Summary Review Memo

Date	August 17, 2020
From	Gerald D. Podskalny, DO Eric Bastings, MD
Subject	Summary Review
NDA/BLA # Supp #	BLA 125360 S-078 (b) (4)
Proprietary / Established (USAN) names	Xeomin (incobotulinumtoxinA)
Dosage forms / strength	Lyophilized powder for injection / 50, 100, and 200 Units/vials
Proposed Indication(s)	1. Treatment of upper limb spasticity in pediatric patients ages 2 to 17 years (S-078) (b) (4)
Recommended:	*Approval for S-078* (b) (4)

1. Background

Xeomin (incobotulinumtoxinA) is a botulinum neurotoxin type A approved for the treatment of cervical dystonia, adult upper limb spasticity, blepharospasm, sialorrhea, and the temporary improvement in the appearance of glabellar lines in adult patients.

This summary review concerns (b) (4) Supplement S-078 (b) (4) to add an indication for the treatment of upper limb spasticity, (b) (4) in pediatric patients 2 to 17 years of age. (b) (4)

Supplement S-078 was submitted in response to Postmarketing Requirement (PMR) 2565-3 from the original BLA approval letter for Xeomin dated July 30, 201 (b) (4) FDA granted a partial PREA waiver for the age group birth to 2 years.

None of the studies submitted in Supplement S-078 (b) (4) were conducted under a Special Protocol Assessment agreement.

Botox is approved for the treatment of spasticity (b) (4) lower limb) in pediatric patients age 2 to 17 years, and has unexpired orphan exclusivity for the treatment of upper limb caused by cerebral palsy in pediatric patients.

2. Clinical/Statistical

Minjeong Park, Ph.D., completed the primary statistical review, with supervisory concurrence from Kun Jin, Ph.D. (Team Lead) and H.M. James Hung, Ph.D., (Division Director) in the Division of Biometrics I.

Supplement S-078 (b) (4) include the results (b) (4) safety and efficacy studies in patients age 2 to 17 years: Study 3072, submitted in support of an indication for the treatment of upper limb spasticity (UL (b) (4) Long-term safety information is provided by the open-label extension phase of Study 3072 for the treatment of UL spasticity, and by open-label Study 3071 for the treatment of LL spasticity.

Efficacy

Study 3072 - Pediatric Upper Limb Spasticity

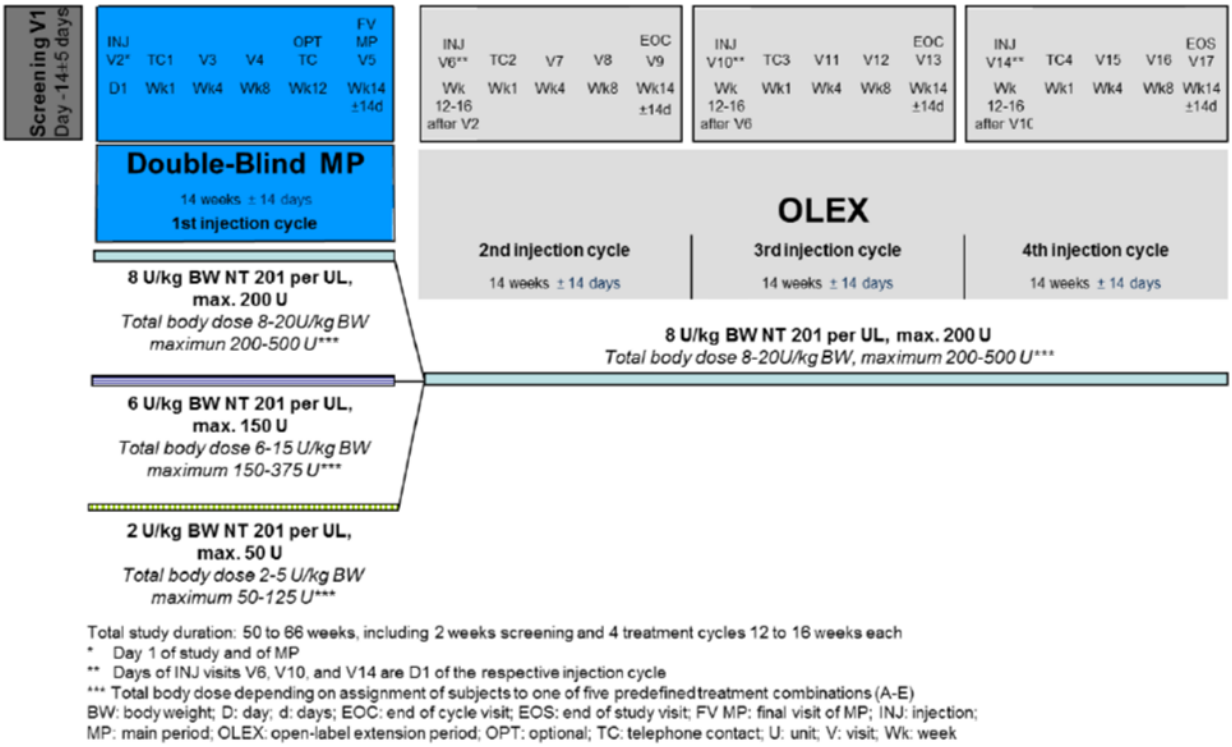
Study 3072 was a multicenter, randomized, double-blind, parallel-group, dose-response study of Xeomin (also called NT 201 in the development program) for the treatment of UL spasticity, or combined treatment of UL and LL spasticity, in children and adolescents (age 2 - 17 years) with spasticity caused by cerebral palsy. Patients were recruited from 28 sites globally, including 6 sites in the US.

