FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Afternoon Session

Wednesday, May 24, 2017

1:00 p.m. to 4:19 p.m.

FDA White Oak Campus

10903 New Hampshire Avenue

Building 31, The Great Room

Silver Spring, MD

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(1:00 p.m.)

Call to Order

Introduction of Committee

DR. RINI: All right. Good afternoon, everybody. We're going to go ahead and get started. I'd first like to remind everyone to silence their cell phones and other devices if you haven't already done so. I'd also like to identify the FDA press contact, Angela Stark. Angela, if you're here -- in the back of the room waving, thank you.

We're going to start with introductions of the panel. Ask each member to go around and give us your name and your role on the panel and where you're from. We'll start with Dr. Morrow.

DR. MORROW: P.K. Morrow, I'm a medical oncologist. I'm with Amgen and I serve as the industry representative.

DR. MENEFEE: Michael Menefee, medical oncologist, Mayo Clinic, Florida.

DR. FITZHUGH: I'm Courtney Fitzhugh with the Sickle Cell Branch at NIH in Bethesda.

MS. MILLER: Shirley Miller. I'm the patient representative from Carolinas Healthcare.

MS. PREUSSE: Courtney Preusse, patient representative and Fred Hutch.

DR. ULDRICK: Thomas Uldrick, hematologist, medical oncologist, Center for Cancer Research, NCI.

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

DR. BURSTEIN: Hal Burstein, medical oncology, Dana-Farber in Boston.

DR. RINI: I'm Brian Rini. I'm a geomedical oncologist at Cleveland Clinic.

DR. TESH: Lauren Tesh, designated federal officer, ODAC.

DR. NOWAKOWSKI: Greg Nowakowski, hematologist at Mayo Clinic, Rochester.

DR. RIELEY: Greg Rieley, medical oncologist, Memorial Sloan Kettering.

DR. KLEPIN: Heidi Klepin, geriatric oncologist, Wake Forest.

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou, oncologist, MD Anderson Cancer

Center.

DR. D'AGOSTINO: Ralph D'Agostino, statistician, Boston University and the Framingham study.

DR. SMITH: Che Smith, statistical reviewer, FDA.

DR. SETSE: Rosanna Setse, clinical reviewer, FDA.

DR. ROBIE-SUH: Kathy Robie-Suh, clinical team lead, FDA.

DR. FARRELL: Ann Farrell, division director, FDA.

DR. PAZDUR: Richard Pazdur, director, OCE.

DR. RINI: For topics such as those being 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 that 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 in their conversations about the topic at hand and that they take place in the open forum of the 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 topics during any breaks. Thank you.

I'll now pass it to Dr. Lauren Tesh, who will read the conflict of interest statement.

Conflict of Interest Statement

DR. TESH: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee meeting 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 federal ethics and conflicts 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 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 involves new drug application 208587 for L-glutamine powder, oral solution submitted by Emmaus Medical Inc. The proposed indication/use for this product is for the treatment of sickle cell disease.

This is a particular matters meeting during which specific matters related to Emmaus Medical's

NDA 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. P.K. Morrow is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Morrow's role at this meeting is to represent industry in general and not any particular company. Dr. Morrow is employed by Amgen.

We would like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the

participants 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 you may have with the firm at issue. Thank you.

DR. RINI: Thank you. We'll now proceed with opening FDA remarks from Kathy Robie-Suh.

Opening Remarks - Kathy Robie-Suh

DR. ROBIE-SUH: Good afternoon and welcome, committee and guests. My name is Kathy Robie-Suh. I am a medical team leader in the Division of Hematology Products.

Sickle cell anemia affects an estimated 100,000 adults and children in the U.S., and millions more worldwide. It is one of the most common genetic disorders in the U.S., occurring in about 1 out of every 365 black or African-American births, and 1 out of every 16,300 Hispanic-American births.

The disease results in increased infant mortality, shortened life span, and severe

morbidity. Finding effective treatments for the disease has been a challenging task, and identifying therapies that provide a benefit on disease pathophysiology, clinical outcomes, and patient symptomatology has been an elusive goal.

Conducting studies in this disease is particularly difficult due to social, cultural, and practical constraints that impact study enrolment and patients continuance in the study for the duration needed to assess efficacy and safety. These factors can often result in high study withdrawal rates.

