased	75	56%	31	23%	33	31%	3	3%
Decreased hemoglobin	68	51%	45	34%	23	22%	17	16%
Hypokalemia	58	43%	49	37%	4	4%	2	2%

PT	Ch14.18 Combination N=134				RA N=106			
	All grades		Severe		All grades		Severe	
	n	%	n	%	n	%	n	%
Granulocytes abnormal	52	39%	45	34%	17	16%	14	13%
White blood cell disorder	46	34%	26	19%	16	15%	9	8%
Hypoalbuminemia	45	34%	9	7%	3	3%	0	0%
Aspartate aminotransferase increased	37	28%	14	10%	7	7%	0	0%
Hypocalcemia	36	27%	9	7%	0	0%	0	0%
Hypophosphatemia	27	20%	10	7%	3	3%	0	0%
Hyperglycemia	24	18%	8	6%	4	4%	1	1%
Hypertriglyceridemia	22	16%	1	1%	12	11%	1	1%
Hypomagnesemia	17	13%	2	1%	1	1%	0	0%
Hyperbilirubinemia	12	9%	1	1%	5	5%	0	0%
Hypercalcemia	11	8%	7	5%	8	8%	6	6%
Hyperkalemia	10	7%	4	3%	4	4%	0	0%
Blood alkaline phosphatase	8	6%	2	1%	7	7%	1	1%
Hematuria	7	5%	0	0%	0	0%	0	0%
Blood bicarbonate decreased	6	4%	0	0%	0	0%	0	0%
Hypoglycemia	5	4%	0	0%	0	0%	0	0%
Hypothyroidism	5	4%	0	0%	2	2%	0	0%
Gamma-glutamyltransferase	6	4%	3	2%	0	0%	0	0%
Hypoglycemia	5	4%	0	0%	0	0%	0	0%
Hypermagnesemia	4	3%	1	1%	1	1%	0	0%
Hyperthyroidism	4	3%	0	0%	0	0%	0	0%
Hypernatremia	3	2%	1	1%	1	1%	0	0%
Weight decreased	3	2%	1	1%	0	0%	0	0%
Activated partial thromboplastin time prolonged	2	1%	1	1%	1	1%	1	1%
Anemia	2	1%	2	1%	0	0%	0	0%
Occult blood positive	2	1%	1	1%	0	0%	0	0%
Blood amylase	1	1%	0	0%	0	0%	0	0%
CD4 lymphocytes abnormal	1	1%	1	1%	1	1%	1	1%
Troponin I	1	1%	1	1%	0	0%	0	0%
Hypercholesterolemia	2	1%	0	0%	1	1%	1	1%
Brain natriuretic peptide increased	1	1%	1	1%	0	0%	0	0%
Hemoglobinuria	1	1%	0	0%	0	0%	0	0%
Neutrophil count increased	1	1%	0	0%	0	0%	0	0%
Urine bilirubin increased	1	1%	0	0%	0	0%	0	0%
White blood cell count increased	1	1%	0	0%	0	0%	0	0%

PT	Ch14.18 Combination N=134				RA N=106			
	All grades		Severe		All grades		Severe	
	n	%	n	%	n	%	n	%
Blood alkaline phosphatase increased	0	0%	0	0%	1	1%	0	0%
Blood phosphorus increased	0	0%	0	0%	1	1%	0	0%
Serum ferritin increased	0	0%	0	0%	1	1%	0	0%

The most common (≥ 10% PPI) laboratory-related adverse events in the ch14.18 combination group were platelet disorder (i.e., decreased platelet count), lymphopenia, hyponatremia, increased alanine aminotransferase, decreased hemoglobin, hypokalemia, abnormal granulocytes, hypoalbuminemia, increased aspartate aminotransferase, hypocalcemia, hypophosphatemia, hyperglycemia, and hypertriglyceridemia and hypomagnesemia.

As illustrated in Table 49, laboratory abnormalities that were considered to be adverse events by the local investigator were more common in the ch14.18 combination therapy group compared to the RA group. Laboratory related adverse include clinically relevant decreases in hematologic parameters and electrolyte abnormalities that could predispose patients to developing serious adverse events, such as infection or conduction abnormalities. Therefore, patients receiving ch14.18 should undergo frequent laboratory monitoring, as would be expected to occur in a hospital-based setting.