Eligible patients were female or male patients ages 2 through 17 years, who had spasticity in one or both ULs caused by cerebral palsy. Patients needed to have an Ashworth Scale (AS) score of ≥2 in the elbow or wrist flexor muscles on at least one side at the baseline visit (Visit 2). Patients were graded at the screening visit using the Gross Motor Function Classification System (GMFCS), a five-level observational instrument that describes self-initiated movement, with emphasis on sitting, walking, and mobility. Levels are described as follows:

Level I	Walks without limitations
Level II	Walks with limitation
Level III	Walks using hand-held mobility device
Level IV	Self-mobility with limitations; may use powered mobility
Level V	Transported in a manual wheelchair

In the study, patients were administered treatment in a double-blind main period (MP), and in three subsequent open-label treatment cycles (OLEX). Patients were observed for 12-16 weeks after treatment on Day 1 (Visit 2) in the main period (MP). Patients who needed retreatment within 12 to 16 weeks of the first injection and met the entry criteria were offered up to 3 additional treatment cycles in an open-label extension period (OLEX). In the OLEX period, the interval between treatments remained 12 to 16 weeks, depending on the need for retreatment (see Figure 1).

Figure 1. Study 3072: Design Schematic (Source: Statistical Review)



Total study duration: 50 to 66 weeks, including 2 weeks screening and 4 treatment cycles 12 to 16 weeks each
* Day 1 of study and of MP
** Days of INJ visits V6, V10, and V14 are D1 of the respective injection cycle
*** Total body dose depending on assignment of subjects to one of five predefined treatment combinations (A-E)
BW: body weight; D: day; d: days; EOC: end of cycle visit; EOS: end of study visit; FV MP: final visit of MP; INJ: injection; MP: main period; OLEX: open-label extension period; OPT: optional; TC: telephone contact; U: unit; V: visit; Wk: week

Two main clinical target patterns were defined: “flexed elbow”, and “flexed wrist”. Randomization was stratified by primary clinical pattern (“flexed elbow” or “flexed wrist”) in a 1:1 ratio within each dose group. Additional clinical patterns that were optional for treatment included “clenched fist”, “thumb in palm”, and “pronated forearm”.

For combined UL + LL treatment, patients could present with clinical need for unilateral or bilateral LL spasticity treatment in one or more of the following clinical patterns: “pes equinus”, “flexed knee”, “adducted thigh”, and/or “extended great toe”.

There were five different treatment paradigms (A through E) that could be selected by the investigator, with both individual limb, and total body dose limits for each patient:

- A: UL, unilateral or bilateral, all GMFCS levels
- B: UL unilateral and ipsilateral LL, all GMFCS
- C: UL unilateral and LL bilateral, GMFCS levels I-III
- D: UL unilateral and LL bilateral, GMFCS levels IV-V
- E: UL bilateral, and LL bilateral, GMFCS level I-III

Treatment of at least one UL was part of all five paradigms, and used for the primary efficacy assessment in the study. The selection of the main clinically targeted UL region (either “flexed elbow” or “flexed wrist”) could not be changed during the study. In addition, if the patient had a need for bilateral UL treatment, the body side analyzed was to be decided by the investigator at screening.

