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
Meeting Roster

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PROCEEDINGS

(7:59 a.m.)

Call to Order

Introduction of Committee

DR. ROTH:  Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices you have if you've not already done so. I'd also like to identify the FDA press contacts, Angela Stark and Andrea Fischer over here on the side.

My name is Bruce Roth. I'm the chairperson of the Oncology Drug Advisory Committee, and I'll be chairing this meeting. I'll now call the meeting of the Oncology Drug Advisory Committee to order. We'll start by going around the table and introduce ourselves. Let's start down at the far right here. Dr. Gordon?

DR. GORDON:  Gary Gordon, AbbVie, industry representative.

DR. BOLLARD:  Cath Bollard, Children's National, Washington, D.C.

DR. CRIPE:  Tim Cripe, Nationwide Children's
Hospital, Columbus, Ohio.

    DR. SMITH: Malcolm Smith, National Cancer
Institute.

    MS. McMILLAN: Gianna McMillan, patient
representative.

    DR. KWAK: Larry Kwak, City of Hope.

    DR. GULLEY: James Gulley, NCI.

    DR. RINI: Brian Rini, Cleveland Clinic.

    DR. ROTH: Bruce Roth, Washington University
in St. Louis.

    LCDR SHEPHERD: Jennifer Shepherd,
designated federal officer.

    DR. NOWAKOWSKI: Grzegorz Nowakowski, Mayo
Clinic.

    DR. REIN: Alan Rein, National Cancer
Institute.

    DR. COLE: Bernard Cole, biostatistics,
University of Vermont.

    DR. LU: Xiaoban Victor Lu, FDA.

    DR. GAVIN: Denise Gavin, FDA.

    DR. O'LEARY: Maura O'Leary, FDA.

    DR. BRYAN: Wilson Bryan with the Office of
Tissues and Advanced Therapies of FDA.

DR. PAZDUR: Rick Pazdur, FDA, Oncology Center of Excellence.

DR. ROTH: For topics such as those discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and those individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the advisory committee members take care that their conversations about the topic at hand take place in the open forum of this meeting.

We are aware that members of the media are anxious to speak with the FDA about these
proceedings. However, FDA will refrain from
discussing the details of this meeting with the
media until its conclusion. Also, the committee is
reminded to please refrain from discussing the
meeting topic during breaks or lunch. Thank you.

Now, I'll pass it on to Lieutenant Commander
Jennifer Shepherd, who is serving as our DFO for
this meeting, who will read the Conflict of
Interest Statement.

Conflicts of Interest Statement

LCDR SHEPHERD: Good morning. The Food and
Drug Administration is convening today's meeting of
the Oncologic Drugs Advisory Committee under the
authority of the Federal Advisory Committee Act of
1972. With the exception of the industry
representative, all members and temporary voting
members of the committee are special government
employees or regular federal employees from other
agencies and are subject to federal conflict of
interest laws and regulations.

The following information on the status of
this committee's compliance with the federal ethics
and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with the federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs his or her potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interest of their own, as
well as those imputed to them, including those of their spouses or minor children, and for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda includes discussion of biologics license application 125646, for tisagenlecleucel suspension for intravenous use. The application was submitted by Novartis Pharmaceuticals Corporation. The proposed indication for this product is for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia.

This is a particular matters meeting during which specific matters related to Novartis's BLA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in
connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Gary Gordon is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Gordon's role at this meeting is to represent industry in general and not any particular company. Dr. Gordon is employed by AbbVie.

We would like to remind members and temporary voting members that if the discussions involve any other product or firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, the parties need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that they
may have with the firm at issue. Thank you.

DR. ROTH: Thank you. I will open the
meeting with the FDA's opening remarks by Dr.
Bryan.

**FDA Introductory Remarks**

DR. BRYAN: Good morning and welcome on
behalf of the FDA, including the Oncology Center of
Excellence, the Center for Biologics Evaluation and
Research, and the Office of Tissues and Advanced
Therapies. This biologics licensing application is
the first BLA to be reviewed through the
collaboration of the FDA's new Oncology Center of
Excellence and the Center for Biologics Evaluation
and Research.

Novartis submitted this BLA in order to make
a new therapy, tisagenlecleucel, available to
patients with relapsed or refractory B-cell acute
lymphoblastic leukemia or ALL. Relapsed or
refractory ALL is a life-threatening disease, and
there's an urgent need for new and improved
therapies.

The clinical development of tisagenlecleucel
suggests that this is a life-saving product. The clinical trials are not always a good predictor of the effectiveness and safety of a marketed product. In particular, we are concerned that the same benefit and safety seen in clinical trials may not carry over to routine clinical use.

This morning, we are asking this committee to focus on manufacturing issues that relate to product quality. Tisagenlecleucel is a complex product. At this time, it is still not fully clear how the FDA or Novartis can assure patients that the marketed product would be the same product, particularly with regard to safety and effectiveness, as the product that was studied in clinical trials.

This afternoon, we are asking this committee to focus on specific safety issues. Tisagenlecleucel has been associated with life-threatening adverse events, including cytokine-release syndrome and neurotoxicity. We are asking for the committee's recommendations with regard to measures to mitigate the risks of these adverse
events.

We are also concerned about the hypothetical risk of secondary malignancies. Therefore, we are asking for the committee's recommendations regarding the nature and duration of follow-up for patients who would receive this product.

Tisagenlecleucel is the first chimeric antigen-receptor T-cell product. The FDA recognizes that there is substantial interest among various stakeholders, including scientists, physicians, patients, and their families in this field of chimeric antigen-receptor T-cell products.

What we hear from this committee may be relevant to and will be considered in the regulation of other products in this class. However, we ask that the committee focus their deliberations on only tisagenlecleucel and the data in this specific BLA.

The FDA appreciates the efforts of the many individuals who have contributed to the development of this technology and this product. Scientists have worked for decades to develop therapies based
on chimeric antigen-receptor technology.

The FDA also thanks the participants in today's open public hearing. It is critical that we hear from patients and patient advocates. Many individuals are not able to be here today, and we appreciate the written comments that we have received regarding this BLA.

We want to thank all the members of this committee who have given their time in order to participate in today's discussion. I also want to thank all the members of the Oncology Center of Excellence, the Center for Biologics, and the advisory committee staff, who have worked tirelessly to prepare for today's meeting.

I now turn to Dr. Roth to continue with the agenda.

DR. ROTH: Thank you, Dr. Bryan.

We will start with the applicant's presentation. Dr. Hirawat?

Applicant Presentation – Samit Hirawat

DR. HIRAWAT: Thank you, Dr. Roth. Thank you, Dr. Bryan, for setting it up for us.
Good morning, members of the advisory committee, FDA staff, and guests. I'm Samit Hirawat. I'm the head of the oncology global development unit at Novartis. Today, my colleagues and I will present the data to support the biologics license application for CTL019 in pediatric and young adult patients with relapsed/refractory B-cell acute lymphoblastic leukemia.

As you heard, B-cell ALL is the most common malignancy diagnosed in children and young adults, accounting for 85 percent of pediatric acute lymphoblastic leukemia. The disease can be treated successfully in most patients. However, there are approximately 15 percent of patients whose disease relapses or is refractory to treatment.

The vast majority of these patients face an incurable disease with short overall survival. Therefore, there is a need for novel treatment options that provide deep and durable remissions, curative treatment opportunities, and improved quality of life for pediatric and young adult
patients with relapsed/refractory B-cell ALL.

Given this important unmet need, Novartis and the University of Pennsylvania formed a collaboration in 2012 to study chimeric antigen-receptor T cells, or CAR T-cell therapies, based on early promising clinical activity of this novel approach. CAR T-cell therapies are a new treatment paradigm in oncology.

CTL019 is different from typical small molecules or biologic therapies because it is manufactured for each individual patient using their own cells. It is designed to harness the power of a patient's own immune system to eliminate cancer cells.

Our early development plan included B-cell acute lymphoblastic leukemia as our first indication. To support this effort in B-cell ALL and future development of other CAR T-cell therapies, Novartis acquired a cellular therapy manufacturing unit in Morris Plains, New Jersey.

So why would we investigate CD19 as a target for CAR T-cell therapy in treating B-cell
malignancies? It is well understood from literature that CD19 is a surface protein which has expression restricted to B cells and B-cell precursors. As such, CD19 is not expressed on pluripotent bone marrow stem cells, and tissue cross-reactivity is not an issue for this target. This reduces the potential for off-target effects on bone marrow cells and red blood cell production.

Importantly, CD19 is expressed on the surface of most B-cell malignancies. Therefore, CD19 is an attractive target for CAR T-cell therapy in treating B-cell malignancies that span different stages of B-cell differentiation such as those shown here.

So let me briefly reflect on how CTL019 functions. CTL019 cells express chimeric antigen receptors. The CARs comprise of CD19 antigen recognition domain fused to a CD8 hinge and a transmembrane region followed by a 4-1BB costimulatory domain and a CD3-zeta signaling domain.

The antigen recognition domain is
responsible for binding to CD19 on normal and malignant B cells. Following CD19 engagement, the CD3-zeta component of the CAR is critical for initiating T-cell activation and tumor cell killing. The 4-1BB signaling further enhances anti-tumor activity and augments the survival and persistence of CTL019 cells.

CTL019 is designed to attack B cells that express CD19 surface antigen. Ex vivo, a lentiviral vector is used to insert the anti-CD19 transgene into a patient's T cells. The transgene is transcribed and translated, and becomes expressed on the surface of the T cells. The resulting CTL019 cells are infused into the patient.

In vivo, upon binding to CD19-expressing cells, the CAR transduces a signal that promotes T-cell expression, activation, target-cell killing, and persistence of the CTL019 cells. This also triggers cytokine release and CTL019 proliferation. In summary, CTL019 is a living drug which demonstrates activity after a single infusion.
CTL019 is provided to patients as an autologous immunocellular therapy. This means that it is developed using cells from the patient receiving treatment. The process starts when white blood cells are collected from the patient. The cells are then transferred to our manufacturing facility, where they're enriched, activated, transfused, and expanded.

Following formulation and quality assessment, the cells are returned to the clinical site where the patient is infused. You will hear more about the overall process of cell collection, manufacturing, and delivery back to the site in the presentations later this morning. But first, let me take a moment to review the regulatory highlights of our development program.

Orphan designation was granted in January 2014, and breakthrough therapy designation was granted to Novartis in April of 2016. The BLA was submitted in February of 2017. In addition, Novartis also participated in the FDA pilot data program and has been sharing clinical data with the
FDA on a regular basis.

CTL019 is also being developed in conjunction with the European Medicines Agency and was granted access to the PRIME pathway for priority medicines. In addition to the trials included in the BLA, Novartis has numerous other studies with CTL019 planned or underway that will follow hundreds of additional patients in the clinical trial setting.

The development program in pediatric and young adult patients with relapsed or refractory B-cell ALL includes three key trials. They enrolled more than 150 patients and provide up to 5 years of follow-up. B2202 study is the global multicenter pivotal trial which is the basis of the BLA submission. The overall design and endpoints of study B2202 were agreed upon with the FDA. Studies B2205J and B2101J are considered supportive.

The data we will share with you today from these three studies support the proposed indication that CTL019, or tisagenlecleucel, is a genetically
modified autologous immunocellular therapy indicated for the treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/refractory B-cell acute lymphoblastic leukemia.

Here is the agenda for the rest of our presentation this morning. Next, we will hear from Dr. Stephen Hunger, who will summarize the treatment landscape and the challenges in managing pediatric and young adult patients with B-cell ALL; then Spencer Fisk will discuss the manufacturing process for CTL019; and Dr. James Miskin will provide an overview of our lentiviral vector.

Finally, we'll conclude the morning presentations with Dr. David Lebwohl, who will discuss the correlation of quality attributes to clinical outcomes. During this afternoon's clinical presentations, I will share our efficacy data, followed by Dr. David Lebwohl again, who will discuss our safety data and review the pharmacovigilance plan.

Finally, Dr. Stephan Grupp will put these
data into context and discuss how CTL019 can add to the armamentarium for physicians treating pediatric and young adult patients with relapsed/refractory B-cell ALL.