Study 303

In study 303, data from clinical laboratory assessments, including hematologic parameters and serum chemistries were collected.

Table 50, submitted to the BLA by the Applicant, provides a summary of treatment emergent hematologic laboratory abnormalities.

Table 50: PPI of Abnormalities in Selected Hematologic Parameters for Study 303

Hematologic Parameter	PPI of Abnormal Result N=104 n (%)
Hemoglobin < 11 g/dL	104 (100)
Hematocrit < 34%	104 (100)

Hematologic Parameter	PPI of Abnormal Result N=104 n (%)
White Blood Cells	
< 5.5 x 1000 cells/mm^3	100 (96)
> 15.5 x 1000 cells/mm^3	66 (64)
Neutrophils	
< 54%	101 (97)
> 62%	101 (97)
Lymphocytes	
< 25%	104 (100)
> 33%	88 (85)
Monocytes	
< 3%	84 (81)
> 7 %	98 (94)
Eosinophils	
< 1%	54 (52)
> 3%	103 (99)
Basophils	
> 0.75%	88 (85)
Platelets	
< 140 x 1000/µL	101 (97)

Source: Modified from table provided by Applicant.

Table 51, submitted to the BLA by the Applicant, provides a summary of treatment emergent serum chemistry and metabolic laboratory abnormalities

Table 51: PPI of Abnormalities in Selected Hematologic Parameters for Study 303

Serum Chemistry/Metabolic Parameter	PPI of Abnormal Result N=104 n (%)
ALT	
> 55 U/L	83 (80)
AST	
> 55 U/L	73 (70)

Serum Chemistry/Metabolic Parameter	PPI of Abnormal Result N=104 n (%)
Albumin	
< 3.4 g/dL	104 (100)
> 4.2 g/dL	59 (57)
Protein	
< 5.7 g/dL	75 (72)
Total Bilirubin	
< 0.3 mg/dL	89 (86)
> 1.0 mg/dL	23 (22)
Triglycerides	
> 114 mg/dL	96 (92)
Sodium	
< 135 mEq/L	97 (93)
Potassium	
< 3.5 mEq/L	85 (82)
> 5.2 mEq/L	19 (18)
Chloride	
< 97 mEq/L	30 (29)
>108 mEq/L	60 (58)
Carbon Dioxide	
< 20 mEq/L	40 (39)
Blood Urea Nitrogen	
< 5 mg/dL	68 (65)
> 26 mg/dL	16 (15)
Glucose	
< 60 mg/dL	12 (12)
> 100 mg/dL	90 (87)
Calcium	
< 8.5 mg/dL	101 (97)
Phosphorus	
< 3.7 mg/dL	81 (78)
> 5.6 mg/dL	41 (39)

Serum Chemistry/Metabolic Parameter	PPI of Abnormal Result N=104 n (%)
Magnesium < 1.6 mg/dL	39 (38)

Source: Modified from table provided by the Applicant

In general, the laboratory abnormalities identified by the Applicant from the laboratory database for Study 303 are consistent with the adverse event profile of laboratory-related adverse events reported for Study 301.

Hy's Law

The July 2009 FDA industry guidance document entitled "Drug-Induced Liver Injury: Premarketing Clinical Evaluation" states that the "most specific predictor found to date of a drug's potential for severe hepatotoxicity…. is the occurrence of a small number of cases of hepatocellular injury (aminotransferase elevation) accompanied by increased serum total bilirubin, not explained by any other cause." The guidance document describes 3 components to Hy's Law, which designates drugs likely to cause severe drug-induced liver injury:

1. A higher incidence of 3-fold or greater elevations of aminotransferase levels seen with the study drug compared to a nonhepatotoxic control group
2. Among trial subjects showing such aminotransferase levels, one or more also have elevations in total bilirubin > 2 times the upper limit of normal (without findings of cholestasis).
3. Lack of another reason to explain the increased aminotransferase and total bilirubin levels.

A review of the laboratory datasets for Study 303 did not uncover any cases consistent with drug-induced liver injury using the Hy's Law criteria.

