FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Morning Session

Wednesday, July 12, 2017

7:59 a.m. to 11:00 a.m.

FDA White Oak Campus

White Oak Conference Center

The Great Room

Silver Spring, Maryland

1 **Meeting Roster**

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9 **(Non-Voting)**

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11 Vice President, Oncology Development

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16 *(Morning Session Only)*
17 Branch Chief
18 GTB, DCGT, OTAT, CBER, FDA
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1 P R O C E E D I N G S

2 (7:59 a.m.)

3 **Call to Order**

4 **Introduction of Committee**

5 DR. ROTH: Good morning. I'd first like to
6 remind everyone to please silence your cell phones,
7 smartphones, and any other devices you have if
8 you've not already done so. I'd also like to
9 identify the FDA press contacts, Angela Stark and
10 Andrea Fischer over here on the side.
11 My name is Bruce Roth. I'm the chairperson
12 of the Oncology Drug Advisory Committee, and I'll
13 be chairing this meeting. I'll now call the
14 meeting of the Oncology Drug Advisory Committee to
15 order. We'll start by going around the table and
16 introduce ourselves. Let's start down at the far
17 right here. Dr. Gordon?
18 DR. GORDON: Gary Gordon, AbbVie, industry
19 representative.
20 DR. BOLLARD: Cath Bollard, Children's
21 National, Washington, D.C.
22 DR. CRIPE: Tim Cripe, Nationwide Children's

1 Hospital, Columbus, Ohio.
2 DR. SMITH: Malcolm Smith, National Cancer
3 Institute.
4 MS. McMILLAN: Gianna McMillan, patient
5 representative.
6 DR. KWAK: Larry Kwak, City of Hope.
7 DR. GULLEY: James Gulley, NCI.
8 DR. RINI: Brian Rini, Cleveland Clinic.
9 DR. ROTH: Bruce Roth, Washington University
10 in St. Louis.
11 LCDR SHEPHERD: Jennifer Shepherd,
12 designated federal officer.
13 DR. NOWAKOWSKI: Grzegorz Nowakowski, Mayo
14 Clinic.
15 DR. REIN: Alan Rein, National Cancer
16 Institute.
17 DR. COLE: Bernard Cole, biostatistics,
18 University of Vermont.
19 DR. LU: Xiaoban Victor Lu, FDA.
20 DR. GAVIN: Denise Gavin, FDA.
21 DR. O'LEARY: Maura O'Leary, FDA.
22 DR. BRYAN: Wilson Bryan with the Office of

1 Tissues and Advanced Therapies of FDA.
2 DR. PAZDUR: Rick Pazdur, FDA, Oncology
3 Center of Excellence.
4 DR. ROTH: For topics such as those
5 discussed at today's meeting, there are often a
6 variety of opinions, some of which are quite
7 strongly held. Our goal is that today's meeting
8 will be a fair and open forum for discussion of
9 these issues and those individuals can express
10 their views without interruption. Thus, as a
11 gentle reminder, individuals will be allowed to
12 speak into the record only if recognized by the
13 chairperson. We look forward to a productive
14 meeting.
15 In the spirit of the Federal Advisory
16 Committee Act and the Government in the Sunshine
17 Act, we ask that the advisory committee members
18 take care that their conversations about the topic
19 at hand take place in the open forum of this
20 meeting.
21 We are aware that members of the media are
22 anxious to speak with the FDA about these

1 proceedings. However, FDA will refrain from
2 discussing the details of this meeting with the
3 media until its conclusion. Also, the committee is
4 reminded to please refrain from discussing the
5 meeting topic during breaks or lunch. Thank you.
6 Now, I'll pass it on to Lieutenant Commander
7 Jennifer Shepherd, who is serving as our DFO for
8 this meeting, who will read the Conflict of
9 Interest Statement.
10 **Conflict of Interest Statement**
11 LCDR SHEPHERD: Good morning. The Food and
12 Drug Administration is convening today's meeting of
13 the Oncologic Drugs Advisory Committee under the
14 authority of the Federal Advisory Committee Act of
15 1972. With the exception of the industry
16 representative, all members and temporary voting
17 members of the committee are special government
18 employees or regular federal employees from other
19 agencies and are subject to federal conflict of
20 interest laws and regulations.
21 The following information on the status of
22 this committee's compliance with the federal ethics

1 and conflict of interest laws, covered by but not
2 limited to those found at 18 U.S.C. Section 208, is
3 being provided to participants in today's meeting
4 and to the public.
5 FDA has determined that members and
6 temporary voting members of this committee are in
7 compliance with the federal ethics and conflict of
8 interest laws. Under 18 U.S.C. Section 208,
9 Congress has authorized FDA to grant waivers to
10 special government employees and regular federal
11 employees who have potential financial conflicts
12 when it is determined that the agency's need for a
13 special government employee's services outweighs
14 his or her potential financial conflict of
15 interest, or when the interest of a regular federal
16 employee is not so substantial as to be deemed
17 likely to affect the integrity of the services
18 which the government may expect from the employee.
19 Related to the discussion of today's
20 meeting, members and temporary voting members of
21 this committee have been screened for potential
22 financial conflicts of interest of their own, as

1 well as those imputed to them, including those of
2 their spouses or minor children, and for purposes
3 of 18 U.S.C. Section 208, their employers. These
4 interests may include investments, consulting,
5 expert witness testimony, contracts, grants,
6 CRADAs, teaching, speaking, writing, patents and
7 royalties, and primary employment.
8 Today's agenda includes discussion of
9 biologics license application 125646, for
10 tisagenlecleucel suspension for intravenous use.
11 The application was submitted by Novartis
12 Pharmaceuticals Corporation. The proposed
13 indication for this product is for the treatment of
14 pediatric and young adult patients 3 to 25 years of
15 age with relapsed/refractory B-cell acute
16 lymphoblastic leukemia.
17 This is a particular matters meeting during
18 which specific matters related to Novartis's BLA
19 will be discussed. Based on the agenda for today's
20 meeting and all financial interests reported by the
21 committee members and temporary voting members, no
22 conflict of interest waivers have been issued in

1 connection with this meeting.
2 To ensure transparency, we encourage all
3 standing committee members and temporary voting
4 members to disclose any public statements that they
5 have made concerning the product at issue.
6 With respect to FDA's invited industry
7 representative, we would like to disclose that
8 Dr. Gary Gordon is participating in this meeting as
9 a non-voting industry representative, acting on
10 behalf of regulated industry. Dr. Gordon's role at
11 this meeting is to represent industry in general
12 and not any particular company. Dr. Gordon is
13 employed by AbbVie.
14 We would like to remind members and
15 temporary voting members that if the discussions
16 involve any other product or firms not already on
17 the agenda for which the FDA participant has a
18 personal or imputed financial interest, the parties
19 need to exclude themselves from such involvement,
20 and their exclusion will be noted for the record.
21 FDA encourages all other participants to advise the
22 committee of any financial relationships that they

1 may have with the firm at issue. Thank you.
2 DR. ROTH: Thank you. I will open the
3 meeting with the FDA's opening remarks by Dr.
4 Bryan.
5 **FDA Introductory Remarks**
6 DR. BRYAN: Good morning and welcome on
7 behalf of the FDA, including the Oncology Center of
8 Excellence, the Center for Biologics Evaluation and
9 Research, and the Office of Tissues and Advanced
10 Therapies. This biologics licensing application is
11 the first BLA to be reviewed through the
12 collaboration of the FDA's new Oncology Center of
13 Excellence and the Center for Biologics Evaluation
14 and Research.
15 Novartis submitted this BLA in order to make
16 a new therapy, tisagenlecleucel, available to
17 patients with relapsed or refractory B-cell acute
18 lymphoblastic leukemia or ALL. Relapsed or
19 refractory ALL is a life-threatening disease, and
20 there's an urgent need for new and improved
21 therapies.
22 The clinical development of tisagenlecleucel

1 suggests that this is a life-saving product. The
2 clinical trials are not always a good predictor of
3 the effectiveness and safety of a marketed product.
4 In particular, we are concerned that the same
5 benefit and safety seen in clinical trials may not
6 carry over to routine clinical use.
7 This morning, we are asking this committee
8 to focus on manufacturing issues that relate to
9 product quality. Tisagenlecleucel is a complex
10 product. At this time, it is still not fully clear
11 how the FDA or Novartis can assure patients that
12 the marketed product would be the same product,
13 particularly with regard to safety and
14 effectiveness, as the product that was studied in
15 clinical trials.
16 This afternoon, we are asking this committee
17 to focus on specific safety issues.
18 Tisagenlecleucel has been associated with life-
19 threatening adverse events, including cytokine-
20 release syndrome and neurotoxicity. We are asking
21 for the committee's recommendations with regard to
22 measures to mitigate the risks of these adverse

1 events.
2 We are also concerned about the hypothetical
3 risk of secondary malignancies. Therefore, we are
4 asking for the committee's recommendations
5 regarding the nature and duration of follow-up for
6 patients who would receive this product.
7 Tisagenlecleucel is the first chimeric
8 antigen-receptor T-cell product. The FDA
9 recognizes that there is substantial interest among
10 various stakeholders, including scientists,
11 physicians, patients, and their families in this
12 field of chimeric antigen-receptor T-cell products.
13 What we hear from this committee may be
14 relevant to and will be considered in the
15 regulation of other products in this class.
16 However, we ask that the committee focus their
17 deliberations on only tisagenlecleucel and the data
18 in this specific BLA.
19 The FDA appreciates the efforts of the many
20 individuals who have contributed to the development
21 of this technology and this product. Scientists
22 have worked for decades to develop therapies based

1 on chimeric antigen-receptor technology.
2 The FDA also thanks the participants in
3 today's open public hearing. It is critical that
4 we hear from patients and patient advocates. Many
5 individuals are not able to be here today, and we
6 appreciate the written comments that we have
7 received regarding this BLA.
8 We want to thank all the members of this
9 committee who have given their time in order to
10 participate in today's discussion. I also want to
11 thank all the members of the Oncology Center of
12 Excellence, the Center for Biologics, and the
13 advisory committee staff, who have worked
14 tirelessly to prepare for today's meeting.
15 I now turn to Dr. Roth to continue with the
16 agenda.
17 DR. ROTH: Thank you, Dr. Bryan.
18 We will start with the applicant's
19 presentation. Dr. Hirawat?
20 **Applicant Presentation - Samit Hirawat**
21 DR. HIRAWAT: Thank you, Dr. Roth. Thank
22 you, Dr. Bryan, for setting it up for us.

1 Good morning, members of the advisory
2 committee, FDA staff, and guests. I'm Samit
3 Hirawat. I'm the head of the oncology global
4 development unit at Novartis. Today, my colleagues
5 and I will present the data to support the
6 biologics license application for CTL019 in
7 pediatric and young adult patients with
8 relapsed/refractory B-cell acute lymphoblastic
9 leukemia.
10 As you heard, B-cell ALL is the most common
11 malignancy diagnosed in children and young adults,
12 accounting for 85 percent of pediatric acute
13 lymphoblastic leukemia. The disease can be treated
14 successfully in most patients. However, there are
15 approximately 15 percent of patients whose disease
16 relapses or is refractory to treatment.
17 The vast majority of these patients face an
18 incurable disease with short overall survival.
19 Therefore, there is a need for novel treatment
20 options that provide deep and durable remissions,
21 curative treatment opportunities, and improved
22 quality of life for pediatric and young adult

1 patients with relapsed/refractory B-cell ALL.
2 Given this important unmet need, Novartis
3 and the University of Pennsylvania formed a
4 collaboration in 2012 to study chimeric antigen-
5 receptor T cells, or CAR T-cell therapies, based on
6 early promising clinical activity of this novel
7 approach. CAR T-cell therapies are a new treatment
8 paradigm in oncology.
9 CTL019 is different from typical small
10 molecules or biologic therapies because it is
11 manufactured for each individual patient using
12 their own cells. It is designed to harness the
13 power of a patient's own immune system to eliminate
14 cancer cells.
15 Our early development plan included B-cell
16 acute lymphoblastic leukemia as our first
17 indication. To support this effort in B-cell ALL
18 and future development of other CAR T-cell
19 therapies, Novartis acquired a cellular therapy
20 manufacturing unit in Morris Plains, New Jersey.
21 So why would we investigate CD19 as a target
22 for CAR T-cell therapy in treating B-cell

1 malignancies? It is well understood from
2 literature that CD19 is a surface protein which has
3 expression restricted to B cells and B-cell
4 precursors. As such, CD19 is not expressed on
5 pluripotent bone marrow stem cells, and tissue
6 cross-reactivity is not an issue for this target.
7 This reduces the potential for off-target effects
8 on bone marrow cells and red blood cell production.
9 Importantly, CD19 is expressed on the
10 surface of most B-cell malignancies. Therefore,
11 CD19 is an attractive target for CAR T-cell therapy
12 in treating B-cell malignancies that span different
13 stages of B-cell differentiation such as those
14 shown here.
15 So let me briefly reflect on how CTL019
16 functions. CTL019 cells express chimeric antigen
17 receptors. The CARs comprise of CD19 antigen
18 recognition domain fused to a CD8 hinge and a
19 transmembrane region followed by a 4-1BB
20 costimulatory domain and a CD3-zeta signaling
21 domain.
22 The antigen recognition domain is

1 responsible for binding to CD19 on normal and
2 malignant B cells. Following CD19 engagement, the
3 CD3-zeta component of the CAR is critical for
4 initiating T-cell activation and tumor cell
5 killing. The 4-1BB signaling further enhances
6 anti-tumor activity and augments the survival and
7 persistence of CTL019 cells.
8 CTL019 is designed to attack B cells that
9 express CD19 surface antigen. Ex vivo, a
10 lentiviral vector is used to insert the anti-CD19
11 transgene into a patient's T cells. The transgene
12 is transcribed and translated, and becomes
13 expressed on the surface of the T cells. The
14 resulting CTL019 cells are infused into the
15 patient.
16 In vivo, upon binding to CD19-expressing
17 cells, the CAR transduces a signal that promotes
18 T-cell expression, activation, target-cell killing,
19 and persistence of the CTL019 cells. This also
20 triggers cytokine release and CTL019 proliferation.
21 In summary, CTL019 is a living drug which
22 demonstrates activity after a single infusion.