Here are some of the points you will hear today to support that CTL019 has a positive benefit-risk profile in pediatric and young adult patients with relapsed/refractory B-cell ALL.

There is a significant unmet need to improve outcomes in these patients. Novartis has developed a highly reproducible and a safe manufacturing process with proven efficacy in three trials in over 150 pediatric and young adult patients. Durable remissions were observed in the three trials, and the pivotal study demonstrated an overall remission rate of 83 percent.

The median duration of remission has not been reached in any of the three trials. And in the pivotal study, 75 percent of patients were relapse-free 6 months after the onset of remission. CTL019 has a well-characterized and manageable safety profile with appropriate site training, and
Novartis is committed to a comprehensive pharmacovigilance plan, including long-term safety follow-up.

With that, I'd like to introduce Dr. Stephen Hunger, chief of the Division of Oncology, director of the Center of Childhood Cancer Research, and holder of the Jeffrey E. Perelman Distinguished Chair in the Department of Pediatrics at Children's Hospital of Philadelphia. Thank you.

**Applicant Presentation – Stephen Hunger**

DR. HUNGER: Thank you, Dr. Hirawat.

Good morning. I'm Stephen Hunger from the Children's Hospital Philadelphia. My clinical and research interests focus on acute lymphoblastic leukemia or ALL. I was the vice chair and then the chairman of the Children's Oncology Group ALL committee from 2001 to 2015. In these roles, I was responsible for oversight of the design and conduct of clinical trials that enrolled 2,000 patients per year or 70 percent of U.S. children diagnosed with ALL annually. I have received compensation for my participation in today's proceedings, but have no
financial interest in the outcome of this meeting.

ALL is the most common malignancy of childhood. There are approximately 5,000 cases of ALL diagnosed annually in the United States. Approximately 60 percent of these are diagnosed in children and adolescents less than 20 years of age with the median age of diagnosis being 15 years.

Eighty-five percent of childhood ALL cases are B lineage ALL or B-ALL. Current multi-agent treatment regimens achieve a cure rate of greater than 85 percent. Primary refractory ALL or induction failure is rare, occurring in 2 to 3 percent of children and remains a major therapeutic challenge. And approximately 15 percent of children and young adults with ALL will relapse, and relapsed ALL is a leading cause of cancer death in children.

Today, you're going to hear about several clinically relevant endpoints in trials that demonstrate clinical benefit. The first are response endpoints, and these include the overall remission rate, which is typically used in relapsed
and refractory ALL trials, and minimal residual
disease, or MRD, which is important in newly
diagnosed and relapsed acute lymphoblastic
leukemia. The second point or time-to-event
endpoints include duration of response and overall
survival.

Overall remission rate is the sum of the
rates of complete remission, or CR, which is
achieving a bone marrow with less than 5 percent
lymphoblasts and a restoration of normal amount of
hematopoiesis with normal blood counts, and
complete remission within complete blood recount
recovery or CRi.

This is a recognized surrogate marker for
overall survival and has been used by the FDA as an
endpoint for accelerated approval of new agents in
relapsed and refractory pediatric ALL. Relevant
eamples include clofarabine and blinatumomab.

Minimal residual disease or MRD is the
detection of sub-microscopic levels of leukemia
cells which can be identified by several
methodologies, including flow cytometry. These
technologies can identify one ALL cell among a
background of 10 to the 4th or 10 to the 5th normal
cells. It's the strongest prognostic factor
identifying good and poor responders and correlates
with outcome. MRD predicts the risk of relapse and
overall survival when measured during and after
induction therapy in both newly diagnosed and
relapsed ALL trials.

This slide depicts the results of a recently
published meta-analysis looking at the impact of
minimal residual disease at the end of induction
therapy, an outcome in pediatric ALL trials. This
meta-analysis included 20 trials in over 11,000
patients, and here we can see the dramatic
difference in outcome between patients who have no
MRD detected at the end of induction and those who
are MRD positive at the end of induction.

This correlates to a hazard risk of 0.23,
which means that patients who are MRD positive have
an approximately 4-fold increased rate of treatment
failure primarily due to relapse.

MRD is also a robust indicator in relapsed
ALL trials. This slide looks at the event-free survival for patients enrolled in a trial conducted by the Children's Oncology Group, AALL01P2, a first relapse of B-cell ALL.

This looks at survival among patients who achieved a clinical remission based upon the minimal residual disease present at the end of the first month of therapy. And here, you can see a substantial difference in event-free survival among those who are MRD positive versus MRD negative. It is highly statistically significant.

Current treatment options for relapsed ALL. The first job is to reinduce remission using induction chemotherapy, then definitive post-induction therapy is required for cure. Patients who relapse after completion of therapy, generally within 3 years of initial diagnosis, and have a good MRD response to induction chemotherapy can be treated with chemotherapy alone with reasonably good outcomes.

In contrast, patients who relapse early, within the 3 years after diagnosis, or those who
relapse late and are MRD positive post-induction, or any patient with second or greater relapse requires chemotherapy to obtain an MRD-negative state followed by hematopoietic stem cell transplantation. Patients who are MRD positive at the time of hematopoietic stem cell transplant rarely survive.

These intensive therapies are associated with significant toxicity, treatment-related mortality, and poor quality of life. Patients with a second relapse have even fewer effective treatment options.

Today, we'll focus our discussion on patients with relapsed and refractory ALL. Treatment options for these patients are quite limited. Standard chemotherapy and hematopoietic stem cell transplant have limited efficacy. Patients who relapse post-transplant have a 2-year overall survival rate of 15 percent. New agents have limited response rates, and even those patients who respond require transplant for cure. Overall survival has not changed for these
patients.

Today, I will show some results of clofarabine. It’s a single-agent or in combination therapy and blinatumomab in this setting. Patients with relapsed/refractory ALL typically have prolonged hospital stays and have an appreciable risk of treatment-related mortality. Thus, most patients with relapsed/refractory ALL, both adult and pediatric, have significant unmet medical needs.

This first slide shows the results of the clofarabine monotherapy phase 2 trial published in 2006 by Sima Jeha and colleagues. Here, we see this trial enrolled 61 patients and had a median overall survival of 3 months.

There have been several trials in relapsed/refractory ALL with clofarabine in combination with other agents, most commonly clofarabine, etoposide, and cyclophosphamide. This slide shows the results of a phase 2 trial conducted in pediatric relapsed/refractory ALL that enrolled 25 patients and had a median overall
survival of 2.5 months. A similar trial was
conducted in Italy, enrolled 17 patients, and had a
median overall survival of 9 months.

This slide shows the recently published results by Aaron von Stackelberg and colleagues, published in late 2016 of the blinatumomab phase 1-2 trial that enrolled 70 patients with relapsed and refractory B-cell ALL. This trial showed a median overall survival of 7.5 months.

This table collates the results of these various trials. All these studies involved a limited number of patients ranging from 17 to 70. They received a variable number of prior treatment regimens. In the clofarabine monotherapy trial, 62 percent of patients have received 3 or more prior regimens. On the blinatumomab phase 1-2 trial, only 7 percent of patients have received 3 or more prior regimens.

They demonstrate overall response rates ranging from 20 to 44 percent in general with the exception of one small study that showed an overall response rate of 76 percent. The median overall
survival ranged from 3 to 9 months with 12-month overall survival of 20 to 40 percent. Early mortality occurring within 30 days of treatment was significant and ranged from 7 to 25 percent in these trials.

Thus, the treatment landscape for relapsed/refractory ALL shows that, despite current treatment options, more than 600 epidemic and young adult patients with ALL experience relapse each year in the United States. Treatment options for patients with relapsed and refractory ALL are limited and are associated with poor outcome and high toxicity. Most patients with relapsed and refractory ALL remain incurable today.

Thus, there is a major unmet medical need for novel treatment options for pediatric and young adult patients with relapsed/refractory ALL to provide deep MRD-negative and durable remissions, curative treatment opportunities, and improved quality of life.

Now, I'd like to invite Spencer Fisk, head of cell and gene technical development and
manufacturing, who will take you through the CTL019 manufacturing process.

**Applicant Presentation – Spencer Fisk**

MR. FISK: Thank you, Dr. Hunger.

Good morning. My name is Spencer Fisk, and I'm the head of cell and gene technical development and manufacturing at Novartis. Novartis is committed to an open dialogue with you today, and we look forward to answering your questions.

With this being said, sometimes the agency will hold these technical manufacturing discussions in a closed session to protect proprietary information. In this case, we agreed that there was greater benefit to having an open discussion. We therefore ask and thank you in advance for your understanding if there are specific details we can't address due to their proprietary nature.

Today, I will provide an overview of the CTL019 manufacturing process. We have designed an integrated process to collect immune cells from a patient, reprogram them, and then return them to the same patient. This process begins when a
patient is identified for treatment and undergoes leukapheresis at an approved site.

The patient leukapheresis is then transferred to our Morris Plains facility, acquired in 2012, which has been dedicated to the advancement of CTL019 over the past five years. It is here where patient leukapheresis undergo reprogramming prior to being returned to the approved site for administration.

Novartis uses well-established standards to maintain a rigorous chain of identity from leukapheresis, through manufacturing, to patient infusion. This includes using procedures from the Foundation for the Accreditation of Cellular Therapy, or FACT, and labeling standards from the International Society of Blood Transfusion or ISBT-128. These standards seamlessly integrate with a Novartis quality system dedicated to managing chain of identity of patient material and final product.

As mentioned previously, Novartis purchased its cell manufacturing facility in 2012. It has
been used to manufacture more than 250 patient cell
products for Novartis CTL019 studies to date, where
we have established rigorous training and quality
standards to ensure consistency in operations. The
facility has the ability to support the anticipated
demand, and we continue to invest in our
capabilities to further support clinical
development and commercial supply.

At the manufacturing facility, cells undergo
an enrichment and activation, transduction,
expansion, formulation, and final quality
assessments, as depicted here on the bottom half of
the slide. The final product is then cryopreserved
and shipped back to the treatment center for
patient administration. Utilizing both
cryopreserved starting material and final product
results in significant flexibility in manufacturing
starts and patient utilization.

Novartis uses a dedicated courier service to
ship leukapheresis material to the manufacturing
facility and to transport CTL019 back to the
treatment center.
As previously mentioned, the chain of identity is crucial to this process. A patient-specific bar code is attached at step 1 by the team performing the leukapheresis and is tracked at each subsequent step in the process. It is then verified again at the clinical site by the team administering CTL019 to the patient.

I will now go over each of the manufacturing steps in greater detail, starting with leukapheresis. Leukapheresis is a well-established clinical procedure for obtaining white blood cells from the patient. The procedure is performed for Novartis without immobilization drugs using FDA-approved equipment and standard mononuclear cell collection parameters.

We qualify and maintain oversight of each leukapheresis site, which supplies patient cells for manufacturing. Each site is an FDA-registered tissue establishment, FACT accredited, and must actively be implementing ISBT-128 labeling standards. Novartis audits, establishes, and maintains quality agreements with these sites.
against these requirements.

After collection, the cells are cryopreserved and are quality-control tested to ensure that there are a sufficient number of cells required for manufacturing.

The frozen cells from the patient are shipped to the manufacturing site, where they are thawed and undergo an initial enrichment step. Depending on the composition of the leukapheresis in terms of T cells, B cells, and monocytes, the cells will either undergo an antibody-based positive selection step, or a density gradient enrichment step, or both.

The different pathways ensure that cells that are detrimental to the growth of the T cells are removed and the purity of the T cells is sufficient to allow effective growth. Following enrichment, the cells are incubated with a lentiviral vector made by Oxford Biomedica, our manufacturing pattern.

The vector enables transduction of the T cells. During this process, the CTL019 transgene
is stably incorporated into the DNA of the T cells, which allows the expression of the T cells to recognize and respond to CD19-expressing cells. After transduction, the cells spend just over a week in specialized culture conditions designed specifically for the selective growth of T cells.

The cell culture includes anti-CD3 and anti-CD28 antibody-coated beads, which as well as interleukin 2 selectively stimulate T-cell growth. This allows us to obtain a sufficient number of highly pure T cells to give back to the patients.