Patients were to receive one of three fixed doses of Xeomin per treated UL:

- High dose: 8 U/kg (maximum of 200 U) per UL.

- Mid dose: 6 U/kg (maximum of 150 U) per UL.
- Low dose: 2 U/kg (maximum of 50 U) per UL.

In the target pattern "flexed elbow", treatment of biceps brachii was mandatory. In addition, the investigator could choose at the baseline visit (V2) to either inject the brachialis or the brachioradialis, based on clinical judgement.

The remaining optional target patterns, "thumb-in-palm", and "pronated forearm muscles", could be selected for treatment by the investigator, as clinically appropriate. The dose range per muscle is shown in Table 1, both for primary and optional clinical patterns.

Table 1. Dose Ranges for UL Primary and Optional Clinical Patterns (MP)

Clinical pattern	Injection sites per muscle min-max*	High Dose* BW-Adjusted Dose U/kg BW	High Dose* Total Dose U NT 201	Mid Dose* BW-Adjusted Dose U/kg BW	Mid Dose* Total Dose U NT 201	Low Dose* BW-Adjusted Dose U/kg BW	Low Dose* Total Dose U NT 201
Main clinical target patterns							
Flexed elbow (mandatory, if AS≥2)	Fixed Dose:	**4**	**100**				
Biceps brachii (mandatory)	1-3	2-3	50-75	1.5-2.3	37.5-56.3	0.5-0.8	12.5-18.8
Brachialis**	1-2	1-2	25-50	0.8-1.5	18.8-37.5	0.3-0.5	6.3-12.5
Brachioradialis**	1-2	1-2	25-50	0.8-1.5	18.8-37.5	0.3-0.5	6.3-12.5
Flexed wrist (mandatory, if AS≥2)	Fixed Dose:	**2**	**50**				
Flexor carpi radialis***	1	1	25	0.8	18.8	0.3	6.3
Flexor carpi ulnaris***	1	1	25	0.8	18.8	0.3	6.3
Optional clinical target patterns							
Clenched fist	Fixed Dose:	**2**	**50**				
Flexor digitorum superficialis***	1	1	25	0.8	18.8	0.3	6.3
Flexor digitorum profundus***	1	1	25	0.8	18.8	0.3	6.3
Thumb in palm							
Flexor pollicis longus	1	1	25	0.8	18.8	0.3	6.3
Adductor pollicis	1	0.5	12.5	0.4	9.4	0.1	3.1
Flexor pollicis brevis/opponens	1	0.5	12.5	0.4	9.4	0.1	3.1
Pronated forearm							
Pronator teres	2	1-2	25-50	0.8-1.5	18.8-37.5	0.3-0.5	6.3-12.5
Pronator quadratus	1	0.5	12.5	0.4	9.4	0.1	3.1
Total dose to UL per side	-	8	200	6	150	2	50

* Doses displayed for Mid and Low Dose are calculated values only. Judgment on clinical need by investigators will be based on the doses of High Dose. Values in Mid and Low Dose rounded to the 1st decimal place. Injection sites per muscle apply for all three dose groups, since the same volume of IP will be administered.
** The investigator has to decide to inject either brachialis or brachioradialis at the Baseline Injection Visit of MP.
*** If the patterns flexed wrist or clenched fist are chosen, both muscles of the respective pattern have to be injected.
BW: body weight, max: maximum, min: minimum, UL: Upper limb, U: unit
The maximum dose per site of 25 U NT 201 for <25 kg BW and 50 U NT 201 for ≥25 kg BW must be adhered.

*Doses displayed for Mid and Low Dose are calculated values only. Judgment on clinical need by investigators were to be based on the doses of High Dose. Injection sites per muscle apply for all three dose groups, since the same volume of IP was to be administered.
** The investigator had to decide to inject either brachialis or brachioradialis at the Baseline Injection Visit of the MP.
*** If the patterns flexed wrist or clenched fist were chosen, both muscles of the respective pattern had to be injected.
BW: body weight, max: maximum, min: minimum, UL: Upper limb, U: unit. The study used a maximum dose per site of 25 U Xeomin for patients <25 kg BW, and 50 U Xeomin for patients ≥25 kg BW. *Source: Statistical Review*

The selection of clinical patterns for lower limb (LL) treatment was up to the discretion of the investigator based on their clinical judgment. The lower limbs were not included in the assessment of efficacy. For a detailed description of the dosing for the five available paradigms, the reader is referred to Dr. Bergmann's clinical review.