1 CTL019 is provided to patients as an
2 autologous immunocellular therapy. This means that
3 it is developed using cells from the patient
4 receiving treatment. The process starts when white
5 blood cells are collected from the patient. The
6 cells are then transferred to our manufacturing
7 facility, where they're enriched, activated,
8 transfused, and expanded.
9 Following formulation and quality
10 assessment, the cells are returned to the clinical
11 site where the patient is infused. You will hear
12 more about the overall process of cell collection,
13 manufacturing, and delivery back to the site in the
14 presentations later this morning. But first, let
15 me take a moment to review the regulatory
16 highlights of our development program.
17 Orphan designation was granted in January
18 2014, and breakthrough therapy designation was
19 granted to Novartis in April of 2016. The BLA was
20 submitted in February of 2017. In addition,
21 Novartis also participated in the FDA pilot data
22 program and has been sharing clinical data with the

1 FDA on a regular basis.
2 CTL019 is also being developed in
3 conjunction with the European Medicines Agency and
4 was granted access to the PRIME pathway for
5 priority medicines. In addition to the trials
6 included in the BLA, Novartis has numerous other
7 studies with CTL019 planned or underway that will
8 follow hundreds of additional patients in the
9 clinical trial setting.
10 The development program in pediatric and
11 young adult patients with relapsed or refractory
12 B-cell ALL includes three key trials. They
13 enrolled more than 150 patients and provide up to
14 5 years of follow-up. B2202 study is the global
15 multicenter pivotal trial which is the basis of the
16 BLA submission. The overall design and endpoints
17 of study B2202 were agreed upon with the FDA.
18 Studies B2205J and B2101J are considered
19 supportive.
20 The data we will share with you today from
21 these three studies support the proposed indication
22 that CTL019, or tisagenlecleucel, is a genetically

1 modified autologous immunocellular therapy
2 indicated for the treatment of pediatric and young
3 adult patients 3 to 25 years of age with
4 relapsed/refractory B-cell acute lymphoblastic
5 leukemia.
6 Here is the agenda for the rest of our
7 presentation this morning. Next, we will hear from
8 Dr. Stephen Hunger, who will summarize the
9 treatment landscape and the challenges in managing
10 pediatric and young adult patients with B-cell ALL;
11 then Spencer Fisk will discuss the manufacturing
12 process for CTL019; and Dr. James Miskin will
13 provide an overview of our lentiviral vector.
14 Finally, we'll conclude the morning
15 presentations with Dr. David Lebwohl, who will
16 discuss the correlation of quality attributes to
17 clinical outcomes. During this afternoon's
18 clinical presentations, I will share our efficacy
19 data, followed by Dr. David Lebwohl again, who will
20 discuss our safety data and review the
21 pharmacovigilance plan.
22 Finally, Dr. Stephan Grupp will put these

1 data into context and discuss how CTL019 can add to
2 the armamentarium for physicians treating pediatric
3 and young adult patients with relapsed/refractory
4 B-cell ALL.
5 Here are some of the points you will hear
6 today to support that CTL019 has a positive
7 benefit-risk profile in pediatric and young adult
8 patients with relapsed/refractory B-cell ALL.
9 There is a significant unmet need to improve
10 outcomes in these patients. Novartis has developed
11 a highly reproducible and a safe manufacturing
12 process with proven efficacy in three trials in
13 over 150 pediatric and young adult patients.
14 Durable remissions were observed in the three
15 trials, and the pivotal study demonstrated an
16 overall remission rate of 83 percent.
17 The median duration of remission has not
18 been reached in any of the three trials. And in
19 the pivotal study, 75 percent of patients were
20 relapse-free 6 months after the onset of remission.
21 CTL019 has a well-characterized and manageable
22 safety profile with appropriate site training, and

1 Novartis is committed to a comprehensive
2 pharmacovigilance plan, including long-term safety
3 follow-up.
4 With that, I'd like to introduce Dr. Stephen
5 Hunger, chief of the Division of Oncology, director
6 of the Center of Childhood Cancer Research, and
7 holder of the Jeffrey E. Perelman Distinguished
8 Chair in the Department of Pediatrics at Children's
9 Hospital of Philadelphia. Thank you.
10 **Applicant Presentation - Stephen Hunger**
11 DR. HUNGER: Thank you, Dr. Hirawat.
12 Good morning. I'm Stephen Hunger from the
13 Children's Hospital Philadelphia. My clinical and
14 research interests focus on acute lymphoblastic
15 leukemia or ALL. I was the vice chair and then the
16 chairman of the Children's Oncology Group ALL
17 committee from 2001 to 2015. In these roles, I was
18 responsible for oversight of the design and conduct
19 of clinical trials that enrolled 2,000 patients per
20 year or 70 percent of U.S. children diagnosed with
21 ALL annually. I have received compensation for my
22 participation in today's proceedings, but have no

1 financial interest in the outcome of this meeting.
2 ALL is the most common malignancy of
3 childhood. There are approximately 5,000 cases of
4 ALL diagnosed annually in the United States.
5 Approximately 60 percent of these are diagnosed in
6 children and adolescents less than 20 years of age
7 with the median age of diagnosis being 15 years.
8 Eighty-five percent of childhood ALL cases
9 are B lineage ALL or B-ALL. Current multi-agent
10 treatment regimens achieve a cure rate of greater
11 than 85 percent. Primary refractory ALL or
12 induction failure is rare, occurring in 2 to
13 3 percent of children and remains a major
14 therapeutic challenge. And approximately
15 15 percent of children and young adults with ALL
16 will relapse, and relapsed ALL is a leading cause
17 of cancer death in children.
18 Today, you're going to hear about several
19 clinically relevant endpoints in trials that
20 demonstrate clinical benefit. The first are
21 response endpoints, and these include the overall
22 remission rate, which is typically used in relapsed

1 and refractory ALL trials, and minimal residual
2 disease, or MRD, which is important in newly
3 diagnosed and relapsed acute lymphoblastic
4 leukemia. The second point or time-to-event
5 endpoints include duration of response and overall
6 survival.
7 Overall remission rate is the sum of the
8 rates of complete remission, or CR, which is
9 achieving a bone marrow with less than 5 percent
10 lymphoblasts and a restoration of normal amount of
11 hematopoiesis with normal blood counts, and
12 complete remission within complete blood recount
13 recovery or CRi.
14 This is a recognized surrogate marker for
15 overall survival and has been used by the FDA as an
16 endpoint for accelerated approval of new agents in
17 relapsed and refractory pediatric ALL. Relevant
18 examples include clofarabine and blinatumomab.
19 Minimal residual disease or MRD is the
20 detection of sub-microscopic levels of leukemia
21 cells which can be identified by several
22 methodologies, including flow cytometry. These

1 technologies can identify one ALL cell among a
2 background of 10 to the 4th or 10 to the 5th normal
3 cells. It's the strongest prognostic factor
4 identifying good and poor responders and correlates
5 with outcome. MRD predicts the risk of relapse and
6 overall survival when measured during and after
7 induction therapy in both newly diagnosed and
8 relapsed ALL trials.
9 This slide depicts the results of a recently
10 published meta-analysis looking at the impact of
11 minimal residual disease at the end of induction
12 therapy, an outcome in pediatric ALL trials. This
13 meta-analysis included 20 trials in over 11,000
14 patients, and here we can see the dramatic
15 difference in outcome between patients who have no
16 MRD detected at the end of induction and those who
17 are MRD positive at the end of induction.
18 This correlates to a hazard risk of 0.23,
19 which means that patients who are MRD positive have
20 an approximately 4-fold increased rate of treatment
21 failure primarily due to relapse.
22 MRD is also a robust indicator in relapsed

1 ALL trials. This slide looks at the event-free
2 survival for patients enrolled in a trial conducted
3 by the Children's Oncology Group, AALL01P2, a first
4 relapse of B-cell ALL.
5 This looks at survival among patients who
6 achieved a clinical remission based upon the
7 minimal residual disease present at the end of the
8 first month of therapy. And here, you can see a
9 substantial difference in event-free survival among
10 those who are MRD positive versus MRD negative. It
11 is highly statistically significant.
12 Current treatment options for relapsed ALL.
13 The first job is to reinduce remission using
14 induction chemotherapy, then definitive post-
15 induction therapy is required for cure. Patients
16 who relapse after completion of therapy, generally
17 within 3 years of initial diagnosis, and have a
18 good MRD response to induction chemotherapy can be
19 treated with chemotherapy alone with reasonably
20 good outcomes.
21 In contrast, patients who relapse early,
22 within the 3 years after diagnosis, or those who

1 relapse late and are MRD positive post-induction,
2 or any patient with second or greater relapse
3 requires chemotherapy to obtain an MRD-negative
4 state followed by hematopoietic stem cell
5 transplantation. Patients who are MRD positive at
6 the time of hematopoietic stem cell transplant
7 rarely survive.
8 These intensive therapies are associated
9 with significant toxicity, treatment-related
10 mortality, and poor quality of life. Patients with
11 a second relapse have even fewer effective
12 treatment options.
13 Today, we'll focus our discussion on
14 patients with relapsed and refractory ALL.
15 Treatment options for these patients are quite
16 limited. Standard chemotherapy and hematopoietic
17 stem cell transplant have limited efficacy.
18 Patients who relapse post-transplant have a 2-year
19 overall survival rate of 15 percent. New agents
20 have limited response rates, and even those
21 patients who respond require transplant for cure.
22 Overall survival has not changed for these

1 patients.

2 Today, I will show some results of

3 clofarabine. It's a single-agent or in combination

4 therapy and blinatumomab in this setting. Patients

5 with relapsed/refractory ALL typically have

6 prolonged hospital stays and have an appreciable

7 risk of treatment-related mortality. Thus, most

8 patients with relapsed/refractory ALL, both adult

9 and pediatric, have significant unmet medical

10 needs.

11 This first slide shows the results of the

12 clofarabine monotherapy phase 2 trial published in

13 2006 by Sima Jeha and colleagues. Here, we see

14 this trial enrolled 61 patients and had a median

15 overall survival of 3 months.

16 There have been several trials in

17 relapsed/refractory ALL with clofarabine in

18 combination with other agents, most commonly

19 clofarabine, etoposide, and cyclophosphamide. This

20 slide shows the results of a phase 2 trial

21 conducted in pediatric relapsed/refractory ALL that

22 enrolled 25 patients and had a median overall

1 survival of 2.5 months. A similar trial was
2 conducted in Italy, enrolled 17 patients, and had a
3 median overall survival of 9 months.
4 This slide shows the recently published
5 results by Aaron von Stackelberg and colleagues,
6 published in late 2016 of the blinatumomab
7 phase 1-2 trial that enrolled 70 patients with
8 relapsed and refractory B-cell ALL. This trial
9 showed a median overall survival of 7.5 months.
10 This table collates the results of these
11 various trials. All these studies involved a
12 limited number of patients ranging from 17 to 70.
13 They received a variable number of prior treatment
14 regimens. In the clofarabine monotherapy trial,
15 62 percent of patients have received 3 or more
16 prior regimens. On the blinatumomab phase 1-2
17 trial, only 7 percent of patients have received 3
18 or more prior regimens.
19 They demonstrate overall response rates
20 ranging from 20 to 44 percent in general with the
21 exception of one small study that showed an overall
22 response rate of 76 percent. The median overall

1 survival ranged from 3 to 9 months with 12-month
2 overall survival of 20 to 40 percent. Early
3 mortality occurring within 30 days of treatment was
4 significant and ranged from 7 to 25 percent in
5 these trials.
6 Thus, the treatment landscape for
7 relapsed/refractory ALL shows that, despite current
8 treatment options, more than 600 epidemic and young
9 adult patients with ALL experience relapse each
10 year in the United States. Treatment options for
11 patients with relapsed and refractory ALL are
12 limited and are associated with poor outcome and
13 high toxicity. Most patients with relapsed and
14 refractory ALL remain incurable today.
15 Thus, there is a major unmet medical need
16 for novel treatment options for pediatric and young
17 adult patients with relapsed/refractory ALL to
18 provide deep MRD-negative and durable remissions,
19 curative treatment opportunities, and improved
20 quality of life.
21 Now, I'd like to invite Spencer Fisk, head
22 of cell and gene technical development and

1 manufacturing, who will take you through the CTL019
2 manufacturing process.

3 **Applicant Presentation - Spencer Fisk**

4 MR. FISK: Thank you, Dr. Hunger.
5 Good morning. My name is Spencer Fisk, and
6 I'm the head of cell and gene technical development
7 and manufacturing at Novartis. Novartis is
8 committed to an open dialogue with you today, and
9 we look forward to answering your questions.
10 With this being said, sometimes the agency
11 will hold these technical manufacturing discussions
12 in a closed session to protect proprietary
13 information. In this case, we agreed that there
14 was greater benefit to having an open discussion.
15 We therefore ask and thank you in advance for your
16 understanding if there are specific details we
17 can't address due to their proprietary nature.
18 Today, I will provide an overview of the
19 CTL019 manufacturing process. We have designed an
20 integrated process to collect immune cells from a
21 patient, reprogram them, and then return them to
22 the same patient. This process begins when a

1 patient is identified for treatment and undergoes
2 leukapheresis at an approved site.
3 The patient leukapheresis is then
4 transferred to our Morris Plains facility, acquired
5 in 2012, which has been dedicated to the
6 advancement of CTL019 over the past five years. It
7 is here where patient leukapheresis undergo
8 reprogramming prior to being returned to the
9 approved site for administration.
10 Novartis uses well-established standards to
11 maintain a rigorous chain of identity from
12 leukapheresis, through manufacturing, to patient
13 infusion. This includes using procedures from the
14 Foundation for the Accreditation of Cellular
15 Therapy, or FACT, and labeling standards from the
16 International Society of Blood Transfusion or
17 ISBT-128. These standards seamlessly integrate
18 with a Novartis quality system dedicated to
19 managing chain of identity of patient material and
20 final product.
21 As mentioned previously, Novartis purchased
22 its cell manufacturing facility in 2012. It has

1 been used to manufacture more than 250 patient cell
2 products for Novartis CTL019 studies to date, where
3 we have established rigorous training and quality
4 standards to ensure consistency in operations. The
5 facility has the ability to support the anticipated
6 demand, and we continue to invest in our
7 capabilities to further support clinical
8 development and commercial supply.
9 At the manufacturing facility, cells undergo
10 an enrichment and activation, transduction,
11 expansion, formulation, and final quality
12 assessments, as depicted here on the bottom half of
13 the slide. The final product is then cryopreserved
14 and shipped back to the treatment center for
15 patient administration. Utilizing both
16 cryopreserved starting material and final product
17 results in significant flexibility in manufacturing
18 starts and patient utilization.
19 Novartis uses a dedicated courier service to
20 ship leukapheresis material to the manufacturing
21 facility and to transport CTL019 back to the
22 treatment center.