7.4.3 Vital Signs

Vital sign and physical examination data were not recorded in the case report forms for Study 301. According to the protocol, investigators were instructed to report any clinically significant findings and physical examination assessments as adverse events. As described in Table 45, common adverse events in the ch14.18 combination therapy group in Study 301 related to vital sign or physical examination parameters included hypotension (60%), hypertension (14%), increased weight (10%), hypoxia (24%), and sinus tachycardia (15%).

A review of the Clinical Study Report for Study 303 revealed no notable differences in height or weight observed during the course of the study. In addition, vital signs were generally consistent across courses and during ch14.18 dosing days.

7.4.4 Electrocardiograms (ECGs)

As a large protein (molecular weight: 147,625-150,744 Daltons), dinutuximab is not expected to inhibit the HERG channel. ECG data obtained in Study 302 and Study 201 are currently being analyzed by the FDA QT-Interdisciplinary Review Team (QT-IRT). In these studies, ECGs were obtained in triplicate at baseline, Day 6 (end of ch14.18 infusion), Day 80 (prior to IL-2), Day 90 (end of ch14.18 infusion) and at the end of the study. Product labeling will be updated to reflect the QT-IRT findings upon completion of their review.

7.4.5 Special Safety Studies/Clinical Trials

None.

7.4.6 Immunogenicity

Preliminary data from Study 301 using an academic nonvalidated ELISA assay found that 8 of 118 patients (7%) receiving ch14.18 tested positive for human anti-chimeric antibody (HACA). Of 414 patients evaluated for HACA by validated assay across Studies 302, 303, and 201, 83 patients (20%) tested positive for HACA with 15 patients (4%) testing positive for neutralizing antibody. Notably, 11 patients had confirmed HACA responses prior to dosing with ch14.18 in study 302 (n=8) and Study 303 (n=3). There is insufficient data from Study 301 to permit assessment of the impact of immunogenicity on pharmacokinetic parameters and pharmacodynamic activity of dinutuximab.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The same dose of ch14.18 (25 mg/m^2/day) was administered in Study 301, Study 302, and Study 303. In Study 201, patients received 25 mg/m^2/day of ch14.18 or 17.5 mg/m^2/day dinutuximab (giving comparable antibody exposure to 25 mg/m^2/day of ch14.18) or 25 mg/m^2/day ch14.18, depending on the treatment cycle. Thus, there are no data to permit assessment of dose dependency for adverse events.

7.5.2 Time Dependency for Adverse Events

As described in Section 5.3, patients enrolled in Study 301 received ch14.18 in combination with GM-CSF during Cycles 1, 3, and 5, and in combination with IL-2 during Cycles 2 and 4. Thus, an exploratory analysis was performed to compare the incidences of adverse reactions reported during Cycles 1,3, and 5 (ch14.18+GM-CSF+RA) with the per-patient incidences of the toxicities observed during Cycles 2 and 4 (ch14.18+IL-2+RA). Table 52 presents the results of this analysis. Rows highlighted in bold are preferred terms with an absolute increase in PPI of at least 5% in the IL-2 containing cycles (either for adverse events of all grades or severe adverse events). Italicized rows highlight the adverse events that were more common in the cycles containing GM-CSF.

Despite the fact that GM-CSF was administered for three cycles compared to two containing IL-2, there was a higher per-patient incidence of many adverse events during IL-2 containing cycles. The adverse events with the largest (≥10%) absolute risk difference for severe adverse events were pyrexia, hypokalemia, lymphopenia, hypotension, and drug hypersensitivity. Nevertheless, most adverse events occurred with at least a 10% PPI in both IL-2 and GM-CSF containing cycles.

Table 52: PPI TEAE in Study 301 by Cytokine Combination

Preferred Term[a]	All Grades					Severe				
	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff
	n	PPI	n	PPI		n	PPI	n	PPI	
Platelet disorder	83	62%	77	61%	1%	41	31%	42	33%	-2%
Pyrexia	**73**	**54%**	**83**	**65%**	**-11%**	**13**	**10%**	**47**	**37%**	**-27%**
Lymphopenia	**72**	**54%**	**77**	**61%**	**-7%**	**44**	**33%**	**64**	**50%**	**-18%**
Drug hypersensitivity	**63**	**47%**	**70**	**55%**	**-8%**	**14**	**10%**	**26**	**20%**	**-10%**
Alanine aminotransferase increased	**58**	**43%**	**61**	**48%**	**-5%**	20	15%	17	13%	2%
Hypotension	**58**	**43%**	**69**	**54%**	**-11%**	**7**	**5%**	**20**	**16%**	**-11%**
Hyponatremia	**48**	**36%**	**70**	**55%**	**-19%**	**7**	**5%**	**27**	**21%**	**-16%**
Hemoglobin	56	42%	53	42%	0%	28	21%	31	24%	-4%
Abdominal pain	*62*	*46%*	*44*	*35%*	*12%*	*27*	*20%*	*23*	*18%*	*2%*