Once we have grown the T cells, we remove the anti-CD3 and anti-CD28 antibody-coated beads. The cells are then frozen to enable shipment back to the site, providing flexibility for both patients and physicians regarding when the patient is infused.

A broad panel of orthogonal tests are conducted to ensure the safety and efficacy of the CTL019 products. Final acceptable results demonstrate consistency of the manufacturing process and product quality assurance. All testing
is completed prior to cell product release to the patient.

To ensure the product is safe for use, we test for sterility, endotoxins, absence of impurities, and replication-competent lentivirus. Functional tests include the identity of the chimeric antigen-receptor, the dose in terms of the number of transduced viable T cells, and the potency of the product. As potency represents a key attribute, I will discuss it further in the next slide.

There are multiple relevant biological activities related to T-cell function that are associated with the potential mechanism of action. For CTL019, we measure interferon gamma secretion as a measure of potency because it is a robust and early indicator of T-cell activation. Other functional measures include proliferation, cytotoxicity, and long-term persistence.

We know that potency requires CAR expression and is highly specific to CD19-expressing cells. Although we only measure cytokine release for
potency, we have established characterization assays for proliferation and cytotoxicity and see a strong qualitative correlation between all three.

We have also seen persistence of CTL019 in patients. Later, during today's presentation, Dr. David Lebwohl will discuss how the potency results correlate with clinical outcomes from the patient and young adult relapsed/refractory B-cell ALL patients.

Shown here on the left is the patient variability in leukapheresis collected at the sites. What can be seen is that there is a potential for a great deal of heterogeneity in incoming material. And now, on the right, we show final product.

As you can see, we have designed and confirmed a robust manufacturing process that uses the pathways I have described to ensure that cells detrimental to the growth of the T cells are removed. Although we occasionally see minimal amounts of NK cells, there are no detectible B cells, monocytes, or dendritic cells. This leads
to the high level of purity that is seen in the final CTL019 cell product.

In addition to ensuring cell product consistency and purity, we have seen consistent levels of transgene copy numbers per cell across the targeted range of transduction. As shown here, we achieve a stable vector integration averaging 1.3 copies per transduced cell. The impact of CAR transduction on clinical response and safety will be discussed by Dr. Lebwohl later this morning.

Novartis performs additional analytical characterization to complement our extensive product quality release testing, which has allowed us to evaluate T-cell subpopulations and other product attributes.

Listed here are some of the methods Novartis has developed and utilized to link CTL019 attributes to our manufacturing success and positive clinical outcomes. While we continue to build knowledge and understanding using these methods, we have not yet identified any additional product attributes that provide greater assurance
of product quality.

As mentioned earlier, once we have completed and checked results of all lot-released tests, the cryopreserved product is shipped to the clinical site, where the patient will be infused. Novartis uses a dedicated courier service to ship the final product and ensure the integrity and temperature are maintained throughout shipping.

Patient identity is verified prior to infusion, and the preparation and infusion of the product is performed by qualified sites in accordance with the prescribing information.

Sites were selected to ensure that an appropriate infrastructure and training is in place to support safe treatment of patients with CTL019. Further details on this will be discussed later by Dr. Lebwohl.

In summary, Novartis has accrued a significant amount of patient-specific manufacturing experience in global multicenter trials with over 250 batches manufactured to date across various indications. We have established a
highly reproducible manufacturing process with demonstrated manufacturing success. Consistent product safety and quality has been demonstrated by extensive product release and characterization testing.

Finally, I would like to share with you a picture of our Wall of Hope displayed at our Morris Plains manufacturing facility. Each light you see displayed here on this board represents a patient that has been treated by CTL019. It is a reminder to us that every batch of product we manufacture represents our hope for a unique cancer patient and is a reminder of our responsibility to them.

Now, I'd like to turn the podium over to Dr. James Miskin of Oxford Biomedica, our vector manufacturer partner, who will present information about our lentiviral vector.

**Applicant Presentation – James Miskin**

DR. MISKIN: Good morning, everybody. Thank you, Spencer.

My name is James Miskin and I'm the chief technical officer of Oxford Biomedica, which is a
company based in the U.K. specializing in the
development and manufacture of lentiviral vectors.
I'm going to run through a number of the key
aspects that relate to the lentiviral vector that
is used to manufacture CTL019. Given the
importance of and potential safety concerns with
the viral vector, great care was put into its
selection.

The lentiviral vector was chosen because it
offered an improved safety profile over other
retroviral vectors while still allowing for the
stable long-term expression of the transgene. The
vector system is designed to minimize the risk of
recombination, preventing potential replication-
competent lentivirus, or oncogenicity.

You will note that the FDA uses the term
RCR, or replication-competent retrovirus, in their
briefing document and discussion questions. In
this presentation, we use the term replication-
competent lentivirus, or RCL, as this is the only
type of RCR which is relevant directly to CTL019.

Vector manufacturing uses single-use
components, chemically defined formulation, and vector is filter sterilized. Vector quality is maintained through our comprehensive testing panel. The patients who receive CTL019 are then followed post-administration, and to date, there have been no evidence for RCL or insertional oncogenesis.

The vector system has been selected because of its safety. The vector integration profile of lentiviral vectors has been well characterized, and it allows for permanent genetic modification of target cells, and it leads to long-term gene expression. Gene expression is durable, with evidence out to 780 days post-infusion in one example case.

The ability to express the CAR transgene is important, and the clinical experience has shown that long-term gene expression from low vector copy numbers per cell is managed.

The system has been designed to be safe whilst using a manufacturing process that enables efficient production. Unlike the original virus, the vector cannot replicate. It also cannot
recombine to generate a replication-competent virus because of a number of features.

First, the vector components have been segregated onto four separate plasmids. Only the essential features of the original virus have been retained within the vector system. The vector components themselves have been modified to remove homology and thereby preventing homologous recombination. The viral promoters and enhancers have also been deleted.

Vector manufacturing is conducted using human HEK293T cells grown in 10-layer cell factories. Cells are transiently transfected with the four plasmid components previously described, and vector is harvested in the supernatant fluid from the cells.

Vector is then purified and concentrated using a combination of ion exchange and membrane-based technologies, and then the vector substance is frozen. Vector product manufacturing occurs in a single day, where multiple vector substances are thawed, pulled, filter sterilized, and then further
concentrated. Vector is filled into glass vials, inspected, labeled, and frozen.

Vector manufacturing takes several weeks, but then coupled with the extensive testing panel that takes place, the entire process takes several months.

The vector is tested to ensure safety and quality. A broad panel of testing methods is guided by a knowledge of the vector system, the vector structure, and the manufacturing process. We use a variety of different safety tests, including one that is very specific for replication-competent lentivirus or RCL for short.

We have spent a lot of time and effort developing a method that is extremely sensitive and highly efficient at the amplification and detection of RCL from any source, irrespective of what that might be. We then utilize a number of different analytical methods to demonstrate purity by measuring both the vector and the process-associated impurities.

Biological function is a functional test
wherein the vector is incubated with target human
cells. Cells are grown up over a number of
pathologies to remove non-integrated DNA. And then
the DNA is extracted and analyzed by quantitative
polymerase chain reaction analysis to determine the
vector titer.

We are managing the theoretical risk of RCL
through our manufacturing and testing approach. We
have adopted a third-generation minimal lentiviral
vector system, which has been designed from first
principles to be safe.

Patient safety is ensured through a
comprehensive panel of highly sensitive tests
conducted on the viral vector itself and its
associated end of production cells. In addition,
CTL019 cells are also tested for RCL.

Finally, in addition to the trial conducted
with CTL019, where there is no evidence for RCL in
patients, there are also a number of other studies
using similar technology supporting the absence of
RCL from these systems. I'll expand on this in the
next slide.
Hundreds of patients have been treated with cell therapies using lentiviral vectors with cumulative decades of follow-up, and there have been no observed cases of RCL in any trial. This experience includes more than 250 manufactured CTL019 cell products across the indications with additional data from academic trials across the U.S. in other indications. We therefore conclude that RCL testing of the vector and the CTL019 product are adequate to ensure patient safety.

Considerable work has been done to analyze the integration site preference of the viral vector system. There is a lentiviral vector site analysis, or LISA study, conducted by Novartis in which over 90,000 unique integration sites have been analyzed in multiple samples, including both healthy volunteers and patients.

Lentiviral vector integration site analysis uses molecular techniques to specifically map the integration sites within the target cells, and then the data are analyzed.

In summary, there is no evidence for
preferential integration near to genes of concern, nor is there any evidence for preferential outgrowth of cells harboring integration in sites of concern.

In summary, CTL019 has been designed from first principles to be safe and to prevent RCL. To date, there has been no evidence for insertional mutagenesis using third-generation lentiviral vectors in any T-cell engineering therapy setting. Oxford Biomedica as a company has been working on this technology for over 20 years. We have developed considerable experience of CTL019 vector manufacturing testing using a highly reproducible manufacturing process and a comprehensive testing panel. Many thanks for your attention, and I'd like now to hand over the podium to Dr. David Lebwohl.

**Applicant Presentation – David Lebwohl**

DR. LEBWOHL: Thank you, Dr. Miskin. Good morning. I am David Lebwohl. I am the CAR key franchise global program head at Novartis. A critical aspect of developing a CAR T-cell
therapy is to understand the correlation of characteristics of the engineered product with the clinical outcomes of the infused patient.

I'll discuss two key aspects of the cell product, CAR transduction and product in vitro potency, and their correlation to the clinical outcomes shown here. These measure the quantity and activity of both the transgene and the cells and are representative of the full set of product attributes measured during the study.

Two aspects of transduction are shown here. On the left, we look at the percent of cells which are positive for CTL019 or the transduction efficiency. On the right, we look at transgene copy number per cell. In both cases, there are positive patient outcomes across a range of transgene-positive cells and transgene copy number per cell, and no correlation between the transduction measure and the response, either CR/CRi or the lack of response.

Looking now at the potency assay, you see all the non-responder patients at the low end of
potency. We don't yet understand why a small number of patients did not respond to CTL019. However, there were positive patient outcomes across the complete range of acceptable potency assay results, including at the low end.

    Future analysis of the potency response across a larger dataset of infused patients will provide greater insight into the use of in vitro measurement for predicting patient response.

    We also correlated product characteristics with cytokine-release syndrome, an important on-target toxicity observed in our trials. Looking again at CAR transduction, the severity of CRS did not correlate with transduction efficiency or with a transgene copy number. There is no correlation of interferon gamma secretion by CD19-stimulated CTL019 cells with the CRS grade observed post-infusion.

    In summary, Novartis has accrued extensive experience in manufacturing CAR T cells. The process that we developed is highly reproducible, and the product is tested to ensure high quality.
As Dr. Miskin explained, the CTL019 vector has been designed to prevent replication and recombination. Thus, we believe that patient RCL testing is not warranted in the commercial setting. The product has been shown to result in a high rate of response across the entire range of product quality attributes.

We look forward to addressing any questions that you may have about the technical manufacturing aspects of CTL019. Thank you.

DR. ROTH: Thank you, Dr. Lebwohl. We'll proceed now with the agency presentation, Dr. Victor Lu?

**FDA Presentation – Victor Lu**

DR. LU: Thank you, Dr. Roth.

Good morning. My name is Xiaoban Victor Lu. I'm one of the product reviewers for this BLA. In the afternoon session, Dr. Maura O'Leary will present clinical aspects of tisagenlecleucel. And the goal of my presentation this morning is to provide the product background information about tisagenlecleucel and to set up the stage for the
product discussion this morning, as well as clinical discussion this afternoon.

We will pose two questions for the committee's discussion this morning. Today, I will outline how the structure of CD19-directed chimeric antigen receptor, or CAR, relates to the product mechanism of action. I will outline some of the safety issues associated with lentiviral vector that is used to express the CAR.

I will also provide a high-level discussion of how control of the manufacturing process and product testing help to assure consistent safety and quality of tisagenlecleucel.

Tisagenlecleucel is a genetically modified autologic cell immunotherapy. It consists of a patients' own T cells that express a chimeric antigen receptor that specifically recognizes CD19-positive cells, and a CAR gene is introduced into the patient's T-cell by gene transfer with an HIV-1-based retroviral vector in a process called a transduction.