1 As previously mentioned, the chain of
2 identity is crucial to this process. A
3 patient-specific bar code is attached at step 1 by
4 the team performing the leukapheresis and is
5 tracked at each subsequent step in the process. It
6 is then verified again at the clinical site by the
7 team administering CTL019 to the patient.
8 I will now go over each of the manufacturing
9 steps in greater detail, starting with
10 leukapheresis. Leukapheresis is a well-established
11 clinical procedure for obtaining white blood cells
12 from the patient. The procedure is performed for
13 Novartis without immobilization drugs using FDA-
14 approved equipment and standard mononuclear cell
15 collection parameters.
16 We qualify and maintain oversight of each
17 leukapheresis site, which supplies patient cells
18 for manufacturing. Each site is an FDA-registered
19 tissue establishment, FACT accredited, and must
20 actively be implementing ISBT-128 labeling
21 standards. Novartis audits, establishes, and
22 maintains quality agreements with these sites

1 against these requirements.
2 After collection, the cells are
3 cryopreserved and are quality-control tested to
4 ensure that there are a sufficient number of cells
5 required for manufacturing.
6 The frozen cells from the patient are
7 shipped to the manufacturing site, where they are
8 thawed and undergo an initial enrichment step.
9 Depending on the composition of the leukapheresis
10 in terms of T cells, B cells, and monocytes, the
11 cells will either undergo an antibody-based
12 positive selection step, or a density gradient
13 enrichment step, or both.
14 The different pathways ensure that cells
15 that are detrimental to the growth of the T cells
16 are removed and the purity of the T cells is
17 sufficient to allow effective growth. Following
18 enrichment, the cells are incubated with a
19 lentiviral vector made by Oxford Biomedica, our
20 manufacturing pattern.
21 The vector enables transduction of the
22 T cells. During this process, the CTL019 transgene

1 is stably incorporated into the DNA of the T cells,
2 which allows the expression of the T cells to
3 recognize and respond to CD19-expressing cells.
4 After transduction, the cells spend just over a
5 week in specialized culture conditions designed
6 specifically for the selective growth of T cells.
7 The cell culture includes anti-CD3 and
8 anti-CD28 antibody-coated beads, which as well as
9 interleukin 2 selectively stimulate T-cell growth.
10 This allows us to obtain a sufficient number of
11 highly pure T cells to give back to the patients.
12 Once we have grown the T cells, we remove
13 the anti-CD3 and anti-CD28 antibody-coated beads.
14 The cells are then frozen to enable shipment back
15 to the site, providing flexibility for both
16 patients and physicians regarding when the patient
17 is infused.
18 A broad panel of orthogonal tests are
19 conducted to ensure the safety and efficacy of the
20 CTL019 products. Final acceptable results
21 demonstrate consistency of the manufacturing
22 process and product quality assurance. All testing

1 is completed prior to cell product release to the
2 patient.
3 To ensure the product is safe for use, we
4 test for sterility, endotoxins, absence of
5 impurities, and replication-competent lentivirus.
6 Functional tests include the identity of the
7 chimeric antigen-receptor, the dose in terms of the
8 number of transduced viable T cells, and the
9 potency of the product. As potency represents a
10 key attribute, I will discuss it further in the
11 next slide.
12 There are multiple relevant biological
13 activities related to T-cell function that are
14 associated with the potential mechanism of action.
15 For CTL019, we measure interferon gamma secretion
16 as a measure of potency because it is a robust and
17 early indicator of T-cell activation. Other
18 functional measures include proliferation,
19 cytotoxicity, and long-term persistence.
20 We know that potency requires CAR expression
21 and is highly specific to CD19-expressing cells.
22 Although we only measure cytokine release for

1 potency, we have established characterization
2 assays for proliferation and cytotoxicity and see a
3 strong qualitative correlation between all three.
4 We have also seen persistence of CTL019 in
5 patients. Later, during today's presentation,
6 Dr. David Lebwohl will discuss how the potency
7 results correlate with clinical outcomes from the
8 patient and young adult relapsed/refractory B-cell
9 ALL patients.
10 Shown here on the left is the patient
11 variability in leukapheresis collected at the
12 sites. What can be seen is that there is a
13 potential for a great deal of heterogeneity in
14 incoming material. And now, on the right, we show
15 final product.
16 As you can see, we have designed and
17 confirmed a robust manufacturing process that uses
18 the pathways I have described to ensure that cells
19 detrimental to the growth of the T cells are
20 removed. Although we occasionally see minimal
21 amounts of NK cells, there are no detectible B
22 cells, monocytes, or dendritic cells. This leads

1 to the high level of purity that is seen in the
2 final CTL019 cell product.
3 In addition to ensuring cell product
4 consistency and purity, we have seen consistent
5 levels of transgene copy numbers per cell across
6 the targeted range of transduction. As shown here,
7 we achieve a stable vector integration averaging
8 1.3 copies per transduced cell. The impact of CAR
9 transduction on clinical response and safety will
10 be discussed by Dr. Lebwohl later this morning.
11 Novartis performs additional analytical
12 characterization to complement our extensive
13 product quality release testing, which has allowed
14 us to evaluate T-cell subpopulations and other
15 product attributes.
16 Listed here are some of the methods Novartis
17 has developed and utilized to link CTL019
18 attributes to our manufacturing success and
19 positive clinical outcomes. While we continue to
20 build knowledge and understanding using these
21 methods, we have not yet identified any additional
22 product attributes that provide greater assurance

1 of product quality.
2 As mentioned earlier, once we have completed
3 and checked results of all lot-released tests, the
4 cryopreserved product is shipped to the clinical
5 site, where the patient will be infused. Novartis
6 uses a dedicated courier service to ship the final
7 product and ensure the integrity and temperature
8 are maintained throughout shipping.
9 Patient identity is verified prior to
10 infusion, and the preparation and infusion of the
11 product is performed by qualified sites in
12 accordance with the prescribing information.
13 Sites were selected to ensure that an
14 appropriate infrastructure and training is in place
15 to support safe treatment of patients with CTL019.
16 Further details on this will be discussed later by
17 Dr. Lebwohl.
18 In summary, Novartis has accrued a
19 significant amount of patient-specific
20 manufacturing experience in global multicenter
21 trials with over 250 batches manufactured to date
22 across various indications. We have established a

1 highly reproducible manufacturing process with
2 demonstrated manufacturing success. Consistent
3 product safety and quality has been demonstrated by
4 extensive product release and characterization
5 testing.
6 Finally, I would like to share with you a
7 picture of our Wall of Hope displayed at our Morris
8 Plains manufacturing facility. Each light you see
9 displayed here on this board represents a patient
10 that has been treated by CTL019. It is a reminder
11 to us that every batch of product we manufacture
12 represents our hope for a unique cancer patient and
13 is a reminder of our responsibility to them.
14 Now, I'd like to turn the podium over to
15 Dr. James Miskin of Oxford Biomedica, our vector
16 manufacturer partner, who will present information
17 about our lentiviral vector.
18 **Applicant Presentation - James Miskin**
19 DR. MISKIN: Good morning, everybody. Thank
20 you, Spencer.
21 My name is James Miskin and I'm the chief
22 technical officer of Oxford Biomedica, which is a

1 company based in the U.K. specializing in the
2 development and manufacture of lentiviral vectors.
3 I'm going to run through a number of the key
4 aspects that relate to the lentiviral vector that
5 is used to manufacture CTL019. Given the
6 importance of and potential safety concerns with
7 the viral vector, great care was put into its
8 selection.
9 The lentiviral vector was chosen because it
10 offered an improved safety profile over other
11 retroviral vectors while still allowing for the
12 stable long-term expression of the transgene. The
13 vector system is designed to minimize the risk of
14 recombination, preventing potential replication-
15 competent lentivirus, or oncogenicity.
16 You will note that the FDA uses the term
17 RCR, or replication-competent retrovirus, in their
18 briefing document and discussion questions. In
19 this presentation, we use the term replication-
20 competent lentivirus, or RCL, as this is the only
21 type of RCR which is relevant directly to CTL019.
22 Vector manufacturing uses single-use

1 components, chemically defined formulation, and
2 vector is filter sterilized. Vector quality is
3 maintained through our comprehensive testing panel.
4 The patients who receive CTL019 are then followed
5 post-administration, and to date, there have been
6 no evidence for RCL or insertional oncogenesis.
7 The vector system has been selected because
8 of its safety. The vector integration profile of
9 lentiviral vectors has been well characterized, and
10 it allows for permanent genetic modification of
11 target cells, and it leads to long-term gene
12 expression. Gene expression is durable, with
13 evidence out to 780 days post-infusion in one
14 example case.
15 The ability to express the CAR transgene is
16 important, and the clinical experience has shown
17 that long-term gene expression from low vector copy
18 numbers per cell is managed.
19 The system has been designed to be safe
20 whilst using a manufacturing process that enables
21 efficient production. Unlike the original virus,
22 the vector cannot replicate. It also cannot

1 recombine to generate a replication-competent virus
2 because of a number of features.
3 First, the vector components have been
4 segregated onto four separate plasmids. Only the
5 essential features of the original virus have been
6 retained within the vector system. The vector
7 components themselves have been modified to remove
8 homology and thereby preventing homologous
9 recombination. The viral promoters and enhancers
10 have also been deleted.
11 Vector manufacturing is conducted using
12 human HEK293T cells grown in 10-layer cell
13 factories. Cells are transiently transfected with
14 the four plasmid components previously described,
15 and vector is harvested in the supernatant fluid
16 from the cells.
17 Vector is then purified and concentrated
18 using a combination of ion exchange and membrane-
19 based technologies, and then the vector substance
20 is frozen. Vector product manufacturing occurs in
21 a single day, where multiple vector substances are
22 thawed, pulled, filter sterilized, and then further

1 concentrated. Vector is filled into glass vials,
2 inspected, labeled, and frozen.
3 Vector manufacturing takes several weeks,
4 but then coupled with the extensive testing panel
5 that takes place, the entire process takes several
6 months.
7 The vector is tested to ensure safety and
8 quality. A broad panel of testing methods is
9 guided by a knowledge of the vector system, the
10 vector structure, and the manufacturing process.
11 We use a variety of different safety tests,
12 including one that is very specific for
13 replication-competent lentivirus or RCL for short.
14 We have spent a lot of time and effort
15 developing a method that is extremely sensitive and
16 highly efficient at the amplification and detection
17 of RCL from any source, irrespective of what that
18 might be. We then utilize a number of different
19 analytical methods to demonstrate purity by
20 measuring both the vector and the process-
21 associated impurities.
22 Biological function is a functional test

1 wherein the vector is incubated with target human
2 cells. Cells are grown up over a number of
3 pathologies to remove non-integrated DNA. And then
4 the DNA is extracted and analyzed by quantitative
5 polymerase chain reaction analysis to determine the
6 vector titer.
7 We are managing the theoretical risk of RCL
8 through our manufacturing and testing approach. We
9 have adopted a third-generation minimal lentiviral
10 vector system, which has been designed from first
11 principles to be safe.
12 Patient safety is ensured through a
13 comprehensive panel of highly sensitive tests
14 conducted on the viral vector itself and its
15 associated end of production cells. In addition,
16 CTL019 cells are also tested for RCL.
17 Finally, in addition to the trial conducted
18 with CTL019, where there is no evidence for RCL in
19 patients, there are also a number of other studies
20 using similar technology supporting the absence of
21 RCL from these systems. I'll expand on this in the
22 next slide.

1 Hundreds of patients have been treated with
2 cell therapies using lentiviral vectors with
3 cumulative decades of follow-up, and there have
4 been no observed cases of RCL in any trial. This
5 experience includes more than 250 manufactured
6 CTL019 cell products across the indications with
7 additional data from academic trials across the
8 U.S. in other indications. We therefore conclude
9 that RCL testing of the vector and the CTL019
10 product are adequate to ensure patient safety.
11 Considerable work has been done to analyze
12 the integration site preference of the viral vector
13 system. There is a lentiviral vector site
14 analysis, or LISA study, conducted by Novartis in
15 which over 90,000 unique integration sites have
16 been analyzed in multiple samples, including both
17 healthy volunteers and patients.
18 Lentiviral vector integration site analysis
19 uses molecular techniques to specifically map the
20 integration sites within the target cells, and then
21 the data are analyzed.
22 In summary, there is no evidence for

1 preferential integration near to genes of concern,
2 nor is there any evidence for preferential
3 outgrowth of cells harboring integration in sites
4 of concern.
5 In summary, CTL019 has been designed from
6 first principles to be safe and to prevent RCL. To
7 date, there has been no evidence for insertional
8 mutagenesis using third-generation lentiviral
9 vectors in any T-cell engineering therapy setting.
10 Oxford Biomedica as a company has been
11 working on this technology for over 20 years. We
12 have developed considerable experience of CTL019
13 vector manufacturing testing using a highly
14 reproducible manufacturing process and a
15 comprehensive testing panel. Many thanks for your
16 attention, and I'd like now to hand over the podium
17 to Dr. David Lebwohl.
18 **Applicant Presentation - David Lebwohl**
19 DR. LEBWOHL: Thank you, Dr. Miskin.
20 Good morning. I am David Lebwohl. I am the
21 CAR key franchise global program head at Novartis.
22 A critical aspect of developing a CAR T-cell

1 therapy is to understand the correlation of
2 characteristics of the engineered product with the
3 clinical outcomes of the infused patient.
4 I'll discuss two key aspects of the cell
5 product, CAR transduction and product in vitro
6 potency, and their correlation to the clinical
7 outcomes shown here. These measure the quantity
8 and activity of both the transgene and the cells
9 and are representative of the full set of product
10 attributes measured during the study.
11 Two aspects of transduction are shown here.
12 On the left, we look at the percent of cells which
13 are positive for CTL019 or the transduction
14 efficiency. On the right, we look at transgene
15 copy number per cell. In both cases, there are
16 positive patient outcomes across a range of
17 transgene-positive cells and transgene copy number
18 per cell, and no correlation between the
19 transduction measure and the response, either
20 CR/CRi or the lack of response.
21 Looking now at the potency assay, you see
22 all the non-responder patients at the low end of

1 potency. We don't yet understand why a small
2 number of patients did not respond to CTL019.
3 However, there were positive patient outcomes
4 across the complete range of acceptable potency
5 assay results, including at the low end.
6 Future analysis of the potency response
7 across a larger dataset of infused patients will
8 provide greater insight into the use of in vitro
9 measurement for predicting patient response.
10 We also correlated product characteristics
11 with cytokine-release syndrome, an important
12 on-target toxicity observed in our trials. Looking
13 again at CAR transduction, the severity of CRS did
14 not correlate with transduction efficiency or with
15 a transgene copy number. There is no correlation
16 of interferon gamma secretion by CD19-stimulated
17 CTL019 cells with the CRS grade observed post-
18 infusion.
19 In summary, Novartis has accrued extensive
20 experience in manufacturing CAR T cells. The
21 process that we developed is highly reproducible,
22 and the product is tested to ensure high quality.