Preferred Term[a]	All Grades					Severe				
	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff
	n	PPI	n	PPI		n	PPI	n	PPI	
Diarrhea	**41**	**31%**	**47**	**37%**	**-6%**	**8**	**6%**	**16**	**13%**	**-7%**
Vomiting	44	33%	45	35%	-3%	5	4%	3	2%	1%
Hypokalemia	**35**	**26%**	**50**	**39%**	**-13%**	**18**	**13%**	**42**	**33%**	**-20%**
Granulocytes abnormal	**34**	**25%**	**40**	**31%**	**-6%**	**26**	**19%**	**35**	**28%**	**-8%**
Hypoalbuminemia	39	29%	38	30%	-1%	4	3%	6	5%	**-2%**
White blood cell disorder	36	27%	35	28%	-1%	21	16%	13	10%	5%
Capillary leak syndrome	**30**	**22%**	**46**	**36%**	**-14%**	**15**	**11%**	**25**	**20%**	**-8%**
Urticaria	**33**	**25%**	**37**	**29%**	**-5%**	**9**	**7%**	**9**	**7%**	**-0%**
Pain	*35*	*26%*	*27*	*21%*	*5%*	*22*	*16%*	*14*	*11%*	*5%*
Hypocalcaemia	**27**	**20%**	**27**	**21%**	**-1%**	**2**	**1%**	**8**	**6%**	**-5%**
Aspartate aminotransferase increased	**21**	**16%**	**26**	**20%**	**-5%**	**5**	**4%**	**9**	**7%**	**-3%**
Hypoxia	22	16%	21	17%	-0%	12	9%	9	7%	2%
Hypophosphatemia	**11**	**8%**	**24**	**19%**	**-11%**	**0**	**0%**	**10**	**8%**	**-8%**
Hypertriglyceridemia	14	10%	17	13%	-3%	0	0%	0	0%	0%
Hyperglycemia	13	10%	17	13%	-4%	3	2%	5	4%	-2%
Decreased appetite	14	10%	14	11%	-1%	9	7%	10	8%	-1%
Pain in extremity	15	11%	14	11%	0%	7	5%	7	6%	-0%
Device related infection	16	12%	13	10%	2%	15	11%	13	10%	1%
Sepsis	12	9%	17	13%	-4%	12	9%	15	12%	-3%
Sinus tachycardia	14	10%	15	12%	-1%	0	0%	2	2%	-2%
Edema	**9**	**7%**	**20**	**16%**	**-9%**	**0**	**0%**	**0**	**0%**	**0%**
Blood creatinine	**10**	**7%**	**16**	**13%**	**-5%**	**0**	**0%**	**2**	**2%**	**-2%**
Proteinuria	**10**	**7%**	**16**	**13%**	**-5%**	**0**	**0%**	**0**	**0%**	**0%**