In the OLEX period, patients were to receive open-label treatment with doses identical to those in the high dose group of the MP, regardless of their dose assignment in the MP. As clinically needed, UL treatment could be administered unilaterally or bilaterally, with doses as listed above for each treated UL.

The primary efficacy endpoint was the change from baseline in the Ashworth (AS) score in the primary clinical target pattern (i.e., elbow flexors or wrist flexors) at Day 29 (Week 4) of the MP. The co-primary efficacy endpoint was the Investigator's Global Impression of Change Scale (GICS) at the same timepoint.

The key secondary efficacy endpoints were:

- The change from baseline in AS score of the other treated main clinical target pattern (i.e., elbow flexors or wrist flexors, if treated) at Day 29 (Week 4) of the MP. This analysis was performed for the main clinical target pattern not analyzed as the primary efficacy variable, if two target patterns qualified as main clinical target pattern.
- The change from baseline in AS score of treated clinical target pattern clenched fist (in subjects treated in combination with flexed wrist) at Day 29 (Week 4) of MP.

There were 11 other secondary efficacy endpoints.

The primary outcome, Ashworth Scale, was evaluated using a mixed-model repeated measurement analysis (two-sided, significance level $\alpha=0.05$). Testing of the primary, co-primary efficacy, and key-secondary efficacy variables of the MP was performed in a 4-step hierarchical testing procedure as described below:

Step 1: Primary and co-primary efficacy variables for Xeomin high dose vs. Xeomin low dose.

Step 2: First key secondary efficacy variable (change from baseline to Week 4 in the AS score for the other treated main clinical target pattern of elbow flexors or wrist flexors, if treated), and co-primary efficacy endpoint (Investigator's GICS) for UL at Week 4 for Xeomin high dose vs. Xeomin low dose. This analysis was only done in patients having two main clinical target patterns.

Step 3: Second key secondary efficacy variable (i.e., clenched fist pattern of spasticity at Week 4) for Xeomin high dose vs. Xeomin low dose.

Step 4: Primary and co-primary efficacy variables for Xeomin mid dose vs. Xeomin low dose, and change from baseline in AS score of the other treated main clinical target pattern (i.e., elbow flexors and wrist flexors, if treated) at Day 29 (Week 4) of the MP, for Xeomin mid dose vs. Xeomin low dose.

The 4-step hierarchical testing strategy was used to control for type 1 error. If 1 of 4 hierarchical tests did not yield a statistically significant result, the subsequent tests were still performed, but considered to be only descriptive.

Efficacy Results

The safety evaluation set (SES) included 350 randomized patients: 176 patients in the Xeomin high-dose arm, 88 in the mid-dose arm, and 87 in the low-dose arm. The full evaluation set (FES) was identical to the SES. Most patients (331 of 351, or 94%) completed the MP.

The median age of patients was 6.5 years. The study population was 63% male, and 90% White, with similar distribution between the study arms. The 2 to 5-year-old age group was the largest (44%); 33% of patients were age 6 to 11 years, and 23% were age 12 to 17 years.

As shown in Table 2, the change from baseline to Week 4 in the AS score was significantly greater for patients treated with Xeomin high dose than for those treated with Xeomin low dose (p=0.017).

Table 2. Study 3072: Change from baseline to Week 4 in Ashworth score in the primary clinical target pattern (Xeomin high vs. low dose)

			NT 201		NT 201
		n	High dose	n	Low dose
Baseline (V2)	Mean (SD)*	173	2.7 (0.56)	85	2.6 (0.52)
Week 4 (V3)	Mean (SD)*	172	1.5 (0.83)	85	1.7 (0.74)
Change	Mean (SD)*	172	-1.2 (0.71)	85	-0.9 (0.69)
	LS-Mean (SE), (95% CI)	172	-1.15 (0.056); (-1.26; -1.04)	85	-0.93 (0.078); (-1.08; -0.78)
LS-Mean difference versus NT 201 low			-0.22 (0.091); (-0.40; -0.04)		-
	p-value		0.017		-