1 As Dr. Miskin explained, the CTL019 vector has been
2 designed to prevent replication and recombination.
3 Thus, we believe that patient RCL testing is not
4 warranted in the commercial setting. The product
5 has been shown to result in a high rate of response
6 across the entire range of product quality
7 attributes.
8 We look forward to addressing any questions
9 that you may have about the technical manufacturing
10 aspects of CTL019. Thank you.
11 DR. ROTH: Thank you, Dr. Lebwohl. We'll
12 proceed now with the agency presentation,
13 Dr. Victor Lu?
14 **FDA Presentation - Victor Lu**
15 DR. LU: Thank you, Dr. Roth.
16 Good morning. My name is Xiaoban Victor Lu.
17 I'm one of the product reviewers for this BLA. In
18 the afternoon session, Dr. Maura O'Leary will
19 present clinical aspects of tisagenlecleucel. And
20 the goal of my presentation this morning is to
21 provide the product background information about
22 tisagenlecleucel and to set up the stage for the

1 product discussion this morning, as well as
2 clinical discussion this afternoon.
3 We will pose two questions for the
4 committee's discussion this morning. Today, I will
5 outline how the structure of CD19-directed chimeric
6 antigen receptor, or CAR, relates to the product
7 mechanism of action. I will outline some of the
8 safety issues associated with lentiviral vector
9 that is used to express the CAR.
10 I will also provide a high-level discussion
11 of how control of the manufacturing process and
12 product testing help to assure consistent safety
13 and quality of tisagenlecleucel.
14 Tisagenlecleucel is a genetically modified
15 autologic cell immunotherapy. It consists of a
16 patients' own T cells that express a chimeric
17 antigen receptor that specifically recognizes
18 CD19-positive cells, and a CAR gene is introduced
19 into the patient's T-cell by gene transfer with an
20 HIV-1-based retroviral vector in a process called a
21 transduction.
22 Throughout this presentation, I will use the

1 term "retroviral vector" for lentiviral vector
2 because the parenteral HIV-1 virus used for the
3 vector is a member of the retrovirus family.
4 CD19-positive B-cell tumors are the intended
5 targets of tisagenlecleucel. However, normal
6 B cells are also targeted. Thus, treatment with
7 tisagenlecleucel results in B-cell deficiency,
8 which can be managed through intravenous infusion
9 of immunoglobulin.
10 Unlike traditional pharmaceutical drugs,
11 tisagenlecleucel is a dynamic living biologic. The
12 T cells in the product can expand and differentiate
13 during the manufacturing process and the following
14 administration into patients. These unique product
15 characteristics should be kept in mind when
16 discussing manufacturing challenges and when
17 discussing clinical aspects of tisagenlecleucel
18 this afternoon.
19 The CAR mark is one of the most critical
20 components of tisagenlecleucel because it
21 determines the specificity and biological function
22 of tisagenlecleucel. It consists of three

1 different protein domains fused together to form a
2 chimeric antigen receptor.
3 The extracellular single-chain variable
4 fragment domains mediates specific binding to CD19
5 molecules on B cells. The high affinity of the
6 scFv binding domain also plays an important role in
7 CAR T-cell activation and effective functions, and
8 can impact the safety and activity of the product.
9 The length and topology of the spacer and
10 transmembrane domains are important for providing
11 appropriate orientation for antigen recognition and
12 the subsequent T-cell activation.
13 The intracellular secondary domains are
14 derived from the human CD3-zeta chain and the
15 costimulatory secondary domains from human 4-1BB.
16 Both intracellular domains contribute to T-cell
17 activation, expansion, and target-cell killing.
18 Because tisagenlecleucel is a rationally
19 designed immunotherapy, the presumed mechanism of
20 action is known and shown schematically on this
21 slide. T-cell activation begins with scFv binding
22 to CD19, which triggers a cascade of CAR signaling

1 activities that eventually leads to T-cell
2 activation and results in CAR T-cell expansion,
3 differentiation, persistence, and target-cell
4 killings. The T cells also release cytokines and
5 autocrine and paracrine signaling, which may result
6 in activation of some other type of cell such as a
7 macrophage. This multi-factorial mode of action is
8 important to keep in mind as we discuss potency
9 assays later on.
10 As mentioned already, the vector used,
11 tisagenlecleucel, was derived from the HIV-1 virus,
12 and the vector was designed to eliminate the vast
13 majority of the risks associated with naturally
14 occurring HIV infections.
15 As shown on this slide, HIV has many
16 accessory proteins that are necessary for viral
17 replication and pathogenesis, and these genes have
18 been removed from the vector, leaving the vector
19 unable to replicate.
20 Tisagenlecleucel vectors have also been
21 modified so that the long-term repeat [ph], or
22 LTRs, are self-activating, and the viral enhancer

1 regions have been removed, and taken
2 together -- and the resultant vector that does not
3 have the usual pathogenetic characteristics of an
4 HIV virus.
5 As shown on this slide, in the lentiviral
6 vector elements, the requirement to make the vector
7 includes 3 packaging plasmids and the CAR vector
8 plasmid. A VSV-G envelope is used as an envelope
9 instead of HIV-1 envelope protein, which means that
10 the vector is able to transduce a broad range of
11 cells, including both CD4 and CD8 T cells.
12 The CAR vector's plasmid contains a CD19 CAR
13 expression cassette along with minimal HIV
14 sequences that are essential for vector function.
15 An HIV packaging sequence site is essential for
16 vector genomes to be packaged into vector
17 particles, and the packaging plasmid elects the
18 site sequence, so the sequences from the packaging
19 plasmid are not packaged into vector particles.
20 The vector is produced by co-transfections of these
21 4 plasmids into a substrate cell line.
22 Theoretically, recombination events during

1 the vector manufacturing process could generate a
2 replication-competent retrovirus or RCR for short.
3 Throughout this talk, I will use RCR for RCL.
4 An early generation of gamma retroviral
5 vector derived from MLV that was contaminated with
6 RCR generated during the vector manufacturing
7 process and caused leukemias in animal studies.
8 However, the chance of RCR generation is reduced by
9 minimizing regions of homology and by segregation
10 of the packaging constructs on separated DNA
11 plasmids.
12 To date, RCR has not been detected in new
13 generation vectors or vector-transduced cells,
14 including tisagenlecleucel, used in the clinical
15 trials. Moreover, as shown in the previous slide,
16 many of the HIV accessory genes have been deleted.
17 So even if a replication-competent retrovirus were
18 generated, it would be severely weakened.
19 During clinical trials, tisagenlecleucel was
20 tested for RCR at multiple strategic steps wherein
21 RCR is most likely to be detected, including
22 testing during vector manufacturing and testing on

1 a cell product. A sensitive culture RCR assay was
2 used to test for the presence of RCR in the
3 retroviral vector and production cells in which the
4 vector was made.
5 In addition, each batch of tisagenlecleucel
6 was tested using a quantitative PCR test and,
7 following administration of tisagenlecleucel,
8 patient samples were collected and tested for RCR
9 according to the FDA guidance as part of a long-
10 term follow-up protocol. There have been no
11 positive results for any of the RCR tests conducted
12 for tisagenlecleucel.
13 In the commercial setting, Novartis will
14 continue to test each vector batch and production
15 cells as part of the vector manufacturing and
16 control. These tests will use the sensitive
17 co-culture RCR assay. In addition, each lot of
18 tisagenlecleucel will be tested by a qPCR assay
19 prior to product administration. We note that the
20 negative RCR test results during the manufacturing
21 process does not mean that there is no risk of RCR.
22 In the commercial setting, however, Novartis

1 does not plan to collect and test patient samples
2 for RCR. This is different from the long-term
3 follow-up that Novartis has been performing during
4 clinical trials.
5 In a previous slide, I pointed out that the
6 vector for tisagenlecleucel is designed to reduce
7 the risk of adverse events related to vector
8 integration. However, it is still possible that
9 integration of the vector into the host and cell
10 chromosomes might change the activity of adjacent
11 host genes. The vector may occasionally integrate
12 into genes and interrupt it. The vector may also
13 enhance the activity of nearby genes due to
14 potential enhancer elements in the vector. If the
15 nearby oncogene is activated by the vector, this
16 might lead to oncogenesis.
17 As we described in the briefing document,
18 insertional mutagenesis from gamma retroviral
19 vectors, has led to leukemia cases in multiple
20 clinical studies, and this can occur many years
21 after treatment. I would like to point out that,
22 to date, these delayed adverse events have only

1 been seen with stem cell products transduced with
2 gamma retroviral vectors. In contrast, to date, no
3 vector-associated leukemia cases have been seen
4 with tisagenlecleucel or any other vector-modified
5 T-cell products.
6 The same vector design lacks retroviral
7 enhancer sequences, and thus is less likely to
8 activate the nearby host genes. This design
9 therefore lowers the risk of oncogenesis.
10 Novartis does not perform vector integration
11 site analysis as part of the routine lot release
12 for testing tisagenlecleucel. However, Novartis
13 did perform a one-time study where they analyzed
14 the integration sites for 14 tisagenlecleucel
15 batches.
16 Overall, the distribution of integration
17 sites was similar to other lentiviral vectors with
18 a preference for open chromatins regions of gene
19 activities and the region of high GC content.
20 There was no preferential integrations of
21 the vector near oncogenes. However, the caveat is
22 that this type of analysis cannot predict whether a

1 rare mutated T-cell will preferentially expand in
2 vivo and possibly lead to oncogenesis. In the
3 past, integration studies in stem cells with other
4 vectors have failed to detect integration events
5 that eventually led to tumors in patients.
6 During clinical trials of tisagenlecleucel,
7 patients' cells were regularly monitored for vector
8 persistence and clonal expansions of the transduced
9 T cells. There have been no instances of clonal
10 expansion or vector-associated oncogenesis. If
11 tisagenlecleucel is licensed, however, no routine
12 collection of patient samples for such monitoring
13 is proposed.
14 However, if the patient develops a new
15 malignancy after infusion of tisagenlecleucel,
16 Novartis has indicated that they will attempt to
17 obtain fresh tumor tissues to analyze for the
18 presence of the tisagenlecleucel vector in the new
19 malignancy tissues.
20 This concludes the discussion of the vector
21 and its associated risk profile. In summary, the
22 potential vector-associated risks can be reduced

1 significantly, however, the risks cannot be
2 entirely eliminated. The issues of vector design
3 and product testing for RCR and insertional
4 mutagenesis will be discussed in this morning's
5 session. The long-term follow-up for patients will
6 be discussed in the afternoon session.
7 Now, I will move on to tisagenlecleucel
8 manufacturing and control. As already presented by
9 Novartis, the tisagenlecleucel manufacturing
10 process is a complex process that includes multiple
11 critical steps such as the collection of patient
12 cells by leukapheresis, transduction with
13 lentiviral vector, and activation and expansion of
14 T cells using CD3/CD28 antibody-coated beads.
15 This is a lengthy and complex manufacturing
16 process with a living, dynamic T-cell population.
17 Therefore, in-process monitoring and controls are
18 necessary to ensure the product lots are
19 consistent.
20 Controls of quality begin with a
21 qualification of critical components, including the
22 leukapheresis material and the vector. Each unit

1 operation is controlled by establishing critical
2 process parameters, for example time limits on
3 various processing steps, and the entire validation
4 of the manufacturing process is expected to be
5 validated.
6 In-process monitoring and lot-release
7 testing confirms that the cell product meets pre-
8 defined specifications beyond lot-release testing.
9 Additional characterization assays were performed,
10 providing further assurance of product quality
11 attributes.
12 In summary, the quality of tisagenlecleucel
13 is controlled by understanding how the
14 manufacturing process affects product quality
15 attributes and then controlling the manufacturing
16 so that product attributes consistently meet their
17 pre-defined limits. We will examine some of these
18 critical aspects of the manufacturing process
19 control in the next few slides.
20 Probably the most variable component of
21 tisagenlecleucel manufacturing process is the
22 starting material. The autologous leukapheresis

1 cells and autologous cells collected from each
2 patient contained many different types of cells
3 from peripheral blood. The composition of the
4 leukapheresis material can vary widely, depending
5 on the patient's genetic background, disease
6 status, age, and prior treatment history. And
7 during process development, Novartis has evaluated
8 how to adjust the manufacturing process to enhance
9 consistency of the final product.
10 As shown in this figure from the Novartis
11 briefing document, also shown in the Novartis
12 presentation early on, their manufacturing process
13 results in a final product that is consistently
14 high in T-cell content, as shown on the right
15 panel, even when the starting material is quite
16 variable, as shown on the left panel.
17 This figure illustrates that it is possible
18 to control the manufacturing process for consistent
19 final product quality even when the starting
20 materials are variable. As noted in the previous
21 slide, tisagenlecleucel contains mostly T cells,
22 however, vector transduction efficiency varies

1 greatly between patients, and only a subset of
2 T cells expresses the CAR. T-cell subpopulations
3 in tisagenlecleucel can also vary in terms of
4 CD4-CD8 ratio, central memory T cells, effector
5 memory T cells, et cetera.
6 It is unknown which T-cell subsets
7 contribute most to tisagenlecleucel activity. As I
8 mentioned earlier in my presentation, the T-cell
9 can change after administration. Cellular
10 interactions after administration may affect how
11 the cell expands, activates, differentiates, and
12 persists in the patients.
13 Lot-release testing for tisagenlecleucel
14 includes and tests for safety such as RCR,
15 sterility, endotoxin, and mycoplasma. In addition,
16 the number of vector copies per cell is controlled
17 because too much integration would increase the
18 risk of insertional mutagenesis.
19 It is important to assure the identity and
20 purity of the product, and strict control of the
21 chain of identity must be maintained throughout the
22 manufacturing process to provide the correct

1 product to the patient.

2 The levels of transduction between the

3 patient lots varies greatly, as we will see

4 shortly. So to ensure that patients are getting

5 the consistent dose of the active ingredient, the

6 dose of tisagenlecleucel is based on the number of

7 viable T cells expressing the CAR protein.

8 Potency is also an important measure for the

9 product's biological activity, and for

10 tisagenlecleucel, Novartis is measuring cytokine

11 production, which is described in more detail on

12 the next slide.

13 The purpose of potency testing is to assess

14 the ability of the final product to function

15 against CD19-positive cells. As I noted earlier,

16 when CD19 activates the CAR, it has many

17 stimulatory effects on the T cells. One of these

18 effects is the release of interferon gamma.