Preferred Term[a]	All Grades					Severe				
	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff	GM-CSF N=134		IL-2[b] N=127		Abs. Risk Diff
	n	PPI	n	PPI		n	PPI	n	PPI	
Dry skin	13	10%	12	9%	0%	0	0%	0	0%	0%
Neuralgia	13	10%	12	9%	0%	9	7%	8	6%	0%
Hypertension	13	10%	12	9%	0%	1	1%	1	1%	-0%
Hypomagnesemia	9	7%	13	10%	-4%	1	1%	2	2%	-1%
Neuropathy peripheral	*15*	*11%*	*5*	*4%*	*7%*	*4*	*3%*	*2*	*2%*	*1%*
Back pain	12	9%	8	6%	3%	4	3%	6	5%	-2%
Rash	8	6%	11	9%	-3%	0	0%	2	2%	-2%
Nausea	11	8%	7	6%	3%	3	2%	1	1%	1%
Weight increased	8	6%	9	7%	-1%	0	0%	0	0%	0%
Pruritus	10	7%	7	6%	2%	0	0%	0	0%	0%
Tachycardia	9	7%	7	6%	1%	1	1%	1	1%	-0%
Hyperbilirubinemia	5	4%	10	8%	-4%	0	0%	1	1%	-1%
Hypercalcemia	6	4%	7	6%	-1%	5	4%	4	3%	1%
Cough	7	5%	8	6%	-1%	1	1%	1	1%	-0%
Infusion related reaction	8	6%	5	4%	2%	3	2%	1	1%	1%
Chills	4	3%	9	7%	-4%	1	1%	1	1%	-0%
Constipation	7	5%	5	4%	1%	0	0%	0	0%	0%
Musculoskeletal chest pain	*10*	*7%*	*2*	*2%*	*6%*	*6*	*4%*	*0*	*0%*	*4%*
Urinary retention	8	6%	4	3%	3%	3	2%	0	0%	2%
Neck pain	7	5%	2	2%	4%	1	1%	1	1%	-0%

Abbreviations: PPI: per-patient incidence; Abs. Risk Diff: Absolute risk difference; GM-CSF: granulocyte-colony macrophage stimulating factor; IL-2: interleukin-2.
[a]PT's included if PPI ≥ 5% for either IL-2 or GM-CSF containing cycles
[b]Seven patients who received GM-CSF in Cycle 1 discontinued prior to starting Cycle 2.

7.5.3 Drug-Demographic Interactions

Neuroblastoma is primarily a disease that affects young children. In Study 301, the median age at enrollment was 3.8 years (range: 0.9 years to 15.3 years).

Table 53 provides the per-patient incidence of severe adverse events by gender for Study 301. In general, the adverse reaction profile for severe adverse events was similar in males and females. There was a trend toward increased incidence in severe adverse events for females. However the numbers of patients in each gender category is small so the significance of the observed differences in the PPI of severe adverse events for some preferred terms (such as decreased hemoglobin, lymphopenia, and capillary leak syndrome) is uncertain.

Table 53: PPI of Treatment Emergent Severe Adverse Events by Gender for Study 301 (PPI ≥10% in Any Gender Category in the ch14.18 Group)

Preferred Term	Ch14.18 Combination N=134		RA N=106	
	Females n=54	Males n=80	Females n=47	Males n=59
Lymphopenia	57%	49%	17%	22%
Platelet disorder	46%	34%	23%	25%
Hemoglobin	43%	28%	17%	15%
Pyrexia	37%	43%	6%	5%
Granulocytes abnormal	43%	28%	11%	15%
Hypokalemia	52%	26%	2%	2%
Abdominal pain	39%	23%	0%	0%
Drug hypersensitivity	28%	25%	0%	2%
Hyponatremia	17%	28%	2%	5%
White blood cell disorder	22%	18%	4%	12%
Alanine aminotransferase increased	28%	20%	2%	3%
Device related infection	19%	15%	11%	12%
Capillary leak syndrome	30%	19%	0%	0%
Sepsis	19%	15%	11%	7%
Pain	26%	18%	0%	0%
Hypotension	15%	18%	0%	0%
Diarrhea	13%	13%	0%	2%
Decreased appetite	11%	9%	2%	5%
Hypoxia	13%	11%	0%	2%
Urticaria	19%	9%	0%	0%
Aspartate aminotransferase	17%	6%	0%	0%

Preferred Term	Ch14.18 Combination N=134		RA N=106	
	Females n=54	Males n=80	Females n=47	Males n=59
increased				
Pain in extremity	11%	8%	2%	2%
Vomiting	11%	4%	0%	5%
Staphylococcal bacteremia	11%	5%	0%	0%

7.5.4 Drug-Disease Interactions

Studies of ch14.18 enrolled patients with similar baseline characteristics, so assessment of drug-disease interactions is not possible.

7.5.5 Drug-Drug Interactions

No formal drug-drug interaction studies have been conducted with ch14.18. Because ch14.18 is a monoclonal antibody that is metabolized by catabolism, it is not expected to impact the metabolic and clearance pathways for small molecules.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The Applicant did not submit carcinogenicity studies to the BLA.