Throughout this presentation, I will use the
term "retroviral vector" for lentiviral vector because the parenteral HIV-1 virus used for the vector is a member of the retrovirus family.

CD19-positive B-cell tumors are the intended targets of tisagenlecleucel. However, normal B cells are also targeted. Thus, treatment with tisagenlecleucel results in B-cell deficiency, which can be managed through intravenous infusion of immunoglobulin.

Unlike traditional pharmaceutical drugs, tisagenlecleucel is a dynamic living biologic. The T cells in the product can expand and differentiate during the manufacturing process and the following administration into patients. These unique product characteristics should be kept in mind when discussing manufacturing challenges and when discussing clinical aspects of tisagenlecleucel this afternoon.

The CAR mark is one of the most critical components of tisagenlecleucel because it determines the specificity and biological function of tisagenlecleucel. It consists of three
different protein domains fused together to form a chimeric antigen receptor.

The extracellular single-chain variable fragment domains mediate specific binding to CD19 molecules on B cells. The high affinity of the scFv binding domain also plays an important role in CAR T-cell activation and effective functions, and can impact the safety and activity of the product. The length and topology of the spacer and transmembrane domains are important for providing appropriate orientation for antigen recognition and the subsequent T-cell activation.

The intracellular secondary domains are derived from the human CD3-ζ chain and the costimulatory secondary domains from human 4-1BB. Both intracellular domains contribute to T-cell activation, expansion, and target-cell killing.

Because tisagenlecleucel is a rationally designed immunotherapy, the presumed mechanism of action is known and shown schematically on this slide. T-cell activation begins with scFv binding to CD19, which triggers a cascade of CAR signaling.
activities that eventually leads to T-cell activation and results in CAR T-cell expansion, differentiation, persistence, and target-cell killings. The T cells also release cytokines and autocrine and paracrine signaling, which may result in activation of some other type of cell such as a macrophage. This multi-factorial mode of action is important to keep in mind as we discuss potency assays later on.

As mentioned already, the vector used, tisagenlecleucel, was derived from the HIV-1 virus, and the vector was designed to eliminate the vast majority of the risks associated with naturally occurring HIV infections.

As shown on this slide, HIV has many accessory proteins that are necessary for viral replication and pathogenesis, and these genes have been removed from the vector, leaving the vector unable to replicate.

Tisagenlecleucel vectors have also been modified so that the long-term repeat [ph], or LTRs, are self-activating, and the viral enhancer

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regions have been removed, and taken
together -- and the resultant vector that does not
have the usual pathogenetic characteristics of an
HIV virus.

As shown on this slide, in the lentiviral
vector elements, the requirement to make the vector
includes 3 packaging plasmids and the CAR vector
plasmid. A VSV-G envelope is used as an envelope
instead of HIV-1 envelope protein, which means that
the vector is able to transduce a broad range of
cells, including both CD4 and CD8 T cells.

The CAR vector's plasmid contains a CD19 CAR
expression cassette along with minimal HIV
sequences that are essential for vector function.
An HIV packaging sequence site is essential for
vector genomes to be packaged into vector
particles, and the packaging plasmid elects the
site sequence, so the sequences from the packaging
plasmid are not packaged into vector particles.
The vector is produced by co-transfections of these
4 plasmids into a substrate cell line.

Theoretically, recombination events during
the vector manufacturing process could generate a replication-competent retrovirus or RCR for short. Throughout this talk, I will use RCR for RCL.

An early generation of gamma retroviral vector derived from MLV that was contaminated with RCR generated during the vector manufacturing process and caused leukemias in animal studies. However, the chance of RCR generation is reduced by minimizing regions of homology and by segregation of the packaging constructs on separated DNA plasmids.

To date, RCR has not been detected in new generation vectors or vector-transduced cells, including tisagenlecleucel, used in the clinical trials. Moreover, as shown in the previous slide, many of the HIV accessory genes have been deleted. So even if a replication-competent retrovirus were generated, it would be severely weakened.

During clinical trials, tisagenlecleucel was tested for RCR at multiple strategic steps wherein RCR is most likely to be detected, including testing during vector manufacturing and testing on
a cell product. A sensitive culture RCR assay was used to test for the presence of RCR in the retroviral vector and production cells in which the vector was made.

In addition, each batch of tisagenlecleucel was tested using a quantitative PCR test and, following administration of tisagenlecleucel, patient samples were collected and tested for RCR according to the FDA guidance as part of a long-term follow-up protocol. There have been no positive results for any of the RCR tests conducted for tisagenlecleucel.

In the commercial setting, Novartis will continue to test each vector batch and production cells as part of the vector manufacturing and control. These tests will use the sensitive co-culture RCR assay. In addition, each lot of tisagenlecleucel will be tested by a qPCR assay prior to product administration. We note that the negative RCR test results during the manufacturing process does not mean that there is no risk of RCR.

In the commercial setting, however, Novartis
does not plan to collect and test patient samples for RCR. This is different from the long-term follow-up that Novartis has been performing during clinical trials.

In a previous slide, I pointed out that the vector for tisagenlecleucel is designed to reduce the risk of adverse events related to vector integration. However, it is still possible that integration of the vector into the host and cell chromosomes might change the activity of adjacent host genes. The vector may occasionally integrate into genes and interrupt it. The vector may also enhance the activity of nearby genes due to potential enhancer elements in the vector. If the nearby oncogene is activated by the vector, this might lead to oncogenesis.

As we described in the briefing document, insertional mutagenesis from gamma retroviral vectors, has led to leukemia cases in multiple clinical studies, and this can occur many years after treatment. I would like to point out that, to date, these delayed adverse events have only
been seen with stem cell products transduced with gamma retroviral vectors. In contrast, to date, no vector-associated leukemia cases have been seen with tisagenlecleucel or any other vector-modified T-cell products.

The same vector design lacks retroviral enhancer sequences, and thus is less likely to activate the nearby host genes. This design therefore lowers the risk of oncogenesis.

Novartis does not perform vector integration site analysis as part of the routine lot release for testing tisagenlecleucel. However, Novartis did perform a one-time study where they analyzed the integration sites for 14 tisagenlecleucel batches.

Overall, the distribution of integration sites was similar to other lentiviral vectors with a preference for open chromatin regions of gene activities and the region of high GC content.

There was no preferential integrations of the vector near oncogenes. However, the caveat is that this type of analysis cannot predict whether a
rare mutated T-cell will preferentially expand in vivo and possibly lead to oncogenesis. In the past, integration studies in stem cells with other vectors have failed to detect integration events that eventually led to tumors in patients.

During clinical trials of tisagenlecleucel, patients' cells were regularly monitored for vector persistence and clonal expansions of the transduced T cells. There have been no instances of clonal expansion or vector-associated oncogenesis. If tisagenlecleucel is licensed, however, no routine collection of patient samples for such monitoring is proposed.

However, if the patient develops a new malignancy after infusion of tisagenlecleucel, Novartis has indicated that they will attempt to obtain fresh tumor tissues to analyze for the presence of the tisagenlecleucel vector in the new malignancy tissues.

This concludes the discussion of the vector and its associated risk profile. In summary, the potential vector-associated risks can be reduced...
significantly, however, the risks cannot be entirely eliminated. The issues of vector design and product testing for RCR and insertional mutagenesis will be discussed in this morning's session. The long-term follow-up for patients will be discussed in the afternoon session.

Now, I will move on to tisagenlecleucel manufacturing and control. As already presented by Novartis, the tisagenlecleucel manufacturing process is a complex process that includes multiple critical steps such as the collection of patient cells by leukapheresis, transduction with lentiviral vector, and activation and expansion of T cells using CD3/CD28 antibody-coated beads.

This is a lengthy and complex manufacturing process with a living, dynamic T-cell population. Therefore, in-process monitoring and controls are necessary to ensure the product lots are consistent.

Controls of quality begin with a qualification of critical components, including the leukapheresis material and the vector. Each unit
operation is controlled by establishing critical
process parameters, for example time limits on
various processing steps, and the entire validation
of the manufacturing process is expected to be
validated.

In-process monitoring and lot-release
testing confirms that the cell product meets pre-
defined specifications beyond lot-release testing.
Additional characterization assays were performed,
providing further assurance of product quality
attributes.

In summary, the quality of tisagenlecleucel
is controlled by understanding how the
manufacturing process affects product quality
attributes and then controlling the manufacturing
so that product attributes consistently meet their
pre-defined limits. We will examine some of these
critical aspects of the manufacturing process
control in the next few slides.

Probably the most variable component of
tisagenlecleucel manufacturing process is the
starting material. The autologous leukapheresis
cells and autologous cells collected from each patient contained many different types of cells from peripheral blood. The composition of the leukapheresis material can vary widely, depending on the patient's genetic background, disease status, age, and prior treatment history. And during process development, Novartis has evaluated how to adjust the manufacturing process to enhance consistency of the final product.

As shown in this figure from the Novartis briefing document, also shown in the Novartis presentation early on, their manufacturing process results in a final product that is consistently high in T-cell content, as shown on the right panel, even when the starting material is quite variable, as shown on the left panel.

This figure illustrates that it is possible to control the manufacturing process for consistent final product quality even when the starting materials are variable. As noted in the previous slide, tisagenlecleucel contains mostly T cells, however, vector transduction efficiency varies
greatly between patients, and only a subset of T cells expresses the CAR. T-cell subpopulations in tisagenlecleucel can also vary in terms of CD4-CD8 ratio, central memory T cells, effector memory T cells, et cetera.

It is unknown which T-cell subsets contribute most to tisagenlecleucel activity. As I mentioned earlier in my presentation, the T-cell can change after administration. Cellular interactions after administration may affect how the cell expands, activates, differentiates, and persists in the patients.

Lot-release testing for tisagenlecleucel includes and tests for safety such as RCR, sterility, endotoxin, and mycoplasma. In addition, the number of vector copies per cell is controlled because too much integration would increase the risk of insertional mutagenesis.

It is important to assure the identity and purity of the product, and strict control of the chain of identity must be maintained throughout the manufacturing process to provide the correct
product to the patient.

The levels of transduction between the patient lots varies greatly, as we will see shortly. So to ensure that patients are getting the consistent dose of the active ingredient, the dose of tisagenlecleucel is based on the number of viable T cells expressing the CAR protein.

Potency is also an important measure for the product's biological activity, and for tisagenlecleucel, Novartis is measuring cytokine production, which is described in more detail on the next slide.

The purpose of potency testing is to assess the ability of the final product to function against CD19-positive cells. As I noted earlier, when CD19 activates the CAR, it has many stimulatory effects on the T cells. One of these effects is the release of interferon gamma.

The lot-release potency test measures interferon gamma release after tisagenlecleucel is exposed to CD19-expressing cells. Novartis also characterized the capacity of tisagenlecleucel to
kill CD19-expressing cells. This was submitted to the BLA as supporting data, but will not be a part of the lot-release test.

During the discussion this morning, we would like the committee to comment on how best to measure the functional activity of tisagenlecleucel. Setting the appropriate range for lot-release acceptance criteria is critical for interpretation of clinical data and to ensure the consistently safe potent and quality product for patients.

The proposed lot-release specifications for tisagenlecleucel were based on analysis of accumulated historical testing data and analyzing these data using appropriate statistical methods for variation assessment and data trending.

Patient outcomes occurred across a broad range of product attributes. It's difficult to establish correlations between the variable product attributes and clinical outcomes when the number of patients is so small.

Some particularly valuable aspects of
tisagenlecleucel are illustrated in the next few slides, including interferon gamma production and transduction efficiency. This is historical potency data for lots that were used in study B2202 in clinical development. The scales on both X- and Y-axis, as well as the actual upper and lower limits, are not shown because this is proprietary information.

The proposed commercial acceptance criteria are indicated by the red dashed lines, and the potency assay measures interferon gamma release upon culturing of tisagenlecleucel with CD19-expressing cells.

There is a wide range of historical data, and as a result, the upper and lower limits of the acceptance criteria are also quite wide. The dataset is still small. As manufacturing experience increases, these values may become less variable.