19 The lot-release potency test measures

20 interferon gamma release after tisagenlecleucel is

21 exposed to CD19-expressing cells. Novartis also

22 characterized the capacity of tisagenlecleucel to

1 kill CD19-expressing cells. This was submitted to
2 the BLA as supporting data, but will not be a part
3 of the lot-release test.
4 During the discussion this morning, we would
5 like the committee to comment on how best to
6 measure the functional activity of
7 tisagenlecleucel. Setting the appropriate range
8 for lot-release acceptance criteria is critical for
9 interpretation of clinical data and to ensure the
10 consistently safe potent and quality product for
11 patients.
12 The proposed lot-release specifications for
13 tisagenlecleucel were based on analysis of
14 accumulated historical testing data and analyzing
15 these data using appropriate statistical methods
16 for variation assessment and data trending.
17 Patient outcomes occurred across a broad
18 range of product attributes. It's difficult to
19 establish correlations between the variable product
20 attributes and clinical outcomes when the number of
21 patients is so small.
22 Some particularly valuable aspects of

1 tisagenlecleucel are illustrated in the next few
2 slides, including interferon gamma production and
3 transduction efficiency. This is historical
4 potency data for lots that were used in study B2202
5 in clinical development. The scales on both X- and
6 Y-axis, as well as the actual upper and lower
7 limits, are not shown because this is proprietary
8 information.
9 The proposed commercial acceptance criteria
10 are indicated by the red dashed lines, and the
11 potency assay measures interferon gamma release
12 upon culturing of tisagenlecleucel with
13 CD19-expressing cells.
14 There is a wide range of historical data,
15 and as a result, the upper and lower limits of the
16 acceptance criteria are also quite wide. The
17 dataset is still small. As manufacturing
18 experience increases, these values may become less
19 variable.
20 This is lot-release data for transduction
21 efficiency and for the lots that were used in the
22 clinical study B2202. As you can see, there is a

1 broad range of variability in terms of transduction
2 efficiency. There is currently a lower limit for
3 transduction efficiency, but not an upper limit.
4 It is important to note, again, that the
5 patient dose of tisagenlecleucel is measured in
6 terms of transduced cell number, therefore,
7 variable transduction efficiency has less impact
8 than if the dose were to be placed on the total
9 cell numbers. However, it should be noted also
10 that the dose of tisagenlecleucel also has a broad
11 range.
12 This diagram shows the number of vector
13 copies per transduced cell for the lots that were
14 used in the study B2202. As you can see, there is
15 also a wide range of values for the various
16 tisagenlecleucel lots early in the clinical trials.
17 Later in the clinical trials, product lots were
18 more consistent, and this coincides with when
19 Novartis finalized their manufacturing process
20 controls. Vector copy numbers affect both activity
21 and safety of tisagenlecleucel. Higher levels of
22 vector transduction will result in a higher

1 percentage of CAR-positive T cells, but also could
2 increase the risk of insertional mutagenesis.
3 In summary, tisagenlecleucel is a dynamic
4 biological product with the capacity to expand and
5 differentiate following administration. Process
6 controls are necessary to ensure product
7 consistency. Some product attributes are highly
8 variable from patient to patient and may have a
9 limited value for predicting safety and efficacy.
10 Products with variable characteristics were
11 administered during clinical studies. Vector
12 design has decreased the risk of RCR and
13 insertional mutagenesis. However, insertional
14 mutagenesis cannot be predicted through lot-release
15 testing alone.
16 RCR has not been detected in
17 tisagenlecleucel cell product or vector lots,
18 clonal dominance outgrowth has not been observed,
19 and long-term follow-up of patients during clinical
20 studies is still ongoing. There have been no
21 events related to RCR or insertional mutagenesis
22 with tisagenlecleucel.

1 With that, I conclude the FDA CMC
2 presentation. I would like to thank my FDA
3 colleagues for their contributions to this
4 presentation and the briefing document, and thank
5 you for your attention.
6 At this point, I would like to bring up the
7 two discussion questions that we prepared for the
8 committee. This is a preview, and we will not
9 discuss right now. We will discuss these questions
10 after the break.
11 Here is the first question. During
12 tisagenlecleucel development, the applicant
13 established product quality specifications to
14 assess chimeric antigen-receptor expression in
15 T-cell activity, including transduction efficiency
16 by flow cytometry, vector copy number per cells,
17 and interferon gamma production following
18 stimulation by CD19-positive cells.
19 Please discuss the following aspects of
20 control of the product quality of tisagenlecleucel
21 with respect to identity, safety, purity, and
22 potency: the design of the CAR construct and the

1 viral vector; the assessment of CAR expression and
2 T-cell activity through the number of transduced
3 T cells, the number of vector copy per cell, and
4 antigen-specific T-cell functions, for example
5 interferon gamma production and cytotoxicity upon
6 stimulation; and any other measurements such as
7 T-cell subpopulations and cell surface marker
8 characterization that could provide greater
9 assurance of product quality.
10 Here's the second question. Potential
11 safety concerns with tisagenlecleucel other
12 retroviral-based gene therapy products include
13 generation of replication-competent retrovirus and
14 insertional mutagenesis. Strategies to address
15 these concerns include vector design and product
16 testing.
17 Please discuss how vector design impacts the
18 risk of RCR.
19 Please discuss how vector design impacts the
20 risk that insertional mutagenesis might cause
21 secondary malignancies.
22 Please discuss the extent to which product

1 testing can mitigate the risk of RCR and
2 insertional mutagenesis.
3 At this point, I would like to turn it over
4 to Dr. Roth.
5 **Clarifying Questions to the Presenters**
6 DR. ROTH: Thank you, Dr. Lu.
7 We'll move on to clarifying questions both
8 for the agency and for the applicant. If you have
9 a question, just let Jen know. She'll write your
10 name down. We'll try to take these in order.
11 Also, for the people who are transcribing this, if
12 you could, identify yourself before you're asking a
13 question.
14 Maybe I can kick it off with a couple of
15 manufacturing questions. I don't know who the
16 appropriate person would be.
17 The first is, in the trial, time from
18 apheresis to infusion was 16 weeks. So my question
19 is, is that a number that you think would change in
20 the future with ramp-up, or is that kind of a fixed
21 ceiling that we have to deal with?
22 The reason I ask, of course, is that some

1 people died of progressive disease before ever
2 getting the infusion. And that's a testament to I
3 guess the relative futility of bridging
4 chemotherapy and maybe all the more reason to have
5 something new. But I was wondering whether you
6 thought that that would change with time. That's
7 the first question.
8 DR. LEBWOHL: Yes. So I'm David Lebwohl
9 again. Yes. We do believe this will change from a
10 clinical trial setting to the commercial setting.
11 I would ask Dr. Natarajan to explain the time we
12 expect in the commercial setting.
13 DR. NATARAJAN: Good morning. I'm Arvind
14 Natarajan from cell and gene technical development
15 and manufacturing at Novartis. In the commercial
16 setting, we expect that the time to manufacture the
17 product from the receipt of apheresis to shipment
18 of the product back to the patient would be
19 22 days.
20 So the timing upon launch for this
21 particular product, we expect to have a day to be
22 able to receive the leukapheresis material and then

1 to start the manufacturing process. The core
2 manufacturing process itself takes 10 to 11 days,
3 depending on the growth of the cells.
4 The testing and the disposition of the
5 product takes 9 days, and this is driven by the
6 longest lead test that we have as part of the
7 testing panel. And then we expect one day to pack
8 and ship the product back to the patients for a
9 total of 22 days.
10 DR. ROTH: Thank you. My second question
11 is, could you tell me a little bit more about the
12 seven, I believe, manufacturing failures? Namely,
13 no product came out and if there was some
14 retrospective analysis that could come up with some
15 common denominator. Or maybe even taking it a step
16 further, is there something that could be screened
17 on the front end by the treating physician to say
18 who is likely to get a manufacturing null?
19 DR. LEBWOHL: So let me first show you the
20 cases that were in our clinical trial B2202. There
21 were 6 cases in that trial; 4 of them were due to
22 insufficient growth. But we think these are

1 intrinsic factors to the patient cells. And as
2 part of the process in improving manufacturing,
3 what we've seen in the last 40 batches is a
4 98 percent success rate. So we do believe the rate
5 of inability to manufacture will be going down in
6 the commercial setting.
7 There are other reasons other than the
8 patient's intrinsic factors. One was low-dose
9 potency also could be factors for the patient and
10 high bead count, which is a manufacturing issue.
11 DR. ROTH: Thank you. Dr. Gulley?
12 DR. GULLEY: So perhaps this one is also for
13 Dr. Lebwohl. Not all the T cells are transduced.
14 So I was wondering if in the product release
15 criteria, if you were looking at the difference in
16 cytokine-release syndrome by total number of cells
17 rather than just the CAR T cells.
18 DR. LEBWOHL: Dr. Hamilton will address
19 this, please.
20 DR. HAMILTON: Hi. Jason Hamilton, cell and
21 gene technical development and manufacturing,
22 Novartis. We have in fact also evaluated the

1 relationships between the total number of viable
2 cells included within the product doses with
3 clinical outcome measures. And as you can see
4 here, we saw no relationship between total number
5 of viable cells infused and the grade of CRS that
6 the patient experienced.
7 DR. GULLEY: Thank you. One other question
8 quickly, and that is, with the intracellular
9 cytokine, have you looked at polyfunctional CAR T
10 cells? For instance, have you looked at other
11 cytokines besides gamma interferon like IL-2, TNF,
12 or CD107A?
13 DR. LEBWOHL: Dr. Brogdon?
14 DR. BROGDON: Hi. Thank you for that
15 question. Jennifer Brogdon, Novartis, pre-clinical
16 research. We do a number of exploratory assays to
17 understand the different cytokine profiles of these
18 cells over a number of different patient
19 characteristics as well.
20 These are still all in process. We
21 certainly see IL-2 and TNF alpha being produced.
22 We have found that interferon gamma is our most

1 reliable robust assay for the purposes of the
2 potency.
3 DR. ROTH: Dr. Bollard?
4 DR. BOLLARD: I have multiple questions. Am
5 I allowed to ask multiple or just a few? So I have
6 questions related to Drs. Lu, Fisk, and Miskin's
7 presentations, and I guess we can start with -- one
8 of the biggest questions I have is surrounding
9 product purity.
10 I know Dr. Fisk talked about the
11 heterogeneity of the leukapheresis products, and
12 then talked in very general terms about antibody
13 selection or Ficoll separation. So I would like to
14 know what sort of positive selection are you doing;
15 is this CD3-positive selection; and what is your
16 release criteria in terms of percent contamination,
17 B cells in particular, given that these are
18 patients where we saw that over 50 percent are
19 blasts in some leukapheresis products you're
20 receiving?
21 DR. LEBWOHL: I'll ask Dr. Natarajan to
22 address this, please.

1 DR. NATARAJAN: Good morning. Arvind
2 Natarajan from Novartis. We did see significant
3 heterogeneity in the composition of the incoming
4 leukapheresis material, and we have developed our
5 processes to be able to enrich T cells against a
6 variable background of the incoming material.
7 We use CD3, CD28 coated, or anti-CD3,
8 anti-CD28 coated antibody beads to be able to
9 positively select and enrich for the T cells prior
10 to the start of -- to initiate the start of
11 manufacturing.
12 DR. BOLLARD: So what's your release
13 criteria for percent B cells allowed in your final
14 product?
15 DR. NATARAJAN: I'm not able to share the
16 exact number because we consider that information
17 to be confidential. However, you can see from the
18 data that's displayed that we routinely did not see
19 B cells in our final product.
20 DR. BOLLARD: So by flow cytometry, it is
21 0 percent B cells in your final product?
22 DR. NATARAJAN: Based on our clinical

1 experience, yes.

2 DR. BOLLARD: So the reason I'm asking these

3 questions is because the CAR is 4-1BB

4 co-stimulatory moiety, which we know is important,

5 plays an important role in promoting B-cell

6 proliferation and survival in human B cells.

7 So obviously, if this lentiviral vector is

8 very powerful at getting into all lymphocyte

9 populations, how are you controlling for that, the

10 prevention of the CD19 CAR T cell getting into

11 B-cell blasts, et cetera?

12 DR. LEBWOHL: So part of what's going on, of

13 course, is that the blasts themselves had CD19, so

14 they would be eliminated as well by the CTL

15 integrated and T cells.

16 DR. BOLLARD: So when patients relapse after

17 CD19-directed therapy, both in blinatumomab and

18 CD19 CAR T cells, there's an appreciable number of

19 patients who relapse with CD19-negative ALL. So

20 how are you looking in those patients, whether your

21 vector is there?

22 DR. LEBWOHL: There is one example that was

1 reported at the RAC this year of a patient who had
2 CD19-negative B cells with CTL019 integrated. And
3 in that example, what was seen is that both the
4 number of blasts went up, but also the number of
5 CTL019-expressing cells. So it can be detected by
6 the presence of CTL019.
7 DR. BOLLARD: Then my last question's about
8 the lentiviral vector, Dr. Miskin's presentation.
9 Am I right in assuming there is not a lentiviral
10 producer cell line produced with your manufacturing
11 strategy for the lentiviral vectors? And if that's
12 the case, how are you controlling for your batch-
13 to-batch variabilities, et cetera?
14 DR. LEBWOHL: Thanks. Dr. Miskin?
15 DR. MISKIN: James Miskin, Oxford Biomedica.
16 Yes, you are correct. We don't use a stable
17 producer cell line. We use a parenteral HEK293T
18 cell.
19 DR. BOLLARD: So how many patients can you
20 treat with one batch, and how do you control for
21 batch-to-batch variability that might occur?
22 DR. MISKIN: Sure. So during the

1 manufacturing process development, we evaluated a
2 lot of different approaches toward transient
3 transfection of plasmid components. This is a
4 complex process. It needs to be very carefully
5 controlled. We believe we control this process to
6 the extent that it can be controlled in our
7 manufacturing process.
8 Simplistically, through the extensive
9 manufacturing that we've conducted specifically for
10 this product, but also for other products and also
11 other platform technologies, we obtain very
12 consistent upstream yields from our transient
13 transfection process.
14 DR. ROTH: Dr. Cripe?
15 DR. CRIPE: Tim Cripe, a follow-up question
16 on the plasmids. What are the different promoters
17 on each plasmid and are they different from each
18 other? And also, the promoter driving the
19 transgene in the final vector product, what is it?
20 How leaky is it? Have you looked at its vial
21 distribution of expression?
22 DR. MISKIN: So I'll tackle the question on

1 the plasmid promoters. These use a CNV promoter in
2 the plasmid. All of them do. I'll defer to the
3 Novartis team to talk about the vector promoter.
4 DR. LEBWOHL: I'll ask Dr. Brogdon to talk
5 about the vector promoter, please.
6 DR. BROGDON: Yes. Jennifer Brogdon,
7 Novartis pre-clinical research. So the promoter
8 for the transgene plasmid is the EF-1 alpha
9 promoter. This was based on early pre-clinical
10 work to understand what promoter would work
11 consistently at high levels of expression in
12 T cells without any silencing. And this was the
13 promoter chosen based on those studies.
14 DR. CRIPE: If all the plasmids contained
15 the same V promoter, doesn't that give you a
16 significant amount of homology between the
17 promoters, where you're sort of led to believe
18 homology was minimal and a chance of homologous
19 recombination quite small?
20 DR. LEBWOHL: Dr. Miskin, please address.
21 DR. MISKIN: James Miskin, Oxford Biomedica.
22 So you're right that the promoters are shared