** observed cases*
AS score: 0 = No increase in tone, 1 = Slight increase in tone, 2 = More marked increase in tone, 3 = Considerable increase in tone, 4 = Limb rigid in flexion or extension
*LS-Means are from mixed model with treatment group, pooled site and pre-treatment status included as fixed factors and AS at baseline as well as GMFCS-E&R level at screening included as covariates. For MMRM visit*treatment is interaction term and visit is repeated factor.*
AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MMRM: mixed model repeated measures; MP: main period; SD: standard deviation; SE: standard error; V: visit
Source: Statistical Review

The difference in investigator's GICS score between Xeomin high dose and low dose did not reach statistical significance (see Table 3); thus, the hierarchical testing procedure was stopped.

Table 3. Study 3072: Investigator's GICS at Week 4 (Xeomin high vs. low dose)

		n	NT 201 High dose	n	NT 201 Low dose
GICS (V3)	Mean (SD)	176	1.7 (0.7)	87	1.6 (0.7)
	LS-Mean (SE); (95% CI)	176	1.64 (0.062); (1.52; 1.76)	87	1.55 (0.083); (1.38; 1.71)
LS-Mean difference versus NT 201 low			0.09 (0.094); (-0.10; 0.28)		-
	p-value		0.340		-

GICS: -3 = Very much worse, -2 = Much worse, -1 = Minimally worse, 0 = No change, +1 = Minimally improved, +2 = Much improved, +3 = Very much improved
No change imputation = missing values are set to '0' (no change)
LS-Means are from ANCOVA with treatment group, pooled site and pre-treatment status included as fixed factors and maximum AS score of the 2 possible primary target patterns flexed elbow or flexed wrist at baseline as well as GMFCS-E&R level at screening included as covariates.
ANCOVA: analysis of covariance; AS: Ashworth scale; CI: confidence interval; FAS: full analysis set; GICS: global impression of change scale; GMFCS-E&R: gross motor function classification system (expanded and revised version); LS: least square; MP: main period; SD: standard deviation; SE: standard error; UL: upper limb; V: visit

Source: Statistical Review

The result for the GICS is compatible with both Xeomin dosages providing a benefit, or neither providing a benefit. Therefore, FDA conducted an alternate analysis to evaluate the clinical meaningfulness of the difference in Ashworth score change between the Xeomin high dose and Xeomin low dose arms: the proportion of patients with at least a 1-point improvement from baseline to Week 4 in AS score (that degree of improvement is considered clinically meaningful). As shown in Table 4, 85% of patients in the Xeomin high dose arm met that responder definition, vs. 60% in the Xeomin low dose arm (nominal p value = 0.0099). This analysis establishes the clinical meaningfulness of the difference in Ashworth score change between the high and low dose arms of Xeomin in Study 3072.

Table 4. Study 3072: Responder rates based on the AS score at Week 4

Characteristic	Statistic	Xeomin High dose (N=173)	Xeomin Mid dose (N=87)	Xeomin Low dose (N=85)
AS score reduction				
Responders	n (%)	148 (86.0%)	66 (76.7%)	60 (70.6%)
Non-responders	n (%)	24 (14.0%)	20 (23.3%)	25 (29.4%)
Missing	n	1	1	0
Logistic regression analysis	p-value*	0.0099	0.9125	--

** Adjusted p-value for multiple comparisons was calculated by using Dunnett's test*
Source: Statistical review

The results for the change from baseline to Week 4 in patients who received optional treatment in a thumb-in-palm or pronated forearm pattern of UL spasticity (see Table 5) did not achieve nominal significance in the comparison of Xeomin high dose vs. low dose, but they trended in the direction of benefit, with a numerical advantage close to that seen for the primary endpoint. This subgroup analysis lacked statistical power. Considering the well-understood mechanism of action, and the magnitude of effect, it is reasonable to include in labeling dosing information for the muscles causing the thumb-in-palm and pronated forearm pattern.

Table 5. Study 3702: Change from baseline to V3 in the Ashworth scale score

Upper Limb Pattern	N	LS-Mean difference High vs low dose	p-value
Thumb in palm	98	-0.18 (-0.44; 0.07)	0.157
Treated pronated forearm	72	-0.14 (-0.33; 0.05)	0.137

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Subgroup analyses did not show that gender, age group, or country subgroups had a disproportionate effect on the efficacy results for Study 3072.