This is lot-release data for transduction efficiency and for the lots that were used in the clinical study B2202. As you can see, there is a
broad range of variability in terms of transduction efficiency. There is currently a lower limit for transduction efficiency, but not an upper limit.

It is important to note, again, that the patient dose of tisagenlecleucel is measured in terms of transduced cell number, therefore, variable transduction efficiency has less impact than if the dose were to be placed on the total cell numbers. However, it should be noted also that the dose of tisagenlecleucel also has a broad range.

This diagram shows the number of vector copies per transduced cell for the lots that were used in the study B2202. As you can see, there is also a wide range of values for the various tisagenlecleucel lots early in the clinical trials. Later in the clinical trials, product lots were more consistent, and this coincides with when Novartis finalized their manufacturing process controls. Vector copy numbers affect both activity and safety of tisagenlecleucel. Higher levels of vector transduction will result in a higher
percentage of CAR-positive T cells, but also could increase the risk of insertional mutagenesis.

In summary, tisagenlecleucel is a dynamic biological product with the capacity to expand and differentiate following administration. Process controls are necessary to ensure product consistency. Some product attributes are highly variable from patient to patient and may have a limited value for predicting safety and efficacy.

Products with variable characteristics were administered during clinical studies. Vector design has decreased the risk of RCR and insertional mutagenesis. However, insertional mutagenesis cannot be predicted through lot-release testing alone.

RCR has not been detected in tisagenlecleucel cell product or vector lots, clonal dominance outgrowth has not been observed, and long-term follow-up of patients during clinical studies is still ongoing. There have been no events related to RCR or insertional mutagenesis with tisagenlecleucel.
With that, I conclude the FDA CMC presentation. I would like to thank my FDA colleagues for their contributions to this presentation and the briefing document, and thank you for your attention.

At this point, I would like to bring up the two discussion questions that we prepared for the committee. This is a preview, and we will not discuss right now. We will discuss these questions after the break.

Here is the first question. During tisagenlecleucel development, the applicant established product quality specifications to assess chimeric antigen-receptor expression in T-cell activity, including transduction efficiency by flow cytometry, vector copy number per cells, and interferon gamma production following stimulation by CD19-positive cells.

Please discuss the following aspects of control of the product quality of tisagenlecleucel with respect to identity, safety, purity, and potency: the design of the CAR construct and the
viral vector; the assessment of CAR expression and
T-cell activity through the number of transduced
T cells, the number of vector copy per cell, and
antigen-specific T-cell functions, for example
interferon gamma production and cytotoxicity upon
stimulation; and any other measurements such as
T-cell subpopulations and cell surface marker
characterization that could provide greater
assurance of product quality.

Here's the second question. Potential
safety concerns with tisagenlecleucel other
retroviral-based gene therapy products include
generation of replication-competent retrovirus and
insertional mutagenesis. Strategies to address
these concerns include vector design and product
testing.

Please discuss how vector design impacts the
risk of RCR.

Please discuss how vector design impacts the
risk that insertional mutagenesis might cause
secondary malignancies.

Please discuss the extent to which product
testing can mitigate the risk of RCR and insertional mutagenesis.

At this point, I would like to turn it over to Dr. Roth.

**Clarifying Questions to the Presenters**

DR. ROTH: Thank you, Dr. Lu.

We'll move on to clarifying questions both for the agency and for the applicant. If you have a question, just let Jen know. She'll write your name down. We'll try to take these in order. Also, for the people who are transcribing this, if you could, identify yourself before you're asking a question.

Maybe I can kick it off with a couple of manufacturing questions. I don't know who the appropriate person would be.

The first is, in the trial, time from apheresis to infusion was 16 weeks. So my question is, is that a number that you think would change in the future with ramp-up, or is that kind of a fixed ceiling that we have to deal with?

The reason I ask, of course, is that some
people died of progressive disease before ever getting the infusion. And that's a testament to I guess the relative futility of bridging chemotherapy and maybe all the more reason to have something new. But I was wondering whether you thought that that would change with time. That's the first question.

DR. LEBWOHL: Yes. So I'm David Lebwohl again. Yes. We do believe this will change from a clinical trial setting to the commercial setting. I would ask Dr. Natarajan to explain the time we expect in the commercial setting.

DR. NATARAJAN: Good morning. I'm Arvind Natarajan from cell and gene technical development and manufacturing at Novartis. In the commercial setting, we expect that the time to manufacture the product from the receipt of apheresis to shipment of the product back to the patient would be 22 days.

So the timing upon launch for this particular product, we expect to have a day to be able to receive the leukapheresis material and then
to start the manufacturing process. The core manufacturing process itself takes 10 to 11 days, depending on the growth of the cells.

The testing and the disposition of the product takes 9 days, and this is driven by the longest lead test that we have as part of the testing panel. And then we expect one day to pack and ship the product back to the patients for a total of 22 days.

DR. ROTH: Thank you. My second question is, could you tell me a little bit more about the seven, I believe, manufacturing failures? Namely, no product came out and if there was some retrospective analysis that could come up with some common denominator. Or maybe even taking it a step further, is there something that could be screened on the front end by the treating physician to say who is likely to get a manufacturing null?

DR. LEBWOHL: So let me first show you the cases that were in our clinical trial B2202. There were 6 cases in that trial; 4 of them were due to insufficient growth. But we think these are
intrinsic factors to the patient cells. And as part of the process in improving manufacturing, what we've seen in the last 40 batches is a 98 percent success rate. So we do believe the rate of inability to manufacture will be going down in the commercial setting.

There are other reasons other than the patient's intrinsic factors. One was low-dose potency also could be factors for the patient and high bead count, which is a manufacturing issue.

DR. ROTH: Thank you. Dr. Gulley?

DR. GULLEY: So perhaps this one is also for Dr. Lebwohl. Not all the T cells are transduced. So I was wondering if in the product release criteria, if you were looking at the difference in cytokine-release syndrome by total number of cells rather than just the CAR T cells.

DR. LEBWOHL: Dr. Hamilton will address this, please.

DR. HAMILTON: Hi. Jason Hamilton, cell and gene technical development and manufacturing, Novartis. We have in fact also evaluated the
relationships between the total number of viable cells included within the product doses with clinical outcome measures. And as you can see here, we saw no relationship between total number of viable cells infused and the grade of CRS that the patient experienced.

DR. GULLEY: Thank you. One other question quickly, and that is, with the intracellular cytokine, have you looked at polyfunctional CAR T cells? For instance, have you looked at other cytokines besides gamma interferon like IL-2, TNF, or CD107A?

DR. LEBWOHL: Dr. Brogdon?

DR. BROGDON: Hi. Thank you for that question. Jennifer Brogdon, Novartis, pre-clinical research. We do a number of exploratory assays to understand the different cytokine profiles of these cells over a number of different patient characteristics as well.

These are still all in process. We certainly see IL-2 and TNF alpha being produced. We have found that interferon gamma is our most
reliable robust assay for the purposes of the
potency.

DR. ROTH: Dr. Bollard?

DR. BOLLARD: I have multiple questions. Am
I allowed to ask multiple or just a few? So I have
questions related to Drs. Lu, Fisk, and Miskin's
presentations, and I guess we can start with -- one
of the biggest questions I have is surrounding
product purity.

I know Dr. Fisk talked about the
heterogeneity of the leukapheresis products, and
then talked in very general terms about antibody
selection or Ficoll separation. So I would like to
know what sort of positive selection are you doing;
is this CD3-positive selection; and what is your
release criteria in terms of percent contamination,
B cells in particular, given that these are
patients where we saw that over 50 percent are
blasts in some leukapheresis products you're
receiving?

DR. LEBWOHL: I'll ask Dr. Natarajan to
address this, please.
DR. NATARAJAN: Good morning. Arvind Natarajan from Novartis. We did see significant heterogeneity in the composition of the incoming leukapheresis material, and we have developed our processes to be able to enrich T cells against a variable background of the incoming material.

We use CD3, CD28 coated, or anti-CD3, anti-CD28 coated antibody beads to be able to positively select and enrich for the T cells prior to the start of -- to initiate the start of manufacturing.

DR. BOLLARD: So what's your release criteria for percent B cells allowed in your final product?

DR. NATARAJAN: I'm not able to share the exact number because we consider that information to be confidential. However, you can see from the data that's displayed that we routinely did not see B cells in our final product.

DR. BOLLARD: So by flow cytometry, it is 0 percent B cells in your final product?

DR. NATARAJAN: Based on our clinical
experience, yes.

   DR. BOLLARD: So the reason I'm asking these
questions is because the CAR is 4-1BB
co-stimulatory moiety, which we know is important,
plays an important role in promoting B-cell
proliferation and survival in human B cells.

   So obviously, if this lentiviral vector is
very powerful at getting into all lymphocyte
populations, how are you controlling for that, the
prevention of the CD19 CAR T cell getting into
B-cell blasts, et cetera?

   DR. LEBWOHL: So part of what's going on, of
course, is that the blasts themselves had CD19, so
they would be eliminated as well by the CTL
integrated and T cells.

   DR. BOLLARD: So when patients relapse after
CD19-directed therapy, both in blinatumomab and
CD19 CAR T cells, there's an appreciable number of
patients who relapse with CD19-negative ALL. So
how are you looking in those patients, whether your
vector is there?

   DR. LEBWOHL: There is one example that was
reported at the RAC this year of a patient who had CD19-negative B cells with CTL019 integrated. And in that example, what was seen is that both the number of blasts went up, but also the number of CTL019-expressing cells. So it can be detected by the presence of CTL019.

DR. BOLLARD: Then my last question's about the lentiviral vector, Dr. Miskin's presentation. Am I right in assuming there is not a lentiviral producer cell line produced with your manufacturing strategy for the lentiviral vectors? And if that's the case, how are you controlling for your batch-to-batch variabilities, et cetera?

DR. LEBWOHL: Thanks. Dr. Miskin?

DR. MISKIN: James Miskin, Oxford Biomedica. Yes, you are correct. We don't use a stable producer cell line. We use a parenteral HEK293T cell.

DR. BOLLARD: So how many patients can you treat with one batch, and how do you control for batch-to-batch variability that might occur?

DR. MISKIN: Sure. So during the
manufacturing process development, we evaluated a lot of different approaches toward transient transfection of plasmid components. This is a complex process. It needs to be very carefully controlled. We believe we control this process to the extent that it can be controlled in our manufacturing process.

Simplistically, through the extensive manufacturing that we've conducted specifically for this product, but also for other products and also other platform technologies, we obtain very consistent upstream yields from our transient transfection process.

DR. ROTH: Dr. Cripe?

DR. CRIPE: Tim Cripe, a follow-up question on the plasmids. What are the different promoters on each plasmid and are they different from each other? And also, the promoter driving the transgene in the final vector product, what is it? How leaky is it? Have you looked at its vial distribution of expression?

DR. MISKIN: So I'll tackle the question on
the plasmid promoters. These use a CNV promoter in
the plasmid. All of them do. I'll defer to the
Novartis team to talk about the vector promoter.

DR. LEBWOHL: I'll ask Dr. Brogdon to talk
about the vector promoter, please.

DR. BROGDON: Yes. Jennifer Brogdon,
Novartis pre-clinical research. So the promoter
for the transgene plasmid is the EF-1 alpha
promoter. This was based on early pre-clinical
work to understand what promoter would work
consistently at high levels of expression in
T cells without any silencing. And this was the
promoter chosen based on those studies.

DR. CRIPE: If all the plasmids contained
the same V promoter, doesn't that give you a
significant amount of homology between the
promoters, where you're sort of led to believe
homology was minimal and a chance of homologous
recombination quite small?

DR. LEBWOHL: Dr. Miskin, please address.

DR. MISKIN: James Miskin, Oxford Biomedica.
So you're right that the promoters are shared
through the plasmids. All the data to date that's been evaluated in different retroviral vector systems has demonstrated that where recombination has occurred, it's been at the RNA level, not at the DNA level. So we don't believe that there is a risk of recombination, and we also don't see recombination in any of our materials.