1 through the plasmids. All the data to date that's
2 been evaluated in different retroviral vector
3 systems has demonstrated that where recombination
4 has occurred, it's been at the RNA level, not at
5 the DNA level. So we don't believe that there is a
6 risk of recombination, and we also don't see
7 recombination in any of our materials.
8 DR. CRIPE: One more question, another
9 follow-up to the purification of the product, do
10 you look at CD34 or other measures of stem cell in
11 that product? Because that's where the biggest
12 risk would be for integration that would be
13 concerning.
14 DR. LEBWOHL: I'll ask Dr. Natarajan to
15 address that.
16 DR. NATARAJAN: We did not test for stem
17 cells, CD34s.
18 DR. ROTH: Dr. Rini?
19 DR. RINI: Thank you. Dr. Lebwohl mentioned
20 that there's no plans for RCL or RCR testing, and I
21 guess my question is, why not? I understand the
22 rationale, but what's the downside of doing it? Is

1 it operational cost? Is it that you wouldn't know
2 what to do with the result per se?
3 DR. LEBWOHL: The most important reason not
4 to do the RCL testing is what Dr. Miskin explained.
5 And let me just show you what is happening in our
6 trials just to start.
7 So we do have a long-term safety study.
8 This is planned now for 15 years per the FDA
9 guidance. And this is an interventional trial,
10 where the patients are actively enrolled. Of
11 course, they give consent to joining this trial.
12 And these are patients all who have been in our
13 clinical trials.
14 As mentioned, we do plan. Not only do we
15 have hundreds of patients right now, but we will
16 have hundreds of patients coming in the future who
17 will be joining this long-term study. What we do
18 in the long-term studies is to study adverse
19 events, efficacy, immunogenicity, persistence by
20 the CAR transgene, VS-g, as we've heard about, as
21 well as secondary malignancies.
22 What we propose in the commercial setting is

1 that we will have a registry. So we do want to
2 follow all patients. This will be managed as bone
3 marrow transplant registries are. And because this
4 is a pediatric population, we do expect to have a
5 very high level of voluntary participation in this.
6 As you see, we do not plan to do the VS-g as
7 we've mentioned. The biggest reason is that, what
8 Dr. Miskin explained, there's a very low risk of
9 possibility of seeing RCL in these trials. In
10 addition, the ability to collect samples, blood
11 samples, over a long period of time of patients who
12 are coming for a one-time treatment, we think is
13 also not very feasible; and more to the point, we
14 don't think it will be very helpful.
15 We can address -- if we do see an event, an
16 unexpected event that may be related to RCL, we can
17 do studies at the time that it's detected.
18 DR. ROTH: Dr. Smith?
19 DR. SMITH: Yes. You showed data for the
20 relationship between potency and CR rate. Do you
21 have similar data for the relationship between
22 potency and duration of response, for example EFS

1 at 6 months, or 9 months, or 12 months?
2 DR. LEBWOHL: Yes. Dr. Hamilton will
3 address that question.
4 DR. HAMILTON: Jason Hamilton, cell and gene
5 technical development and manufacturing, Novartis.
6 We have looked at this. We essentially do not see
7 any relationship between the potency readout and
8 duration of response.
9 DR. ROTH: Roth, St. Louis. Maybe I could
10 just ask one more question. I heard some allusion
11 to possibly a relationship between the number of
12 infused cells and safety. So the product that
13 comes out, does the same total product go into a
14 3-year-old and a 25-year-old?
15 DR. LEBWOHL: So the dosing is based on
16 weight; if you could pull up a dosing slide. And I
17 should mention, the patients who are less than
18 50 kilograms get dosed by weight. Patients above
19 50 kilograms get a fixed dose.
20 Of course, this is a living drug, as we've
21 described it, so the dose in the person and the
22 effective dose obviously changes a great deal once

1 it's infused into the patient. And just to show
2 you the doses for patients who are greater than
3 50 kilograms, the median dose is 1.85 times 10 to
4 the 8 cells. In the less than 50 kilograms, it was
5 3 times 10 to the 6 per kilogram.
6 DR. ROTH: Thank you. Go ahead, Dr. Kwak.
7 DR. KWAK: I apologize if I missed this, but
8 what cells do you use to measure the viral titer?
9 Is it primary T cells or some other cell line?
10 DR. LEBWOHL: I'll ask Dr. Miskin to address
11 that, please.
12 DR. MISKIN: James Miskin from Oxford
13 Biomedica. So as part of the panel of release
14 tests that we at Oxford Biomedica perform, we use a
15 human HEK293 cell to evaluate titer. In our
16 experience, we find that that's very representative
17 of measuring the functional activity of that
18 vector.
19 DR. KWAK: Sorry. Have you compared this
20 against primary T cells?
21 DR. MISKIN: Yes. As part of the work that
22 Novartis does, they also do work in primary T cells

1 as well, as part of their MOI assay. And that's
2 performed as well, but it's performed by Novartis
3 rather than Oxford.
4 DR. KWAK: Thank you.
5 DR. ROTH: Roth, St Louis. Just one quick
6 question in terms of the duration, you were talking
7 about the following of people, possibly looking for
8 cases of insertional mutagenesis, or RCL, or
9 whatever.
10 Do you have a prospective timeline? Not
11 that I do, but I was wondering what you thought
12 about this as someone who gets lung cancer 25 years
13 later and has 75 pack-years or whatever, it's not
14 necessarily something that you'd want to delve
15 into. So I didn't know what your horizon was for
16 following that.
17 DR. LEBWOHL: The registry itself doesn't
18 have a fixed time on it yet so far. Of course, the
19 15 years certainly is a starting point related to
20 the long-term follow-up and our initial thought.
21 But we're going to learn a lot in the next 15
22 years, and I think we'll consider it based on that.

1 But the registry is not time defined.
2 DR. ROTH: Any other clarifying questions?
3 Go ahead, Dr. Cripe.
4 DR. CRIPE: Do patients develop anti-
5 idiotypic antibodies against the T-cell receptor?
6 Have you looked at that?
7 DR. LEBWOHL: I'll ask Dr. Thudium to
8 address the immunogenicity of CTL019.
9 DR. THUDIUM: Karen Thudium, Novartis
10 clinical pharmacology. So we do see immunogenicity
11 present in patients at baseline coming into the
12 trial, but I think it's more important and more
13 relevant to look at the treatment-induced
14 immunogenicity that we see. And we've assessed and
15 determined that the presence of immunogenicity does
16 not have an impact on the expansion, persistence,
17 nor the safety or duration of remission.
18 DR. ROTH: Go ahead.
19 DR. CRIPE: Tim Cripe again. The T cells
20 not only have the TCR that you express in the
21 transgene, but also in native T-cell receptors. So
22 is there a polyclonal expansion, or does one

1 predominate following engagement of the antigen?
2 Is there any concern about expansion of an
3 autoimmune T-cell, for example?
4 DR. LEBWOHL: I'll ask Dr. Brogdon to
5 address that, please.
6 DR. BROGDON: Thank you. Dr. Brogdon.
7 Sorry, Jennifer Brogdon, Novartis pre-clinical
8 research. So we're continuing to explore in the
9 space of expansion of T cells post-infusion. These
10 are exploratory measures to understand whether it's
11 clonality or heterogeneous.
12 The studies we've looked at to date are
13 largely quite heterogeneous in nature. You can see
14 expansions, of course, at the CARs. You can't look
15 at cells that are untransduced and measure any
16 level of expansion of those cells, but with
17 isolated exceptions, we've seen very heterogeneous
18 expansion of these populations of CAR-positive
19 cells.
20 DR. ROTH: Dr. Nowakowski?
21 DR. NOWAKOWSKI: Greg Nowakowski. As with
22 any new therapy, promising therapy, there is

1 sometimes demand, which can outpace manufacturing
2 capacity. Have you experienced it in the 2202
3 study? In other words, was there a wait list of
4 patients who were trying to enter the trial, but
5 couldn't enter because of limited manufacturing
6 capacity? And if so, have you been able to meet
7 the demand by the end of the trial?
8 DR. LEBWOHL: Yes. So there was limitation
9 in the clinical trial setting. There were waits
10 for some patients. I'll ask Dr. Natarajan to
11 address the commercial setting.
12 DR. NATARAJAN: Arvind Natarajan from
13 Novartis. In the commercial setting, we expected
14 to have adequate capacity to be able to meet the
15 expected commercial demand. The facility that we
16 have at Morris Plains is designed as a modular
17 facility, and we use only a small fraction of the
18 facility over the course of manufacturing for the
19 clinical trials. And we are expanding the use of
20 the facility to support the expected commercial
21 demand. So we expect to have adequate supply to
22 meet the demand.

1 DR. NOWAKOWSKI: Going back to your trial
2 experience, have you been able to meet the demand
3 by the end of the trial, or was there still some
4 wait list by the --
5 DR. LEBWOHL: By the end of the trial, there
6 was no wait for the patients as the capacity was
7 growing.
8 DR. NOWAKOWSKI: The number of patients in
9 the trials is really small, but is there any
10 evidence of different clinical activity or any
11 other difference in the product itself with this
12 expansion of the capacity, production capacity, for
13 the duration of the trial?
14 DR. LEBWOHL: I'll ask Dr. Natarajan to
15 address that.
16 DR. NATARAJAN: Arvind Natarajan from
17 Novartis again. We maintained control over the
18 manufacturing for each patient on an individualized
19 basis. So we had dedicated operators who perform
20 the manufacturing unit operations for each patient
21 and are dedicated for the duration of that unit
22 operation. So we're able to scale this out as we

1 manufacture multiple patients, so we did not see
2 any differences.
3 DR. ROTH: Thank you. Any other --
4 Dr. Cripe? I didn't know you had another question.
5 DR. CRIPE: Sorry. Jim Cripe. So you're
6 proposing certain release criteria, but you have
7 some patients that, if I understand correctly,
8 those products were used in the trial that fell
9 below those release criteria, 3 or 4 on each of
10 these graphs.
11 So one, is that correct? And if so, did
12 those patients have benefit so that there's even a
13 reason to have these lower-limit release criteria?
14 Because this is going to be their one shot at this
15 treatment. Right? You get to collect it, and
16 that's it.
17 DR. LEBWOHL: I'd say there are two types of
18 specifications. One, I should mention because that
19 was clinical. You see in the FDA slides a certain
20 dose range. During the trial, we actually expanded
21 from the initial target dose range to go to a lower
22 dose range because we saw in the trial from

1 Dr. Grupp at CHOP that he was seeing responses at
2 this lower range.
3 So we did expand. We asked the FDA
4 specifically for permission to give those lower-
5 range number of cells to patients, and we found in
6 fact that there was success with a lower number of
7 cells. And I'll ask Dr. Natarajan to address other
8 types of that specification.
9 DR. NATARAJAN: So over the course of the
10 clinical trials, the specifications that have been
11 set have been based on our range of experience. So
12 they accommodate the expected variability of the
13 patient material in a commercial setting.
14 DR. CRIPE: I guess I don't feel like I've
15 gotten an answer to my question. So the question
16 is, if you make a product on a patient, and it
17 doesn't pass your criteria, and then they don't get
18 that product, are there any instances where they
19 wouldn't have passed that criteria but they had
20 benefit because your assays in the lab maybe don't
21 correlate with the clinical living drug concept?
22 DR. NATARAJAN: Sure. So the specifications

1 that have been set for the commercial product are
2 based on the totality of the clinical experience,
3 so this includes the patients that Dr. Lebwohl
4 talked about, where we worked with the FDA to be
5 able to provide those products to the patients.
6 So the commercial specifications that we
7 have proposed in the BLA reflect that experience,
8 so those patients will be able to get that product.
9 Does that answer your question?
10 DR. CRIPE: Not really.
11 (Laughter.)
12 DR. NATARAJAN: Sorry.
13 DR. CRIPE: I'm worried about someone
14 not -- being excluded from getting potential
15 benefit because you have a lab assay that doesn't
16 correlate with clinical benefit. In other words,
17 I'm just trying to justify these lower-limit
18 exclusions since this is their one shot at it.
19 DR. NATARAJAN: Sure.
20 DR. LEBWOHL: I would say we don't have any
21 example of a patient, for example, potency who was
22 given cells below the limited potency that had a

1 response. No.

2 DR. CRIPE: I got my answer.

3 DR. LEBWOHL: Dr. Grupp?

4 DR. GRUPP: Steve Grupp, clinical advisor.
5 With the discussions about timing to receiving a
6 product, I just want to sort of break down what we
7 see from a clinical standpoint that may help the
8 committee understand the processes as they've
9 evolved over time in a clinical trial setting.

10 So we very consciously decoupled the actual
11 collection of the cells from enrollment on the
12 trial so that we would have the maximum number of
13 patients who had cells available for manufacturing
14 if they became eligible in the future. So that
15 16-week period between actual collection and
16 infusion was highly, highly variable and could be
17 many months in length because some of these
18 patients were attempting to get to transplant and
19 only became eligible for the trial over time.