7.6.2 Human Reproduction and Pregnancy Data

There are no human reproduction or pregnancy data available for dinutuximab and animal reproduction studies have not been conducted.

7.6.3 Pediatrics and Assessment of Effects on Growth

Long term evaluation of patient height and weight to assess the effects of dinutuximab on growth of pediatric patients has not been performed. Additionally, an analysis of data on height and weight parameters in patients with high-risk neuroblastoma is likely to be confounded by prior and concomitant therapies and underlying malignancies.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Although there were two cases of overdose of IL-2 reported in Study 301, there are no reported cases of overdose of ch14.18. Ch14.18 will be administered in a hospital setting, and there is no known abuse potential for ch14.18. Given the relatively long half-life of ch14.18 (approximately 10 days), signs and symptoms of withdrawal or rebound are not expected.

7.7 Additional Submissions / Safety Issues

The Division requested that the Applicant provide an analysis of the incidence of adverse observed with dinutuximab (ch14.18-UTC) in comparison with those observed with the NCI-produced ch14.18 in Study 201.

Table 54 provides the Applicant's analysis of the per-patient incidence of severe (≥ Grade 3) adverse events reported in at least 10% of patients treated with ch14.18 produced by NCI or dinutuximab produced by UTC. Twenty-five (93%) patients reported at least one treatment-emergent severe adverse event in both ch14.18-NCI and dinutuximab groups.

Table 54: Summary of Treatment Emergent Severe Adverse Events Occurring in at Least 10% of Patients Receiving Either ch14.18 Product in Study 201

	ch14.18-UTC n (%) [# of events]	ch14.18-NCI n (%) [# of events]
No. of Subjects with at least one Adverse Event	25 (92.6%)	25 (92.6%)
PYREXIA	14 (51.9%) [17]	13 (48.1%) [15]
HYPOKALAEMIA	8 (29.6%) [12]	9 (33.3%) [10]
ANAEMIA	8 (29.6%) [10]	10 (37.0%) [11]
HYPONATRAEMIA	5 (18.5%) [5]	5 (18.5%) [6]
PLATELET COUNT DECREASED	5 (18.5%) [6]	5 (18.5%) [6]
ALANINE AMINOTRANSFERASE INCREASED	5 (18.5%) [7]	2 (7.4%) [2]
NEUTROPHIL COUNT DECREASED	3 (11.1%) [3]	4 (14.8%) [5]
ABDOMINAL PAIN	2 (7.4%) [3]	3 (11.1%) [3]
DEVICE RELATED INFECTION	4 (14.8%) [4]	1 (3.7%) [1]
HYPOCALCAEMIA	3 (11.1%) [3]	2 (7.4%) [2]
LYMPHOCYTE COUNT DECREASED	2 (7.4%) [3]	3 (11.1%) [4]
PAIN	5 (18.5%) [9]	2 (7.4%) [3]
PAIN IN EXTREMITY	2 (7.4%) [3]	3 (11.1%) [3]
HYPOTENSION	2 (7.4%) [2]	3 (11.1%) [3]
WHITE BLOOD CELL COUNT DECREASED	1 (3.7%) [1]	3 (11.1%) [3]
HYPOXIA	1 (3.7%) [2]	3 (11.1%) [4]
URINE OUTPUT DECREASED	3 (11.1%) [6]	1 (3.7%) [2]

Source: Applicant's submission to the BLA

Overall, the toxicity profile for the two products appears comparable.

8 Postmarket Experience

There is no postmarketing experience with dinutuximab because dinutuximab is a new molecular entity that has not previously received marketing authorization from any country.

9 Appendices

9.1 Literature Review/References

Please see footnotes cited in the previous sections of this review.

9.2 Labeling Recommendations

At the time of completion of this review, labeling negotiations were underway. Please refer to the Unituxin package insert for final labeling recommendations.