DR. CRIPE: One more question, another follow-up to the purification of the product, do you look at CD34 or other measures of stem cell in that product? Because that's where the biggest risk would be for integration that would be concerning.

DR. LEBWOHL: I'll ask Dr. Natarajan to address that.

DR. NATARAJAN: We did not test for stem cells, CD34s.

DR. ROTH: Dr. Rini?

DR. RINI: Thank you. Dr. Lebwohl mentioned that there's no plans for RCL or RCR testing, and I guess my question is, why not? I understand the rationale, but what's the downside of doing it? Is
it operational cost? Is it that you wouldn't know what to do with the result per se?

DR. LEBWOHL: The most important reason not to do the RCL testing is what Dr. Miskin explained. And let me just show you what is happening in our trials just to start.

So we do have a long-term safety study. This is planned now for 15 years per the FDA guidance. And this is an interventional trial, where the patients are actively enrolled. Of course, they give consent to joining this trial. And these are patients all who have been in our clinical trials.

As mentioned, we do plan. Not only do we have hundreds of patients right now, but we will have hundreds of patients coming in the future who will be joining this long-term study. What we do in the long-term studies is to study adverse events, efficacy, immunogenicity, persistence by the CAR transgene, VS-g, as we've heard about, as well as secondary malignancies.

What we propose in the commercial setting is
that we will have a registry. So we do want to follow all patients. This will be managed as bone marrow transplant registries are. And because this is a pediatric population, we do expect to have a very high level of voluntary participation in this. As you see, we do not plan to do the VS-g as we've mentioned. The biggest reason is that, what Dr. Miskin explained, there's a very low risk of possibility of seeing RCL in these trials. In addition, the ability to collect samples, blood samples, over a long period of time of patients who are coming for a one-time treatment, we think is also not very feasible; and more to the point, we don't think it will be very helpful.

We can address -- if we do see an event, an unexpected event that may be related to RCL, we can do studies at the time that it's detected.

DR. ROTH: Dr. Smith?

DR. SMITH: Yes. You showed data for the relationship between potency and CR rate. Do you have similar data for the relationship between potency and duration of response, for example EFS
at 6 months, or 9 months, or 12 months?

DR. LEBWOHL: Yes. Dr. Hamilton will address that question.

DR. HAMILTON: Jason Hamilton, cell and gene technical development and manufacturing, Novartis. We have looked at this. We essentially do not see any relationship between the potency readout and duration of response.

DR. ROTH: Roth, St. Louis. Maybe I could just ask one more question. I heard some allusion to possibly a relationship between the number of infused cells and safety. So the product that comes out, does the same total product go into a 3-year-old and a 25-year-old?

DR. LEBWOHL: So the dosing is based on weight; if you could pull up a dosing slide. And I should mention, the patients who are less than 50 kilograms get dosed by weight. Patients above 50 kilograms get a fixed dose.

Of course, this is a living drug, as we've described it, so the dose in the person and the effective dose obviously changes a great deal once
it's infused into the patient. And just to show you the doses for patients who are greater than 50 kilograms, the median dose is $1.85 \times 10^8$ cells. In the less than 50 kilograms, it was $3 \times 10^3$ to the 6 per kilogram.

DR. ROTH: Thank you. Go ahead, Dr. Kwak.

DR. KWAK: I apologize if I missed this, but what cells do you use to measure the viral titer? Is it primary T cells or some other cell line?

DR. LEBWOHL: I'll ask Dr. Miskin to address that, please.

DR. MISKIN: James Miskin from Oxford Biomedica. So as part of the panel of release tests that we at Oxford Biomedica perform, we use a human HEK293 cell to evaluate titer. In our experience, we find that that's very representative of measuring the functional activity of that vector.

DR. KWAK: Sorry. Have you compared this against primary T cells?

DR. MISKIN: Yes. As part of the work that Novartis does, they also do work in primary T cells
as well, as part of their MOI assay. And that's performed as well, but it's performed by Novartis rather than Oxford.

DR. KWAK: Thank you.

DR. ROTH: Roth, St Louis. Just one quick question in terms of the duration, you were talking about the following of people, possibly looking for cases of insertional mutagenesis, or RCL, or whatever.

Do you have a prospective timeline? Not that I do, but I was wondering what you thought about this as someone who gets lung cancer 25 years later and has 75 pack-years or whatever, it's not necessarily something that you'd want to delve into. So I didn't know what your horizon was for following that.

DR. LEBWOHL: The registry itself doesn't have a fixed time on it yet so far. Of course, the 15 years certainly is a starting point related to the long-term follow-up and our initial thought. But we're going to learn a lot in the next 15 years, and I think we'll consider it based on that.
But the registry is not time defined.

DR. ROTH: Any other clarifying questions?

Go ahead, Dr. Cripe.

DR. CRIPE: Do patients develop anti-idiotypic antibodies against the T-cell receptor? Have you looked at that?

DR. LEBWOHL: I'll ask Dr. Thudium to address the immunogenicity of CTL019.

DR. THUDIUM: Karen Thudium, Novartis clinical pharmacology. So we do see immunogenicity present in patients at baseline coming into the trial, but I think it's more important and more relevant to look at the treatment-induced immunogenicity that we see. And we've assessed and determined that the presence of immunogenicity does not have an impact on the expansion, persistence, nor the safety or duration of remission.

DR. ROTH: Go ahead.

DR. CRIPE: Tim Cripe again. The T cells not only have the TCR that you express in the transgene, but also in native T-cell receptors. So is there a polyclonal expansion, or does one
predominate following engagement of the antigen?

Is there any concern about expansion of an autoimmune T-cell, for example?

DR. LEBWOHL: I'll ask Dr. Brogdon to address that, please.

DR. BROGDON: Thank you. Dr. Brogdon.

Sorry, Jennifer Brogdon, Novartis pre-clinical research. So we're continuing to explore in the space of expansion of T cells post-infusion. These are exploratory measures to understand whether it's clonality or heterogeneous.

The studies we've looked at to date are largely quite heterogeneous in nature. You can see expansions, of course, at the CARs. You can't look at cells that are untransduced and measure any level of expansion of those cells, but with isolated exceptions, we've seen very heterogeneous expansion of these populations of CAR-positive cells.

DR. ROTH: Dr. Nowakowski?

DR. NOWAKOWSKI: Greg Nowakowski. As with any new therapy, promising therapy, there is
sometimes demand, which can outpace manufacturing capacity. Have you experienced it in the 2202 study? In other words, was there a wait list of patients who were trying to enter the trial, but couldn't enter because of limited manufacturing capacity? And if so, have you been able to meet the demand by the end of the trial?

DR. LEBWOHL: Yes. So there was limitation in the clinical trial setting. There were waits for some patients. I'll ask Dr. Natarajan to address the commercial setting.

DR. NATARAJAN: Arvind Natarajan from Novartis. In the commercial setting, we expected to have adequate capacity to be able to meet the expected commercial demand. The facility that we have at Morris Plains is designed as a modular facility, and we use only a small fraction of the facility over the course of manufacturing for the clinical trials. And we are expanding the use of the facility to support the expected commercial demand. So we expect to have adequate supply to meet the demand.
DR. NOWAKOWSKI: Going back to your trial experience, have you been able to meet the demand by the end of the trial, or was there still some wait list by the --

DR. LEBWOHL: By the end of the trial, there was no wait for the patients as the capacity was growing.

DR. NOWAKOWSKI: The number of patients in the trials is really small, but is there any evidence of different clinical activity or any other difference in the product itself with this expansion of the capacity, production capacity, for the duration of the trial?

DR. LEBWOHL: I'll ask Dr. Natarajan to address that.

DR. NATARAJAN: Arvind Natarajan from Novartis again. We maintained control over the manufacturing for each patient on an individualized basis. So we had dedicated operators who perform the manufacturing unit operations for each patient and are dedicated for the duration of that unit operation. So we're able to scale this out as we
manufacture multiple patients, so we did not see any differences.

DR. ROTH: Thank you. Any other -- Dr. Cripe? I didn't know you had another question.

DR. CRIPE: Sorry. Jim Cripe. So you're proposing certain release criteria, but you have some patients that, if I understand correctly, those products were used in the trial that fell below those release criteria, 3 or 4 on each of these graphs.

So one, is that correct? And if so, did those patients have benefit so that there's even a reason to have these lower-limit release criteria? Because this is going to be their one shot at this treatment. Right? You get to collect it, and that's it.

DR. LEBWOHL: I'd say there are two types of specifications. One, I should mention because that was clinical. You see in the FDA slides a certain dose range. During the trial, we actually expanded from the initial target dose range to go to a lower dose range because we saw in the trial from
Dr. Grupp at CHOP that he was seeing responses at 
this lower range.

So we did expand. We asked the FDA 
specifically for permission to give those lower- 
range number of cells to patients, and we found in 
fact that there was success with a lower number of 
cells. And I'll ask Dr. Natarajan to address other 
types of that specification.

DR. NATARAJAN: So over the course of the 
clinical trials, the specifications that have been 
set have been based on our range of experience. So 
they accommodate the expected variability of the 
patient material in a commercial setting.

DR. CRIPE: I guess I don't feel like I've 
gotten an answer to my question. So the question 
is, if you make a product on a patient, and it 
doesn't pass your criteria, and then they don't get 
that product, are there any instances where they 
wouldn't have passed that criteria but they had 
benefit because your assays in the lab maybe don't 
correlate with the clinical living drug concept?

DR. NATARAJAN: Sure. So the specifications
that have been set for the commercial product are based on the totality of the clinical experience, so this includes the patients that Dr. Lebwohl talked about, where we worked with the FDA to be able to provide those products to the patients. 

So the commercial specifications that we have proposed in the BLA reflect that experience, so those patients will be able to get that product. Does that answer your question?

DR. CRIPE: Not really.

(Laughter.)

DR. NATARAJAN: Sorry.

DR. CRIPE: I'm worried about someone not -- being excluded from getting potential benefit because you have a lab assay that doesn't correlate with clinical benefit. In other words, I'm just trying to justify these lower-limit exclusions since this is their one shot at it.

DR. NATARAJAN: Sure.

DR. LEBWOHL: I would say we don't have any example of a patient, for example, potency who was given cells below the limited potency that had a
response. No.

DR. CRIPE: I got my answer.

DR. LEBWOHL: Dr. Grupp?

DR. GRUPP: Steve Grupp, clinical advisor.

With the discussions about timing to receiving a product, I just want to sort of break down what we see from a clinical standpoint that may help the committee understand the processes as they've evolved over time in a clinical trial setting.

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

Our goal at the single-institution trial and then across the multicenter trials was to preserve this option for as many patients as possible. So
that is quite fungible and is probably not the length of time that actually mattered to the patients in terms of this really key issue of losing eligibility because the patient's disease progressed, or they got infected, or had organ issues.

I think what we really saw over time was the compression of the time to get a slot for manufacturing. That in my opinion is the most important criterion and the thing that really affected our ability to treat patients, and that got better over time.

So you can decrease the manufacturing time from 29 to 22 days. That's a great benefit, but it's a relatively modest benefit. That week is not going to really make or break any patient. But waiting a couple months for a manufacturing slot, that did make a difference for a patient or two that I can personally remember. So getting rid of that time frame I think is really important.

DR. ROTH: Dr. Bollard, and then Dr. Smith?

DR. BOLLARD: Sorry. Just back to the
vector question, so I'm interested in the B2202 study. How many batches of vector were required to treat the 88 patients on that study? I guess that's my first question.

DR. LEBWOHL: Dr. Natarajan will address that, please.

DR. NATARAJAN: Arvind Natarajan from Novartis. We used three different vector batches over the course of patients enrolled in B2202.

DR. BOLLARD: And did you look at whether there was any effect on outcome based on the vector batch?

DR. NATARAJAN: So we looked at the performance of the manufacturing product attributes across the three vector batches, and we did not see any differences across them.

DR. ROTH: Dr. Smith?

DR. SMITH: I wanted to follow up on Dr. Grupp's comments. The briefing documents state that the time from most recent relapse to infusion was 4.1 months mean and 3.4 months median. So I'm trying to understand how that relates to if that's
going to improve over time and how that relates to Dr. Grupp's comments about when the cells were harvested.