The subsequent endpoint analyses were exploratory, and will not be described here. The reader is referred to the clinical review for more discussion on the results for those endpoints.

Efficacy conclusion for Study 3072

The Applicant has provided evidence that Xeomin 8 U/kg (maximum of 200 U) per UL is effective for the treatment of upper limb spasticity in pediatric patients 2 to less than 17 years of age. Dosing information for the elbow flexors, wrist, finger, thumb flexors and the opponens pollicis will be included in the label. Because of the unexpired orphan exclusivity for Botox, the indication statement for Xeomin will exclude the treatment of pediatric patients ages 2 to 17 years with spasticity caused by cerebral palsy.

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3. Safety

Kenneth Bergmann, MD was the primary clinical reviewer [redacted] (b) (4)

The clinical safety review focused on the dose-response phase of Study 3072 (UL), dose-response Study 3070 (LL), open-label Study 3071 (LL), and the open-label safety extension of Study 3072 (UL).

Exposure

In Study 3071, long-term exposure for pediatric patients treated for lower limb spasticity included 370 patients ages 2 to 17 years; of these, 55 patients received four consecutive injections with 400 U (high dose) or more for four treatment cycles. Of these 55 patients, 24 received at least 500 U for four consecutive treatments.

Long-term exposure for treatment of UL spasticity comes from Study 3072. Including patients who continued treatment in the open-label extension phase (OLEX) of Study 3072, 44 patients received four consecutive treatments with 400 U (high dose) or more. Of these, 12 received four consecutive treatments of 500 U or more.

The number of patients treated for approximately one year fulfills the requirements of the postmarketing requirement to study pediatric spasticity. The long-term exposure is adequate to support a maximum recommended dose of 400 U for the treatment of pediatric UL spasticity.

Deaths

No deaths were reported among patients participating in any of the three studies.

Nonfatal serious adverse events

In the main phase (MP) of Study 3072, 5 patients reported 10 serious adverse events (SAEs). One patient had a SAE plausibly related to treatment with Xeomin based on the temporal relationship to treatment. A 5-year-old male with a previous history of pseudobulbar palsy, epilepsy, hydrocephalus, and spasticity of all four limbs choked on food on Day 19 after treatment with 225 U of Xeomin, causing aspiration, respiratory arrest, and cerebral edema. The patient was discontinued from the study, but his outcome was listed as recovered with sequelae. In the OLEX portion of Study 3072, 16 patients reported 27 SAEs, but none appeared related to treatment with Xeomin.

In Study 3070 and 3071 (LL), 30 patients experienced 57 SAEs, none of which appeared related to Xeomin treatment.

Adverse events resulting in discontinuation

In Study 3072, two patients discontinued from the study in the MP because of SAEs; one patient with aspiration that was possibly related to study treatment was discussed above. In the OLEX phase of Study 3072, five patients withdrew because of an adverse event; of these, one patient developed angioedema and coagulopathy 10 days after the second treatment with Xeomin. In Study 3070, two patients discontinued because of nonserious adverse events, and three patients discontinued because of SAEs; none of these appeared related to treatment.

Adverse events of special interest related to spread of toxin effect

The patient in the MP of Study 3072 who developed aspiration and respiratory arrest was discussed above. The other events reported as possible distant spread of toxin events include muscular weakness, constipation, dysphonia, and dyspnea, and were single events that resolved spontaneously. A patient experienced muscle weakness, and another experienced urinary incontinence (pelvic floor muscular weakness) 12 days after treatment. The symptoms resolved without additional treatment.

All adverse events

The most frequently reported adverse reactions (observed in at least 2% of patients in the MP of Study 3072) were related to respiratory tract or oropharyngeal infections common in the pediatric population (see Table 10). There was no evidence of dose-response for any of the common adverse reactions.

Table 10. Study 3072: Adverse Reactions Observed in ≥ 2% of Patients

Adverse Reactions	XEOMIN 2 Units/kg N=87 %	XEOMIN 6 Units/kg N=87 %	XEOMIN 8 Units/kg N=176 %
Infections and infestations			
Nasopharyngitis	6	3	3
Bronchitis	2	1	3
Pharyngotonsillitis[1]	2	6	2
Upper respiratory tract infection	2	0	2
Respiratory tract infection viral	1	0	2
Injury, poisoning and procedural complications			
Fall	0	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity	0	2	2

[1] Includes pharyngotonsillitis, pharyngitis, and tonsillitis

Adverse reactions occurring in at least 2% of patients in pooled treatment periods 1 and 2 of Study 3070 are listed in Table 11. Respiratory tract and oropharyngeal infection were reported most frequently without a relationship to dose.