9.3 Advisory Committee Meeting

The Division did not seek advice from the Oncologic Drugs Advisory Committee (ODAC) for this BLA. At the time of completion of this review, the Division is attempting to gain clearance of selected Special Government Employees (SGEs) to serve as external consultants for this application. Identification and clearance of SGEs for this application has been unusually challenging because virtually all pediatric oncologists with expertise in neuroblastoma have either been investigators or subinvestigators for Study 301, Study 302, Study 303, or Study 201; are seen as having significant conflicts of interest because they work at institutions that have enrolled patients onto one of these studies; or are involved in oversight of related clinical trials of competing products under development for high-risk neuroblastoma. Additionally, virtually all pediatric oncologists, even those without specific expertise in neuroblastoma, are employed at COG institutions that have enrolled patients onto one or more of the studies submitted to support this BLA and therefore are determined to have imputed conflict of interest . By the time of this review, the Division, in consultation with the FDA Division of Advisory Committee and Consultant Management have determined that approximately 15 potential SGEs were ineligible because they were either investigators or subinvestigators for one of the trials, were involved in overseeing the related clinical trials at COG, or had imputed conflicts of interest from their academic institution. At this time, The Division of Advisory Committee and Consultant Management is determining whether the Division of Oncology Products 2 can pursue a waiver for a divisional assignment in order to obtain advice from one of the selected SGEs.

9.4 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA125516

Submission Date(s): April 11, 2014

Applicant: United Therapeutics Corporation

Product: Unituxin (dinutuximab, ch14.18)

Reviewer: Martha Donoghue

Date of Review: May 7, 2014

Covered Clinical Study (Name and/or Number): DIV-NB-201, "A Comparative Pharmacokinetic and Safety Study of Chimeric Monoclonal Antibody ch14.19 with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interleukin-2 and Isotretinoin in High Risk Neuroblastoma Patients Following Myeloablative Therapy

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 126		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure*

by Clinical Investigators.[38] Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant has adequately disclosed financial interests/arrangements with clinical investigators, as recommended in FDA's February 2013 Guidance for Clinical Investigators, Industry, and FDA Staff, entitled *Financial Disclosure by Clinical Investigators.* In Form 3454, the applicant attests that the applicant has not entered into any financial arrangement with any of the listed clinical investigators for Study 201. In a subsequent submission to the BLA (May 19, 2014), the applicant clarified that this list comprised all clinical investigators and subinvestigators currently directly involved in the treatment or evaluation of research subjects in Study 201. The applicant also provided a comprehensive list of all the investigators either actively or previously involved in Study 201, who had no disclosable financial interests.

Clinical Investigator Financial Disclosure
Review Template

Application Number: BLA125516

Submission Date(s): April 11, 2014

Applicant: United Therapeutics Corporation

Product: Unituxin (dinutuximab, ch14.18)

Reviewer: Martha Donoghue

Date of Review: May 7, 2014

Covered Clinical Study (Name and/or Number): DIV-NB-301, "Phase III Randomized Study of Chimeric Antibody ch14.18 (ch14.18) in High-Risk Neuroblastoma Following Myeloablative Therapy and Autologous Stem Cell Rescue."

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from

38 See http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM341008.pdf.

		applicant)
Total number of investigators identified: 90		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The applicant has adequately disclosed financial interests/arrangements with clinical investigators, as recommended in FDA's February 2013 Guidance for Clinical Investigators, Industry, and FDA Staff, entitled *Financial Disclosure by Clinical Investigators.* Per the 2013 FDA Guidance, if a public or academic institution conducts a covered clinical study without any support from a commercial sponsor, but the study is later used by an applicant to support its marketing application, the clinical investigator's financial interests in and arrangements with the applicant do not need to be reported because the company was not a sponsor of the covered clinical study. In Form 3454, the applicant attests that there have been no financial arrangements with any of the listed clinical investigators for Study 301 (the randomized portion of COG Study ANBL0032). In a subsequent submission to the BLA (May 19, 2014), the applicant clarified that this list "reflects all the available information that UTC was able to obtain from NCI…" The applicant also included a letter signed by Sherry Ansher, Associate

Chief of the Agreement Coordination Group, Regulatory Affairs Branch of CTEP/NCI, indicating that NCI did not provide an equity interest to its clinical investigators and that NCI did not give ANBL0032 clinical investigators any form of compensation that was affected by trial outcome and did not provide significant payments of other sorts to the investigators or the investigators' institution (s) exclusive of the costs of conducting ANBL0032, and that investigators did not report any proprietary interest in ch14.18.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARTHA B DONOGHUE
09/13/2014

SUZANNE G DEMKO
09/16/2014
I have read this review and agree with the content, conclusions and recommendations.