DR. LEBWOHL: I think that number is not so useful for you to understand about the timing of patients being treated. But let me show you the manufacturing time in terms of the various pieces.

So a patient, obviously, if they are in relapse, they have to approach their physician, be evaluated for the trial. And then the moment of enrollment occurs when the apheresis is received and accepted.

So you see here the timing both in the U.S. and ex-U.S. where things did take a little bit longer to travel from apheresis receipt to the manufacturing start. This is a factor that is affected by capacity most of all, and this is a factor that will come down to one day in the commercial setting. And then the time for manufacturing start to release, as we've said, will be based on improvements in the process. It will be 22 days. And then the last part of it has
always been very quick. The release to sending out
to the site will be one day as well.

DR. ROTH: Any other clarifying questions?

(No response.)

DR. ROTH: Let's take a break now before the
open public hearing. Let's resume at 10:20.

(Whereupon, at 10:00 a.m., a recess was
taken.)

Open Public Hearing

DR. ROTH: Thank you. We'll proceed with
the open public hearing. Both the Food and Drug
Administration and the public believe in a
transparent process for information-gathering and
decision-making. To ensure the transparency at the
open public hearing session of the advisory
committee meeting, FDA believes it is important to
understand the context of an individual's
presentation.

For this reason, FDA encourages you, the
open public hearing speaker, at the beginning of
your written or oral statement, to advise the
committee of any financial relationship that you
may have with any industry group, its products, and if known, its direct competitors. For example, this financial information may include industry's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated
with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

Will speaker number 1 step up to the podium and introduce yourself? Please state your name and any organization you are representing for the record.

MS. KAPPEN: Thank you. Hello. My name is Amy Kappen. I have no financial relationship whatsoever. I am here today to represent our family, who had first-hand experience with CAR T-cell therapy. I'm not a medical expert, although I received an unconventional medical education starting in April 2016 when my 5-year-old daughter, Sophia, was diagnosed with pre-B cell ALL.

We were told Sophia was considered a standard risk. Her remission rates were greater than 85 percent. All we had to do was get her through the 3-year treatment protocol. It sounded so straightforward, simple compared to the initial shock of the diagnosis.

Sophia achieved remission after her
induction period. However, a month later, Sophia had a seizure as a result of side effects from the current standard chemotherapy protocol. We then realized that, while overall cure rates were very high for kids with ALL, the toxic side effects of conventional treatment had not advanced much at all.

In July of 2016, we believed Sophia was experiencing yet another toxic side effect of the chemotherapy with severe leg pain. In reality, she had relapsed faster than any of her doctors had ever seen. Sophia's cancer returned within 3 months of achieving remission. As I'm sure most of you are aware of the standard protocol for a relapsed cancer patient, the next step was to go after Sophia's cancer with more aggressive chemo treatments, hoping to obtain remission again, and move directly to bone marrow transplant. That never happened.

Thankfully, Sophia's primary oncologist at Cincinnati Children's was aware of the CAR T-cell clinical trials at the Children's Hospital of
Philadelphia. We harvested Sophia's T cells on August 1, 2016 with the hope of never needing them, much like an emergency fund. Once we quickly realized Sophia's cancer had become resistant to chemo, we knew time was working against us.

As the CAR T-cell therapy was still in trial, things do not always move with ease or expedition. Sophia's cancer was extremely challenging to keep at bay while we waited for her T-cell date. During that waiting period, Sophia became unable to walk or ambulate to use the bathroom. This resulted in Sophia wearing diapers, which infuriated her. She was not speaking or interacting with anyone, and she could barely move.

Sophia was miserable. She looked pitiful. She was on a continuous narcotic pain infusion. Our previously vibrant, spunky, inquisitive 5-year-old, now almost 6, had transformed into a withdrawn and frustrated little girl overwhelmed with pain. She was losing her zest for life. We could not bear to watch our daughter suffer like this.

By October, her body began to swell. We
assumed it was yet another side effect from some of the medications. When we arrived in Philadelphia, we learned Sophia's leukemia was not only in her blood, but had mutated into lumpy solid tumors scattered throughout her body. We were blindsided and had no idea leukemia could do this. Our already large list of concerns grew significantly more at this point.

After Sophia received her manufactured T cells in November, she endured a severe storm, her cytokine-release syndrome, as anticipated based on her high level of disease. In all honesty, after what we had already been through, the storm hardly scared us, likely because we knew it was our only hope to save our daughter. During the storm, Sophia turned 6.

After the storm, we witnessed something we never expected, a miraculous change. Sophia's swelling began to decrease. She was more alert and engaged. She was coming back to us. Her spunk resurfaced, her smiles returned. Sophia's fight was back. Sophia's bone marrow went from greater
than 90 percent disease burden to 1 percent at
28 days post-infusion. Her tumors shrunk
significantly, although not completely.

Sophia was on her way to try to walk again.
She was determined. The transformation from
October to December 2016 was unbelievable. The
sparkle in her eyes returned. Sophia never looked
more beautiful.

We were given 3 and a half months with our
spirited and strong daughter. We made every minute
count. The trial and the doctors at Children's
Hospital Philadelphia gave us the most incredible
gift and level of hope we had ever experienced.
The CAR T-cell therapy did what it was intended to
do for her marrow. Unfortunately, the mutation of
her disease was too much. We could not stop her
cancer.

In those few months, Sophia taught us more
about life than most of us will learn in a
lifetime. Sophia passed away in April of this
year, exactly one year to the date she was
diagnosed with her standard-risk leukemia.
Sophia was so close. Although we never lost hope and Sophia never gave up, we did not receive the same outcome as some of these other families. Our hope is to see this incredible treatment option available to children sooner. It is a remarkable therapy that spares children the toxic side effects of conventional chemotherapy.

Close is not good enough. We know there's no point to imagine what CAR T-cell therapy could have done for Sophia if it had been further along in the approval process. Instead, our family wants to express its support for approving this incredible breakthrough in pediatric cancer treatments with hope that more families have a longer time with their children fighting this evil disease. Our children deserve this chance.

Thank you for allowing me to share Sophia's journey.

**Clarifying Questions (continued)**

DR. ROTH: Thank you for sharing.

The open public hearing portion of this meeting is now concluded, and we'll no longer take
comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

Before we get to the discussion questions, we just want to mop up one thing, and Novartis would like to make a couple comments in response to Dr. Cripe's final questions about release points; and maybe if you want to rephrase your question for the transcribers.

DR. CRIPE: Yes. It was based on the concept that we are unsure what's going to happen in vivo after the product is infused and do those release criteria really measure that. And if we go to the trouble of making a product, did they have any experience where any of the release criteria that they're proposing were not met but they used it anyway, and did they then get any effects from that.

DR. LEBWOHL: Thank you, Dr. Cripe. I just want to repeat that we did have experience with giving cells out of spec during the trial when we
gave the lower cells, and that was successful.

In the commercial setting, we would give cells only if they were within spec on a routine basis. However, this same question will come up in the commercial setting. There will be some patients where they're slightly different from the specifications.

We think that the cells will be both safe and possibly effective. And our idea is that we would talk to the FDA as well in the commercial setting and talk to them about the possibility of the patients receiving those cells.

DR. CRIPE: Would that require a single patient IND or that sort of thing, do you think?

DR. LEBWOHL: We would have to talk to the FDA about the mechanism for that.

DR. ROTH: Did that answer sufficiently?

DR. CRIPE: Yes. Thank you.

Questions to the Committee and Discussion

DR. ROTH: We will now proceed with the questions to the committee and panel discussions. I would like to remind public observers that while
this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. We can proceed to the first question, please.

During tisagenlecleucel development, the applicant established product quality specifications to assess CAR expression and T-cell activity, including transduction efficiency by flow cytometry, vector copy number per cell, and interferon gamma production following stimulation by CD19-positive cells.

Please discuss the following aspects of the control of product quality of tisagenlecleucel with respect to identity, safety, purity, and potency; first the design of the CAR construct and viral vector, secondly the assessment of CAR expression and T-cell activity through, number one, the number of transduced T cells; number two, the number of vector copies per cell; number three, antigen-specific T-cell functions such as interferon gamma production and cytotoxicity upon stimulation; and finally any other measurements such as T-cell
subpopulations, cell surface marker characterization that could provide greater assurance of product quality.

So again, if you want to make comments, just let Jen know. We'll go in order. And again, please identify yourself before commenting. First, Dr. Gulley.

DR. GULLEY: Thank you. James Gulley. I think there are several things to consider here. First, the patient-specific products face unique challenges in the manufacturing process, and we were asked to comment on identity, safety, purity, and potency.

Based on what was provided to us in the briefing documents, in terms of the identity, there is really a nice set-up for tracking and segregation with proper chain of identity using the FACT-accredited institutions that incorporate the ISBT-128 labeling standards. So from that standpoint, I thought this is well-designed with respect to the identity.

Now, with respect to the safety, purity, and
potency, I have several questions and things that perhaps we could talk about.

    First of all, for the purity, the number of T cells in the product is greater than 80 percent, is what they say, and virtually all of the cells in the product look to be, based on what was clinically done, T cells with exception of maybe a few NK cells. The product parameters also include greater than 10 percent CAR T cells.

    So I think that from a purity standpoint, I think we have a product here that is virtually all T cells with a high proportion of the CAR T cells. So that appears to be also well thought through here.

    I think the main thing, though, is the potency, and that is demonstrated in the clinical activities seen with this product. So from my standpoint, this is a product that has shown patient benefit, and I think our goal here is really to try and find ways that we can make sure we have optimal safety of the product and optimal potency of the product.
DR. ROTH: Dr. Kwak?

DR. KWAK: So I would highlight a few points that Dr. Gulley didn't mention. So first, as a general statement, the challenge with this therapy is that the technology is rapidly changing, and secondly, that there are multiple steps. It's a very complex manufacturing process, as outlined both by the sponsor and the FDA, which makes it inherently a high potential risk for manufacturing failure.

Then you add to that the aspect of the autologous nature, in other words the need to manufacture the product on a patient-specific basis, leading to potential batch-to-batch variability. But having said all that, the sponsor should be congratulated for, in most of the cases, manufacturing and releasing product for the clinical trials.

Let me give you a few examples to underline these two issues. The first is that the construct used for the CAR is a murine antibody as I understand it. And the sponsor did acknowledge
immunogenicity observed in patients.

Many affected firms and academic groups now are using humanized antibody constructs where this is not a concern. And this is an example of something that's changing that could well become, if you will, standard of care for vector construction in the future. The implication is that this could affect persistence, for example, and therefore efficacy, as well as safety, of the resulting CAR T cells.

A second consideration is a very serious side effect, which we may hear more about in the afternoon session, but of an on-target/off-tumor effect on normal B cells, causing prolonged B-cell aplasia. And again, here a number of affected firms and academic groups are addressing this by introducing suicide gene strategies and other strategies to exert greater control over the infused T cells.

With respect to potential batch-to-batch variability, purity, and quality, I think one should highlight the fact that, generally, only
30 percent of the T cells infused actually did bear the chimeric antigen receptors. This means that up to two-thirds of the cells actually were not the T cells that are specific for CD19.

As a clinician, I'm very much encouraged that that apparently did not affect efficacy when looked at in the sample size that was available to the sponsor, but I think a greater concern is the safety considerations introduced by that heterogeneity and the presence of non-CAR T cells, which may also be activated by cytokines during the expansion phase, for example the IL-2, and contribute to toxicities such as the cytokine-release syndrome.

I think the final consideration that I'd comment on that really hasn't been addressed by the sponsor this morning is the T-cell subpopulations and the heterogeneity of T cells in the final product. This is one area that really could affect the future development of this therapy.

There's emerging evidence that specific T-cell populations are somewhat better than others
in terms of efficacy as well as safety with regard
to not just central memory or effector memory
phenotype, but also the optimal proportions of CD4-
versus CD8-positive T cells.

So a better characterization of the products
that were infused I think would be informative to
the agency, both for the purposes of greater
quality assurance, and secondly to help guide
prospective testing of this question of different
subpopulations of T cells and how to optimize
those.