Table 11. Study 3070: Adverse Reactions Observed in ≥ 2% of Patients (Pooled Period 1 and Period 2)

Adverse Reactions	Xeomin 4 Units/kg N=78 %	Xeomin 12 Units/kg N=77 %	Xeomin 16 Units/kg N=156 %
Infections and infestations			
Nasopharyngitis	12	10	11
Bronchitis	9	1	2
Pharyngitis	0	4	3
Respiratory tract infection viral	1	3	3
Upper respiratory tract infection	3	1	3
Respiratory tract infection	1	1	3
Pneumonia	3	3	1
Tonsillitis	3	1	1
Conjunctivitis	0	0	2
Laryngitis	0	0	2
Respiratory, thoracic, and mediastinal disorders			
Cough	5	1	2
Rhinorrhoea	3	1	1
Investigations			
Blood potassium increased	1	3	2
General disorders and administration site conditions			
Pyrexia	3	3	3
Injection site pain	1	0	2
Musculoskeletal and connective tissue disorders			
Pain in extremity	3	1	3
Muscular weakness	0	1	3

Patients reported a similar pattern of upper respiratory and oropharyngeal infections in the open-label portion of Study 3072 and in open-label Study 3071. An FDA MedDRA Query (FMQ) using broad and narrow search terms revealed similar results. There were no meaningful differences in the frequency of adverse reactions by gender or age group.

Clinical laboratory testing

Clinical laboratory testing was only performed at the screening and end-of-study visits, or when patients transitioned to an open-label phase from the MP. No signal of concern was identified.

Safety conclusions

No safety issue of concern was identified. The type and frequency of adverse reactions reported in pediatric patients treated for UL spasticity with Xeomin are similar to those reported with other botulinum toxin type A products (Botox and Dysport) approved for that indication. The safety database is adequate to support a 400 Units highest recommended dose of Xeomin for the treatment of patients with upper limb spasticity.

4. Other Relevant Regulatory Issues

(b) (4)

Postmarketing requirements

PMR 25653, which required safety data assessing distant spread of toxin effects after multiple administrations of Xeomin, during a minimum period of 12 months, collected in at least 100 pediatric patients (ages 2-17 years), with approximately one half of the patients treated for upper limb spasticity, and the other half treated for lower limb spasticity, is fulfilled.

PREA PMR 3012-2, which required a randomized, double-blind, adequate, and well controlled, multiple fixed-dose, parallel group clinical trial of Xeomin in botulinum toxin-naïve children age 2-17 years with upper extremity spasticity, with a minimum duration of 12 weeks, is fulfilled.

5. Financial Disclosure

The Applicant met the reporting requirement for financial disclosures under 21 CFR 54.2 by certifying the absence of a disclosable financial relationship with any investigator in any of the covered studies in the supplements.

6. Labeling

Agreement has been reached with the Applicant regarding labeling.

7. DSI Audits

DSI inspections were not requested for this supplement. Most sites did not enroll enough patients to alter the outcome of the study. COVID-19 travel restrictions and diversion of resources also made foreign site inspections impossible.

8. Conclusions and Recommendations

The efficacy of Xeomin (8 U/kg per upper limb) for the treatment of upper limb spasticity in children 2 to 17-years-old was clearly established using endpoints for which the division has considerable experience. The meaningfulness of muscle tone changes was established by the proportion of patients with at least a 1-point change on the Ashworth Scale. The data support a maximum recommended dose of 200 U per limb, up to 400 U when both upper limbs are treated in a single session.

The site and mechanism of action of botulinum toxins (including Xeomin), which interfere with the release of acetylcholine into the synapse at the neuromuscular junction, are well understood, and the data support a broad indication for the treatment of upper limb spasticity in pediatric patients 2 to 17 years of age. The approved indication will exclude treatment of upper limb spasticity due to cerebral palsy in children 2 to 17 years of age because of Botox's orphan exclusivity that blocks approval for the treatment of pediatric upper limb spasticity caused by cerebral palsy.


(b) (4)

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/s/

GERALD D PODSKALNY
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