20 Our goal at the single-institution trial and
21 then across the multicenter trials was to preserve
22 this option for as many patients as possible. So

1 that is quite fungible and is probably not the
2 length of time that actually mattered to the
3 patients in terms of this really key issue of
4 losing eligibility because the patient's disease
5 progressed, or they got infected, or had organ
6 issues.
7 I think what we really saw over time was the
8 compression of the time to get a slot for
9 manufacturing. That in my opinion is the most
10 important criterion and the thing that really
11 affected our ability to treat patients, and that
12 got better over time.
13 So you can decrease the manufacturing time
14 from 29 to 22 days. That's a great benefit, but
15 it's a relatively modest benefit. That week is not
16 going to really make or break any patient. But
17 waiting a couple months for a manufacturing slot,
18 that did make a difference for a patient or two
19 that I can personally remember. So getting rid of
20 that time frame I think is really important.
21 DR. ROTH: Dr. Bollard, and then Dr. Smith?
22 DR. BOLLARD: Sorry. Just back to the

1 vector question, so I'm interested in the B2202
2 study. How many batches of vector were required to
3 treat the 88 patients on that study? I guess
4 that's my first question.
5 DR. LEBWOHL: Dr. Natarajan will address
6 that, please.
7 DR. NATARAJAN: Arvind Natarajan from
8 Novartis. We used three different vector batches
9 over the course of patients enrolled in B2202.
10 DR. BOLLARD: And did you look at whether
11 there was any effect on outcome based on the vector
12 batch?
13 DR. NATARAJAN: So we looked at the
14 performance of the manufacturing product attributes
15 across the three vector batches, and we did not see
16 any differences across them.
17 DR. ROTH: Dr. Smith?
18 DR. SMITH: I wanted to follow up on
19 Dr. Grupp's comments. The briefing documents state
20 that the time from most recent relapse to infusion
21 was 4.1 months mean and 3.4 months median. So I'm
22 trying to understand how that relates to if that's

1 going to improve over time and how that relates to
2 Dr. Grupp's comments about when the cells were
3 harvested.
4 DR. LEBWOHL: I think that number is not so
5 useful for you to understand about the timing of
6 patients being treated. But let me show you the
7 manufacturing time in terms of the various pieces.
8 So a patient, obviously, if they are in
9 relapse, they have to approach their physician, be
10 evaluated for the trial. And then the moment of
11 enrollment occurs when the apheresis is received
12 and accepted.
13 So you see here the timing both in the U.S.
14 and ex-U.S. where things did take a little bit
15 longer to travel from apheresis receipt to the
16 manufacturing start. This is a factor that is
17 affected by capacity most of all, and this is a
18 factor that will come down to one day in the
19 commercial setting. And then the time for
20 manufacturing start to release, as we've said, will
21 be based on improvements in the process. It will
22 be 22 days. And then the last part of it has

1 always been very quick. The release to sending out
2 to the site will be one day as well.
3 DR. ROTH: Any other clarifying questions?
4 (No response.)
5 DR. ROTH: Let's take a break now before the
6 open public hearing. Let's resume at 10:20.
7 (Whereupon, at 10:00 a.m., a recess was
8 taken.)
9 **Open Public Hearing**
10 DR. ROTH: Thank you. We'll proceed with
11 the open public hearing. Both the Food and Drug
12 Administration and the public believe in a
13 transparent process for information-gathering and
14 decision-making. To ensure the transparency at the
15 open public hearing session of the advisory
16 committee meeting, FDA believes it is important to
17 understand the context of an individual's
18 presentation.
19 For this reason, FDA encourages you, the
20 open public hearing speaker, at the beginning of
21 your written or oral statement, to advise the
22 committee of any financial relationship that you

1 may have with any industry group, its products, and
2 if known, its direct competitors. For example,
3 this financial information may include industry's
4 payment of your travel, lodging, or other expenses
5 in connection with your attendance at the meeting.
6 Likewise, FDA encourages you, at the
7 beginning of your statement, to advise the
8 committee if you do not have any such financial
9 relationships. If you choose not to address this
10 issue of financial relationships at the beginning
11 of your statement, it will not preclude you from
12 speaking.
13 The FDA and this committee place great
14 importance in the open public hearing process. The
15 insights and comments provided can help the agency
16 and this committee in their consideration of the
17 issues before them.
18 That said, in many instances and for many
19 topics, there will be a variety of opinions. One
20 of our goals today is for this open public hearing
21 to be conducted in a fair and open way, where every
22 participant is listened to carefully and treated

1 with dignity, courtesy, and respect. Therefore,
2 please speak only when recognized by the
3 chairperson. Thank you for your cooperation.
4 Will speaker number 1 step up to the podium
5 and introduce yourself? Please state your name and
6 any organization you are representing for the
7 record.
8 MS. KAPPEN: Thank you. Hello. My name is
9 Amy Kappen. I have no financial relationship
10 whatsoever. I am here today to represent our
11 family, who had first-hand experience with CAR
12 T-cell therapy. I'm not a medical expert, although
13 I received an unconventional medical education
14 starting in April 2016 when my 5-year-old daughter,
15 Sophia, was diagnosed with pre-B cell ALL.
16 We were told Sophia was considered a
17 standard risk. Her remission rates were greater
18 than 85 percent. All we had to do was get her
19 through the 3-year treatment protocol. It sounded
20 so straightforward, simple compared to the initial
21 shock of the diagnosis.
22 Sophia achieved remission after her

1 induction period. However, a month later, Sophia
2 had a seizure as a result of side effects from the
3 current standard chemotherapy protocol. We then
4 realized that, while overall cure rates were very
5 high for kids with ALL, the toxic side effects of
6 conventional treatment had not advanced much at
7 all.
8 In July of 2016, we believed Sophia was
9 experiencing yet another toxic side effect of the
10 chemotherapy with severe leg pain. In reality, she
11 had relapsed faster than any of her doctors had
12 ever seen. Sophia's cancer returned within
13 3 months of achieving remission. As I'm sure most
14 of you are aware of the standard protocol for a
15 relapsed cancer patient, the next step was to go
16 after Sophia's cancer with more aggressive chemo
17 treatments, hoping to obtain remission again, and
18 move directly to bone marrow transplant. That
19 never happened.
20 Thankfully, Sophia's primary oncologist at
21 Cincinnati Children's was aware of the CAR T-cell
22 clinical trials at the Children's Hospital of

1 Philadelphia. We harvested Sophia's T cells on
2 August 1, 2016 with the hope of never needing them,
3 much like an emergency fund. Once we quickly
4 realized Sophia's cancer had become resistant to
5 chemo, we knew time was working against us.
6 As the CAR T-cell therapy was still in
7 trial, things do not always move with ease or
8 expedition. Sophia's cancer was extremely
9 challenging to keep at bay while we waited for her
10 T-cell date. During that waiting period, Sophia
11 became unable to walk or ambulate to use the
12 bathroom. This resulted in Sophia wearing diapers,
13 which infuriated her. She was not speaking or
14 interacting with anyone, and she could barely move.
15 Sophia was miserable. She looked pitiful.
16 She was on a continuous narcotic pain infusion.
17 Our previously vibrant, spunky, inquisitive 5-year-
18 old, now almost 6, had transformed into a withdrawn
19 and frustrated little girl overwhelmed with pain.
20 She was losing her zest for life. We could not
21 bear to watch our daughter suffer like this.
22 By October, her body began to swell. We

1 assumed it was yet another side effect from some of
2 the medications. When we arrived in Philadelphia,
3 we learned Sophia's leukemia was not only in her
4 blood, but had mutated into lumpy solid tumors
5 scattered throughout her body. We were blindsided
6 and had no idea leukemia could do this. Our
7 already large list of concerns grew significantly
8 more at this point.
9 After Sophia received her manufactured
10 T cells in November, she endured a severe storm,
11 her cytokine-release syndrome, as anticipated based
12 on her high level of disease. In all honesty,
13 after what we had already been through, the storm
14 hardly scared us, likely because we knew it was our
15 only hope to save our daughter. During the storm,
16 Sophia turned 6.
17 After the storm, we witnessed something we
18 never expected, a miraculous change. Sophia's
19 swelling began to decrease. She was more alert and
20 engaged. She was coming back to us. Her spunk
21 resurfaced, her smiles returned. Sophia's fight
22 was back. Sophia's bone marrow went from greater

1 than 90 percent disease burden to 1 percent at
2 28 days post-infusion. Her tumors shrank
3 significantly, although not completely.
4 Sophia was on her way to try to walk again.
5 She was determined. The transformation from
6 October to December 2016 was unbelievable. The
7 sparkle in her eyes returned. Sophia never looked
8 more beautiful.
9 We were given 3 and a half months with our
10 spirited and strong daughter. We made every minute
11 count. The trial and the doctors at Children's
12 Hospital Philadelphia gave us the most incredible
13 gift and level of hope we had ever experienced.
14 The CAR T-cell therapy did what it was intended to
15 do for her marrow. Unfortunately, the mutation of
16 her disease was too much. We could not stop her
17 cancer.
18 In those few months, Sophia taught us more
19 about life than most of us will learn in a
20 lifetime. Sophia passed away in April of this
21 year, exactly one year to the date she was
22 diagnosed with her standard-risk leukemia.

1 Sophia was so close. Although we never lost
2 hope and Sophia never gave up, we did not receive
3 the same outcome as some of these other families.
4 Our hope is to see this incredible treatment option
5 available to children sooner. It is a remarkable
6 therapy that spares children the toxic side effects
7 of conventional chemotherapy.
8 Close is not good enough. We know there's
9 no point to imagine what CAR T-cell therapy could
10 have done for Sophia if it had been further along
11 in the approval process. Instead, our family wants
12 to express its support for approving this
13 incredible breakthrough in pediatric cancer
14 treatments with hope that more families have a
15 longer time with their children fighting this evil
16 disease. Our children deserve this chance.
17 Thank you for allowing me to share Sophia's
18 journey.
19 **Clarifying Questions (continued)**
20 DR. ROTH: Thank you for sharing.
21 The open public hearing portion of this
22 meeting is now concluded, and we'll no longer take

1 comments from the audience. The committee will now
2 turn its attention to address the task at hand, the
3 careful consideration of the data before the
4 committee as well as the public comments.
5 Before we get to the discussion questions,
6 we just want to mop up one thing, and Novartis
7 would like to make a couple comments in response to
8 Dr. Cripe's final questions about release points;
9 and maybe if you want to rephrase your question for
10 the transcribers.
11 DR. CRIPE: Yes. It was based on the
12 concept that we are unsure what's going to happen
13 in vivo after the product is infused and do those
14 release criteria really measure that. And if we go
15 to the trouble of making a product, did they have
16 any experience where any of the release criteria
17 that they're proposing were not met but they used
18 it anyway, and did they then get any effects from
19 that.
20 DR. LEBWOHL: Thank you, Dr. Cripe. I just
21 want to repeat that we did have experience with
22 giving cells out of spec during the trial when we

1 gave the lower cells, and that was successful.
2 In the commercial setting, we would give
3 cells only if they were within spec on a routine
4 basis. However, this same question will come up in
5 the commercial setting. There will be some
6 patients where they're slightly different from the
7 specifications.
8 We think that the cells will be both safe
9 and possibly effective. And our idea is that we
10 would talk to the FDA as well in the commercial
11 setting and talk to them about the possibility of
12 the patients receiving those cells.
13 DR. CRIPE: Would that require a single
14 patient IND or that sort of thing, do you think?
15 DR. LEBWOHL: We would have to talk to the
16 FDA about the mechanism for that.
17 DR. ROTH: Did that answer sufficiently?
18 DR. CRIPE: Yes. Thank you.
19 **Questions to the Committee and Discussion**
20 DR. ROTH: We will now proceed with the
21 questions to the committee and panel discussions.
22 I would like to remind public observers that while

1 this meeting is open for public observation, public
2 attendees may not participate except at the
3 specific request of the panel. We can proceed to
4 the first question, please.
5 During tisagenlecleucel development, the
6 applicant established product quality
7 specifications to assess CAR expression and T-cell
8 activity, including transduction efficiency by flow
9 cytometry, vector copy number per cell, and
10 interferon gamma production following stimulation
11 by CD19-positive cells.
12 Please discuss the following aspects of the
13 control of product quality of tisagenlecleucel with
14 respect to identity, safety, purity, and potency;
15 first the design of the CAR construct and viral
16 vector, secondly the assessment of CAR expression
17 and T-cell activity through, number one, the number
18 of transduced T cells; number two, the number of
19 vector copies per cell; number three, antigen-
20 specific T-cell functions such as interferon gamma
21 production and cytotoxicity upon stimulation; and
22 finally any other measurements such as T-cell

1 subpopulations, cell surface marker
2 characterization that could provide greater
3 assurance of product quality.
4 So again, if you want to make comments, just
5 let Jen know. We'll go in order. And again,
6 please identify yourself before commenting. First,
7 Dr. Gulley.
8 DR. GULLEY: Thank you. James Gulley. I
9 think there are several things to consider here.
10 First, the patient-specific products face unique
11 challenges in the manufacturing process, and we
12 were asked to comment on identity, safety, purity,
13 and potency.
14 Based on what was provided to us in the
15 briefing documents, in terms of the identity, there
16 is really a nice set-up for tracking and
17 segregation with proper chain of identity using the
18 FACT-accredited institutions that incorporate the
19 ISBT-128 labeling standards. So from that
20 standpoint, I thought this is well-designed with
21 respect to the identity.
22 Now, with respect to the safety, purity, and

1 potency, I have several questions and things that
2 perhaps we could talk about.
3 First of all, for the purity, the number of
4 T cells in the product is greater than 80 percent,
5 is what they say, and virtually all of the cells in
6 the product look to be, based on what was
7 clinically done, T cells with exception of maybe a
8 few NK cells. The product parameters also include
9 greater than 10 percent CAR T cells.
10 So I think that from a purity standpoint, I
11 think we have a product here that is virtually all
12 T cells with a high proportion of the CAR T cells.
13 So that appears to be also well thought through
14 here.
15 I think the main thing, though, is the
16 potency, and that is demonstrated in the clinical
17 activities seen with this product. So from my
18 standpoint, this is a product that has shown
19 patient benefit, and I think our goal here is
20 really to try and find ways that we can make sure
21 we have optimal safety of the product and optimal
22 potency of the product.

1 DR. ROTH: Dr. Kwak?
2 DR. KWAK: So I would highlight a few points
3 that Dr. Gulley didn't mention. So first, as a
4 general statement, the challenge with this therapy
5 is that the technology is rapidly changing, and
6 secondly, that there are multiple steps. It's a
7 very complex manufacturing process, as outlined
8 both by the sponsor and the FDA, which makes it
9 inherently a high potential risk for manufacturing
10 failure.
11 Then you add to that the aspect of the
12 autologous nature, in other words the need to
13 manufacture the product on a patient-specific
14 basis, leading to potential batch-to-batch
15 variability. But having said all that, the sponsor
16 should be congratulated for, in most of the cases,
17 manufacturing and releasing product for the
18 clinical trials.
19 Let me give you a few examples to underline
20 these two issues. The first is that the construct
21 used for the CAR is a murine antibody as I
22 understand it. And the sponsor did acknowledge

1 immunogenicity observed in patients.
2 Many affected firms and academic groups now
3 are using humanized antibody constructs where this
4 is not a concern. And this is an example of
5 something that's changing that could well become,
6 if you will, standard of care for vector
7 construction in the future. The implication is
8 that this could affect persistence, for example,
9 and therefore efficacy, as well as safety, of the
10 resulting CAR T cells.
11 A second consideration is a very serious
12 side effect, which we may hear more about in the
13 afternoon session, but of an on-target/off-tumor
14 effect on normal B cells, causing prolonged B-cell
15 aplasia. And again, here a number of affected
16 firms and academic groups are addressing this by
17 introducing suicide gene strategies and other
18 strategies to exert greater control over the
19 infused T cells.
20 With respect to potential batch-to-batch
21 variability, purity, and quality, I think one
22 should highlight the fact that, generally, only

1 30 percent of the T cells infused actually did bear
2 the chimeric antigen receptors. This means that up
3 to two-thirds of the cells actually were not the
4 T cells that are specific for CD19.
5 As a clinician, I'm very much encouraged
6 that that apparently did not affect efficacy when
7 looked at in the sample size that was available to
8 the sponsor, but I think a greater concern is the
9 safety considerations introduced by that
10 heterogeneity and the presence of non-CAR T cells,
11 which may also be activated by cytokines during the
12 expansion phase, for example the IL-2, and
13 contribute to toxicities such as the cytokine-
14 release syndrome.
15 I think the final consideration that I'd
16 comment on that really hasn't been addressed by the
17 sponsor this morning is the T-cell subpopulations
18 and the heterogeneity of T cells in the final
19 product. This is one area that really could affect
20 the future development of this therapy.
21 There's emerging evidence that specific
22 T-cell populations are somewhat better than others