The final issue that is a minor technical
one to highlight is that in our experience in terms
of vector production for various clients at our
institution, City of Hope, we found that primary
T cells are the most accurate in terms of
determining viral titer.

So if the sponsor has done comparisons
between AGK cells and primary T cells, this is some
data perhaps the agency would want to request and
examine. Thank you.

DR. ROTH: Thank you. Maybe for the two of
you, Dr. Kwak and Dr. Gulley, it seems like we're still on square one in terms of predictive factors here and we're kind of swimming in the dark.

So I don't know if you had some sense of if you were lead scientist who developed an additional or hypothesis-generating panel of things to look at, are there other things that you would suggest, because now there's a real disconnect I think between the factors that have been looked at and ultimate outcome clinically.

DR. GULLEY: I think that you're absolutely right. There is a disconnect between what assays have been done and what the outcomes are, both in terms of side effects as well as in terms of activity. The good news is that the majority of patients do have evidence of benefit with this.

I think that as we get more data, I think it would be nice to look at the different T-cell types that are in here as well as the different functionality of those T cells with different intracellular cytokines, for instance, and their lytic potential; so some more functional analysis
and see if there are markers that correlate with functional analysis because functional analysis may be difficult to do for lot-release criteria. But I think that would be helpful to understand this product better.

DR. KWAK: So my comments were meant as guidance for things to pay attention to as in the commercialization phase and as CAR T cells are being developed by other affected firms.

But just to put it in context -- so those are things that I would like as a scientist. But as a clinician who still sees patients, I think we'll hear about the clinical results. And I don't think any of these considerations that either of us have raised would be showstoppers for the outstanding clinical results that have been obtained to date.

DR. GULLEY: I would just like to add to what Dr. Kwak said, which I completely agree with. I think that there are many agents that we don't have good assays for predicting clinical outcomes necessarily. I think that these are great things
to look at from a scientific standpoint to help move the field forward.

DR. ROTH: Dr. Bollard?

DR. BOLLARD: I guess I would just like to go back to the purity issue just for the record because the answers that were provided I guess I still have concerns with, given that we're seeing in the slide CM-11 that you're not getting necessarily 100 percent CD3 T cells in your final product. And while there are clearly some NK cells, which I have less worries about, what are the other cells remaining since you acknowledge that what you're starting with is very heterogeneous leukapheresis material.

So I guess my comment is related to how can we increase that purity in terms of absolute T-cell numbers to really 100 percent if possible. And I'm further unclear because we were told there was a positive selection happening, but on questioning, it was just CD3-28 beads, which I don't sort of equate to a positive selection.

So I guess I am not seeing that a product
that's greater than 80 percent or 80 percent pure
is a highly pure T-cell product. And there is
that, while rare, known risk of possibly
transducing a B-cell population that could have a
survival advantage in vivo.

    DR. ROTH: Dr. Rein?

    DR. REIN: I guess I have a comment about a
safety question. The early experience with the
gamma retroviral vectors included insertional
mutagenesis leading to leukemia by the vector
itself, not by an RCR.

    I think that reflects the enormous
multiplicity of infection that was used in those
early trials in which so many viruses were used and
so many integration sites were hit, that some
damaging integration sites were obtained.

    So I think this tells us that more is not
necessarily better in terms of multiplicity of
infection, number of initial infection events. So
I just think this hasn't been mentioned in the
discussions by Novartis, what sort of target they
have for how many cells get infected in the initial
infection, which means how many integration sites will be hit.

DR. ROTH: Thank you. Dr. Cripe?

DR. CRIPE: My comments were a bit of a follow-up to that. I had wanted to recognize the fact that we've come a long way from those days of when we didn't know. And I'm encouraged by all the advances that have been made and would like to commend the CHOP and Penn teams and Novartis because what we've seen today is a lot of safety things that have been built that are far different from those days with this kind of trial; integration site numbers, which they showed us, which were on average 1 or less, and in those trials there were many; the separation of the plasmids and the efforts to reduce recombinations amongst those plasmids; the fact that we're transducing non-stem cells, although a bit concerning they don't measure that or look for stem cells.

These are peripherally apheresis products, but they could still contain circulating stem
cells, particularly after chemotherapy, albeit that's unlikely in someone with frequent relapse who probably doesn't have many stem cells around.

So I'm impressed by the advancements we've made over the last 10 to 15 years in this field that we've been able to get to this point. And ultimately, the proof is in the pudding and haven't been able to measure RCR, et cetera. So I think that's very encouraging, and I want to recognize the fact that we've come a long way in this field.

I think the concern for me is what happens after the infusion. So we don't know. This is an unknown, and perhaps more understanding of that would benefit us in the future. So continuing to monitor patients and clonality, et cetera, may be important as we move this field forward.

DR. REIN: We were shown integration sites per cell. We were not shown total integration sites. That's what I'm talking about.

DR. ROTH: Other comments? Go ahead.

DR. CRIPE: Is it an integration site per cell that counts? Because it's --
DR. REIN: If you do enough infections of enough cells with enough viruses, you are likely to hit a bad site. If you only infect a few cells, you will only hit a few integration sites.

DR. CRIPE: Sure. It's all probabilistic.

DR. ROTH: Other comments? Sorry.

DR. CRIPE: Another issue. So we didn't really talk about the design or the production of the vector itself, so we didn't ask any questions about the -- we only asked questions about the product, the transduced product. What about the GMP production of the virus?

So we're assuming that -- is the FDA looking at that, do they have any concerns about that, which would be the main discussion topic in just a straightforward gene therapy trial, where the vector is pretty important in terms of its production, its potency, its purity, its identity. So there was no data given about that. Is that even manufactured at the same site? Where does that come from?

DR. ROTH: Anybody from the agency want to
respond to that?

    DR. GAVIN:  Novartis talked extensively
about where the vector was manufactured and the
 testing that was done on the vector.  I think that
 was covered in the discussion earlier.

    DR. CRIPE:  The vector's made at the same
 site that the transduction and the cells are
 produced.

    DR. GAVIN:  No.  The Oxford Biomedica
 representative was here and talked about the vector
 production.

    DR. ROTH:  Any other comments?
      (No response.)

    DR. ROTH:  Just to summarize, in terms of
 the question 1 discussion, we discussed about the
 disconnect between current proposed predictive
 factors and the ultimate response, and possibly the
 chance of looking at more specific T-cell
 subpopulations might be a benefit in this
 situation.

    It was raised, the purity issue, both
 positive and negative selection possibly how to do
additional selection factors to increase T-cell numbers and possibly decrease stem cell numbers if they are in significant numbers.

Then from a safety issue, how many cells get infected as that pertains to potentially a safety issue down the road and possibly long-term problems with insertional mutagenesis or RCL. And I think maybe, most importantly, further information on what happens post-infusion, since it appears to be somewhat of a black box currently and has significant implications both for long-term safety and for acute response.

So if that does not summarize, are there any other comments? Go ahead, Dr. Bollard.

DR. BOLLARD: Just to clarify about the purity, it's not just the stem cells getting transduced. It's the B cells, the CD19-negative B cells, as well as actually also potentially leukemia stem cells, given these are patients with high disease burden at the time of leukapheresis.

DR. ROTH: Good point. Anything else? Dr. Kwak?
DR. KWAK: And the heterogeneity of the T cells in the final product, so those transduced versus non-transduced.

DR. ROTH: Thank you.

We'll go to the second question, more safety issues. Potential safety concerns with tisagenlecleucel and other retrovirus-based gene therapy products include generation of RCR/RCL and insertional mutagenesis. Can you address the strategies to address those concerns, including vector design and product testing?

Part 2, please discuss how vector design impacts the risk of RCR. Please discuss how vector design impacts the risk that insertional mutagenesis might cause secondary malignancies. And then finally, please discuss the extent to which product testing can mitigate the risk of RCR and insertional mutagenesis.

Dr. Rein?

DR. REIN: I probably said what I wanted to say under question 1. I guess I feel that RCR is no longer a serious safety risk. Insertional
mutagenesis still needs attention, the extent to which product testing can mitigate the risk of insertional mutagenesis. So I was wondering about is there a target for how many infections are intended in the initial infection event.

DR. LEBWOHL: Maybe we can come back to the slide from the core on the ratio on integrated viruses. This shows what was shown in the presentation, and what you can see, particularly towards the end as was expressed, the ratio is 1.3 copies per transduced cell and with a fairly small range. And I'll ask Dr. Natarajan to add.

DR. NATARAJAN: Good morning. Arvind Natarajan from Novartis again. We do target a specific percent transduction when we add the vector for each patient batch. And the amount of vector that's added is calibrated for each vector batch that's produced.

DR. REIN: So how many cells -- not percent, number. How many cells get infected? In other words, how many integration sites are you hitting?

DR. NATARAJAN: In terms of the actual
numbers, it depends on the culture itself because we have patients coming in with different weight ranges. So the absolute number of cells varies by patient.

So we normalize our reporting on a percent transduction. The dose itself is formulated based on an absolute number of cells. So the dose range or the dose that's provided to patients measures the number of viable transduced cells that's provided back to the patient.

DR. REIN: So would you care to state a number, for example?

DR. NATARAJAN: Due to the confidential nature of that information, I'm not able to share the exact number in this setting.

DR. ROTH: Dr. Bollard

DR. BOLLARD: Can you bring back up the questions again? Sorry. So firstly, I think I just want to reiterate for the record that there's no stable producer cell line used for this vector manufacturing. We're told that probably only one batch of vector only treats about 30 patients.
So I think we need to understand that there's always going to be multiple, multiple batches as we move forward, and there is obviously that potential for batch-to-batch variability in terms of how that vector performs functionally. So if we're happy with the rigor of vector release, then I think we just need to acknowledge that.

I do agree with Dr. Rein's assessment about the risk of RCR if your vector is RCR negative or RCL negative. And given the huge wealth of data now in the retroviral transduced and lentiviral transduced T-cell field, I think not performing RCL on the prospective patients is probably okay.

I think, as far as insertional mutagenesis, I agree there's a wealth of data with mature T cells in the safety profile of mature T-cell transduced cells in vivo, but I go back to why I think product purity is so important, because we can't guarantee that we're just transducing mature T cells. So I think that's something to consider.

While I do acknowledge, though, that it is laudable that Novartis will look for vector in the
development of any individuals with secondary malignancies, I would also say that we should extend that to patients who are relapsing with their leukemia with a different immunophenotype or genotype.

So I think I've hopefully addressed all those questions.

DR. ROTH: Thank you. Other comments? Go ahead, Dr. Cripe.

DR. CRIPE: I'm encouraged by the use of self-inactivating vector, which obviously is going to reduce the risk of insertional mutagenesis even if it integrates near an ELMO 2 gene or some other scary gene, and the use of a tissue-specific promoter in driving that transgene. I think both of those are mitigating factors for insertional mutagenesis.

One question that's just arisen in my mind is what's the risk of contaminating virus in the final product. I might have missed it, but I don't recall them measuring that. So is there a possibility of any virus that's not transduced into
cells yet, but tagging along with the product and then in the body infecting other cells? Is there a measure of that in their release criteria?

DR. ROTH: Any other comments?

DR. LEBWOHL: Dr. Hamilton will address the question on virus.

DR. HAMILTON: Hi. Jason Hamilton, cell and gene technical development and manufacturing, Novartis. You're correct. We don't perform testing for remaining vector or virus that could be present in the final product. However, calculations of the dilution factors that occur during the entire length of the manufacturing process make it essentially impossible for vector to be remaining at the end of culture.

DR. CRIPÉ: So it's homeopathic.

DR. ROTH: Any other comments?

(No response.)

DR. ROTH: So just to summarize here, there's some concern about batch variability in terms of vector batches being reproducible, some concerns in terms of RCR and I assume insertional
mutagenesis based on information about the number of cells infected and the number of infections per cell. And certainly, that's abrogated a little bit by the self-inactivating component.

So that's my summary. Any other questions, or did I misstate anyone's discussion?

(No response.)

Adjournment

DR. ROTH: So we'll go ahead and break for lunch. I would remind the panel members not to discuss the topic during the lunch and break. And we will resume at 12:30.

(Whereupon, at 11:00 a.m., the morning session was concluded.)