1 in terms of efficacy as well as safety with regard
2 to not just central memory or effector memory
3 phenotype, but also the optimal proportions of CD4-
4 versus CD8-positive T cells.
5 So a better characterization of the products
6 that were infused I think would be informative to
7 the agency, both for the purposes of greater
8 quality assurance, and secondly to help guide
9 prospective testing of this question of different
10 subpopulations of T cells and how to optimize
11 those.
12 The final issue that is a minor technical
13 one to highlight is that in our experience in terms
14 of vector production for various clients at our
15 institution, City of Hope, we found that primary
16 T cells are the most accurate in terms of
17 determining viral titer.
18 So if the sponsor has done comparisons
19 between AGK cells and primary T cells, this is some
20 data perhaps the agency would want to request and
21 examine. Thank you.
22 DR. ROTH: Thank you. Maybe for the two of

1 you, Dr. Kwak and Dr. Gulley, it seems like we're
2 still on square one in terms of predictive factors
3 here and we're kind of swimming in the dark.
4 So I don't know if you had some sense of if
5 you were lead scientist who developed an additional
6 or hypothesis-generating panel of things to look
7 at, are there other things that you would suggest,
8 because now there's a real disconnect I think
9 between the factors that have been looked at and
10 ultimate outcome clinically.
11 DR. GULLEY: I think that you're absolutely
12 right. There is a disconnect between what assays
13 have been done and what the outcomes are, both in
14 terms of side effects as well as in terms of
15 activity. The good news is that the majority of
16 patients do have evidence of benefit with this.
17 I think that as we get more data, I think it
18 would be nice to look at the different T-cell types
19 that are in here as well as the different
20 functionality of those T cells with different
21 intracellular cytokines, for instance, and their
22 lytic potential; so some more functional analysis

1 and see if there are markers that correlate with
2 functional analysis because functional analysis may
3 be difficult to do for lot-release criteria. But I
4 think that would be helpful to understand this
5 product better.
6 DR. KWAK: So my comments were meant as
7 guidance for things to pay attention to as in the
8 commercialization phase and as CAR T cells are
9 being developed by other affected firms.
10 But just to put it in context -- so those
11 are things that I would like as a scientist. But
12 as a clinician who still sees patients, I think
13 we'll hear about the clinical results. And I don't
14 think any of these considerations that either of us
15 have raised would be showstoppers for the
16 outstanding clinical results that have been
17 obtained to date.
18 DR. GULLEY: I would just like to add to
19 what Dr. Kwak said, which I completely agree with.
20 I think that there are many agents that we don't
21 have good assays for predicting clinical outcomes
22 necessarily. I think that these are great things

1 to look at from a scientific standpoint to help
2 move the field forward.
3 DR. ROTH: Dr. Bollard?
4 DR. BOLLARD: I guess I would just like to
5 go back to the purity issue just for the record
6 because the answers that were provided I guess I
7 still have concerns with, given that we're seeing
8 in the slide CM-11 that you're not getting
9 necessarily 100 percent CD3 T cells in your final
10 product. And while there are clearly some NK
11 cells, which I have less worries about, what are
12 the other cells remaining since you acknowledge
13 that what you're starting with is very
14 heterogeneous leukapheresis material.
15 So I guess my comment is related to how can
16 we increase that purity in terms of absolute T-cell
17 numbers to really 100 percent if possible. And I'm
18 further unclear because we were told there was a
19 positive selection happening, but on questioning,
20 it was just CD3-28 beads, which I don't sort of
21 equate to a positive selection.
22 So I guess I am not seeing that a product

1 that's greater than 80 percent or 80 percent pure
2 is a highly pure T-cell product. And there is
3 that, while rare, known risk of possibly
4 transducing a B-cell population that could have a
5 survival advantage in vivo.
6 DR. ROTH: Dr. Rein?
7 DR. REIN: I guess I have a comment about a
8 safety question. The early experience with the
9 gamma retroviral vectors included insertional
10 mutagenesis leading to leukemia by the vector
11 itself, not by an RCR.
12 I think that reflects the enormous
13 multiplicity of infection that was used in those
14 early trials in which so many viruses were used and
15 so many integration sites were hit, that some
16 damaging integration sites were obtained.
17 So I think this tells us that more is not
18 necessarily better in terms of multiplicity of
19 infection, number of initial infection events. So
20 I just think this hasn't been mentioned in the
21 discussions by Novartis, what sort of target they
22 have for how many cells get infected in the initial

1 infection, which means how many integration sites
2 will be hit.
3 DR. ROTH: Thank you. Dr. Cripe?
4 DR. CRIPE: My comments were a bit of a
5 follow-up to that. I had wanted to recognize the
6 fact that we've come a long way from those days of
7 when we didn't know. And I'm encouraged by all the
8 advances that have been made and would like to
9 commend the CHOP and Penn teams and Novartis
10 because what we've seen today is a lot of safety
11 things that have been built that are far different
12 from those days with this kind of trial;
13 integration site numbers, which they showed us,
14 which were on average 1 or less, and in those
15 trials there were many; the separation of the
16 plasmids and the efforts to reduce recombinations
17 amongst those plasmids; the fact that we're
18 transducing non-stem cells, although a bit
19 concerning they don't measure that or look for stem
20 cells.
21 These are peripherally apheresis products,
22 but they could still contain circulating stem

1 cells, particularly after chemotherapy, albeit
2 that's unlikely in someone with frequent relapse
3 who probably doesn't have many stem cells around.
4 So I'm impressed by the advancements we've
5 made over the last 10 to 15 years in this field
6 that we've been able to get to this point. And
7 ultimately, the proof is in the pudding and haven't
8 been able to measure RCR, et cetera. So I think
9 that's very encouraging, and I want to recognize
10 the fact that we've come a long way in this field.
11 I think the concern for me is what happens
12 after the infusion. So we don't know. This is an
13 unknown, and perhaps more understanding of that
14 would benefit us in the future. So continuing to
15 monitor patients and clonality, et cetera, may be
16 important as we move this field forward.
17 DR. REIN: We were shown integration sites
18 per cell. We were not shown total integration
19 sites. That's what I'm talking about.
20 DR. ROTH: Other comments? Go ahead.
21 DR. CRIPE: Is it an integration site per
22 cell that counts? Because it's --

1 DR. REIN: If you do enough infections of
2 enough cells with enough viruses, you are likely to
3 hit a bad site. If you only infect a few cells,
4 you will only hit a few integration sites.
5 DR. CRIPE: Sure. It's all probabilistic.
6 DR. ROTH: Other comments? Sorry.
7 DR. CRIPE: Another issue. So we didn't
8 really talk about the design or the production of
9 the vector itself, so we didn't ask any questions
10 about the -- we only asked questions about the
11 product, the transduced product. What about the
12 GMP production of the virus?
13 So we're assuming that -- is the FDA looking
14 at that, do they have any concerns about that,
15 which would be the main discussion topic in just a
16 straightforward gene therapy trial, where the
17 vector is pretty important in terms of its
18 production, its potency, its purity, its identity.
19 So there was no data given about that. Is that
20 even manufactured at the same site? Where does
21 that come from?
22 DR. ROTH: Anybody from the agency want to

1 respond to that?
2 DR. GAVIN: Novartis talked extensively
3 about where the vector was manufactured and the
4 testing that was done on the vector. I think that
5 was covered in the discussion earlier.
6 DR. CRIPE: The vector's made at the same
7 site that the transduction and the cells are
8 produced.
9 DR. GAVIN: No. The Oxford Biomedica
10 representative was here and talked about the vector
11 production.
12 DR. ROTH: Any other comments?
13 (No response.)
14 DR. ROTH: Just to summarize, in terms of
15 the question 1 discussion, we discussed about the
16 disconnect between current proposed predictive
17 factors and the ultimate response, and possibly the
18 chance of looking at more specific T-cell
19 subpopulations might be a benefit in this
20 situation.
21 It was raised, the purity issue, both
22 positive and negative selection possibly how to do

1 additional selection factors to increase T-cell
2 numbers and possibly decrease stem cell numbers if
3 they are in significant numbers.
4 Then from a safety issue, how many cells get
5 infected as that pertains to potentially a safety
6 issue down the road and possibly long-term problems
7 with insertional mutagenesis or RCL. And I think
8 maybe, most importantly, further information on
9 what happens post-infusion, since it appears to be
10 somewhat of a black box currently and has
11 significant implications both for long-term safety
12 and for acute response.
13 So if that does not summarize, are there any
14 other comments? Go ahead, Dr. Bollard.
15 DR. BOLLARD: Just to clarify about the
16 purity, it's not just the stem cells getting
17 transduced. It's the B cells, the CD19-negative
18 B cells, as well as actually also potentially
19 leukemia stem cells, given these are patients with
20 high disease burden at the time of leukapheresis.
21 DR. ROTH: Good point. Anything else?
22 Dr. Kwak?

1 DR. KWAK: And the heterogeneity of the
2 T cells in the final product, so those transduced
3 versus non-transduced.
4 DR. ROTH: Thank you.
5 We'll go to the second question, more safety
6 issues. Potential safety concerns with
7 tisagenlecleucel and other retrovirus-based gene
8 therapy products include generation of RCR/RCL and
9 insertional mutagenesis. Can you address the
10 strategies to address those concerns, including
11 vector design and product testing?
12 Part 2, please discuss how vector design
13 impacts the risk of RCR. Please discuss how vector
14 design impacts the risk that insertional
15 mutagenesis might cause secondary malignancies.
16 And then finally, please discuss the extent to
17 which product testing can mitigate the risk of RCR
18 and insertional mutagenesis.
19 Dr. Rein?
20 DR. REIN: I probably said what I wanted to
21 say under question 1. I guess I feel that RCR is
22 no longer a serious safety risk. Insertional

1 mutagenesis still needs attention, the extent to
2 which product testing can mitigate the risk of
3 insertional mutagenesis. So I was wondering about
4 is there a target for how many infections are
5 intended in the initial infection event.
6 DR. LEBWOHL: Maybe we can come back to the
7 slide from the core on the ratio on integrated
8 viruses. This shows what was shown in the
9 presentation, and what you can see, particularly
10 towards the end as was expressed, the ratio is
11 1.3 copies per transduced cell and with a fairly
12 small range. And I'll ask Dr. Natarajan to add.
13 DR. NATARAJAN: Good morning. Arvind
14 Natarajan from Novartis again. We do target a
15 specific percent transduction when we add the
16 vector for each patient batch. And the amount of
17 vector that's added is calibrated for each vector
18 batch that's produced.
19 DR. REIN: So how many cells -- not percent,
20 number. How many cells get infected? In other
21 words, how many integration sites are you hitting?
22 DR. NATARAJAN: In terms of the actual

1 numbers, it depends on the culture itself because
2 we have patients coming in with different weight
3 ranges. So the absolute number of cells varies by
4 patient.
5 So we normalize our reporting on a percent
6 transduction. The dose itself is formulated based
7 on an absolute number of cells. So the dose range
8 or the dose that's provided to patients measures
9 the number of viable transduced cells that's
10 provided back to the patient.
11 DR. REIN: So would you care to state a
12 number, for example?
13 DR. NATARAJAN: Due to the confidential
14 nature of that information, I'm not able to share
15 the exact number in this setting.
16 DR. ROTH: Dr. Bollard
17 DR. BOLLARD: Can you bring back up the
18 questions again? Sorry. So firstly, I think I
19 just want to reiterate for the record that there's
20 no stable producer cell line used for this vector
21 manufacturing. We're told that probably only one
22 batch of vector only treats about 30 patients.

1 So I think we need to understand that
2 there's always going to be multiple, multiple
3 batches as we move forward, and there is obviously
4 that potential for batch-to-batch variability in
5 terms of how that vector performs functionally. So
6 if we're happy with the rigor of vector release,
7 then I think we just need to acknowledge that.
8 I do agree with Dr. Rein's assessment about
9 the risk of RCR if your vector is RCR negative or
10 RCL negative. And given the huge wealth of data
11 now in the retroviral transduced and lentiviral
12 transduced T-cell field, I think not performing RCL
13 on the prospective patients is probably okay.
14 I think, as far as insertional mutagenesis,
15 I agree there's a wealth of data with mature
16 T cells in the safety profile of mature T-cell
17 transduced cells in vivo, but I go back to why I
18 think product purity is so important, because we
19 can't guarantee that we're just transducing mature
20 T cells. So I think that's something to consider.
21 While I do acknowledge, though, that it is
22 laudable that Novartis will look for vector in the

1 development of any individuals with secondary
2 malignancies, I would also say that we should
3 extend that to patients who are relapsing with
4 their leukemia with a different immunophenotype or
5 genotype.
6 So I think I've hopefully addressed all
7 those questions.
8 DR. ROTH: Thank you. Other comments? Go
9 ahead, Dr. Cripe.
10 DR. CRIPE: I'm encouraged by the use of
11 self-inactivating vector, which obviously is going
12 to reduce the risk of insertional mutagenesis even
13 if it integrates near an ELMO 2 gene or some other
14 scary gene, and the use of a tissue-specific
15 promoter in driving that transgene. I think both
16 of those are mitigating factors for insertional
17 mutagenesis.
18 One question that's just arisen in my mind
19 is what's the risk of contaminating virus in the
20 final product. I might have missed it, but I don't
21 recall them measuring that. So is there a
22 possibility of any virus that's not transduced into

1 cells yet, but tagging along with the product and
2 then in the body infecting other cells? Is there a
3 measure of that in their release criteria?
4 DR. ROTH: Any other comments?
5 DR. LEBWOHL: Dr. Hamilton will address the
6 question on virus.
7 DR. HAMILTON: Hi. Jason Hamilton, cell and
8 gene technical development and manufacturing,
9 Novartis. You're correct. We don't perform
10 testing for remaining vector or virus that could be
11 present in the final product. However,
12 calculations of the dilution factors that occur
13 during the entire length of the manufacturing
14 process make it essentially impossible for vector
15 to be remaining at the end of culture.
16 DR. CRIPE: So it's homeopathic.
17 DR. ROTH: Any other comments?
18 (No response.)
19 DR. ROTH: So just to summarize here,
20 there's some concern about batch variability in
21 terms of vector batches being reproducible, some
22 concerns in terms of RCR and I assume insertional

1 mutagenesis based on information about the number
2 of cells infected and the number of infections per
3 cell. And certainly, that's abrogated a little bit
4 by the self-inactivating component.
5 So that's my summary. Any other questions,
6 or did I misstate anyone's discussion?
7 (No response.)

8 **Adjournment**

9 DR. ROTH: So we'll go ahead and break for
10 lunch. I would remind the panel members not to
11 discuss the topic during the lunch and break. And
12 we will resume at 12:30.
13 (Whereupon, at 11:00 a.m., the morning
14 session was concluded.)
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