There's currently only one FDA-approved therapy to treat sickle cell disease, hydroxyurea, which was approved for use in adult patients with sickle cell disease in 1998. The need for additional therapeutic options for adult and pediatric patients with this serious and debilitating disease remains a prominent health concern for the U.S. public.

Today, we are presenting a new drug marketing application for L-glutamine, an agent

which has shown promise as a possible therapeutic option to treat patients with sickle cell disease. The applicant has conducted a phase 3 study and a smaller phase 2 study to support the application.

We applaud Emmaus Medical recognition of this as an important area of unmet medical need, and we certainly commend the company's work in designing and conducting these studies, and for bringing this application to the agency for consideration.

Again, thank you for your attendance and participation, and we look forward to your input and perspective on this application. Thank you.

DR. RINI: Thank you. Both the FDA and the public believe in making a transparent process for information gathering and decision making. To ensure such transparency at the advisory committee meeting, FDA believes that it's important to understand the context of an individual's presentation.

For this reason, FDA encourages all participants, including the sponsor's non-employee

presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria, and interests in the sponsor, including equity interests and those based on the outcomes of the meeting.

Likewise, FDA encourages you at the beginning of your presentation 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 presentation, it will not preclude you from speaking.

I now invite the applicant up to start their presentation.

Applicant Presentation - Lan Tran

MR. TRAN: Thank you, Dr. Rini, members of the advisory committee, FDA staff, and guests. Emmaus appreciates the opportunity to present L-glutamine for the treatment of sickle cell disease.

My name is Lan Tran with Emmaus. I've been working on the project for the past nine years, and

it's my pleasure to start today's sponsor presentation. First, some perspective.

The early studies on L-glutamine were conducted by Dr. Yutaka Niihara, co-founder of Emmaus under an investigator-initiated IND. Funding for some of this work was provided by the NIH, and the FDA Office of Orphan Drug Products in recognition of the needs of the sickle cell community.

Emmaus is a small company with 19 employees. We are based in California and began as a spinoff from LA BioMed, a non-profit medical research and education institute. The date on our application supports our request that oral L-glutamine be labeled for the treatment of sickle cell disease in children and adults. Our proposed dose is 0.3 grams per kilogram, given twice daily, for a maximum total daily dose of 30 grams.

Our product will be supplied in 5 gram packets in powder form. It is to be mixed with food or drink prior to administration. An investigator-initiated IND was submitted in 1997.

Since this submission, orphan and fast track designations were received.

We have been granted a series of meetings over the years to discuss the development program. From these meetings we receive guidance and agreement on the toxicology, non-clinical and clinical pharmacology aspects of this NDA, as well as key study design features and statistical analyses for the phase 3 study.

The agency's advice has been invaluable in the development and submission of the L-glutamine NDA, and we thank them for their guidance.

Following the IND, L-glutamine was studied in a series of early in vitro pharmacology studies and clinical trials. These studies informed our understanding of the mechanism of action, confirmed the target of interest, and provided evidence of clinical effects and benefits.

These observations were expanded in a phase 2 study in sickle cell patients and confirmed in a large phase 3 study leading to a new drug application submission in September 2016.

During our presentation today, we will share data supporting the positive benefit-risk profile of L-glutamine. Sickle cell disease is a rare and devastating condition. Crises cause significant morbidity and early mortality.

Data from our pivotal phase 3 study, as well as supportive data from earlier studies, clearly established efficacy. This has been demonstrated by a significant difference from placebo in the number of sickle cell crises and analyses of other clinically important endpoints in both children and adults.

These endpoints include fewer hospitalizations, fewer occurrences of acute chest syndrome, delayed time to first and second crisis, and fewer transfusions. The data established the safety of L-glutamine and the products positive benefit-risk profile in the proposed indication.

Our agenda includes presentations by Dr. Niihara and external expert clinicians, Drs. Gordeuk and Smith. In addition, these external experts are available to help answer any

questions you may have. All of our external experts are consultants to Emmaus. They have been compensated for their time in preparing for this meeting, but have no financial interests in its outcome.

I now turn the presentation to Dr. Victor Gordeuk from the University of Illinois at Chicago, College of Medicine, who will present the medical need for the reduction and the frequency of sickle cell crises.

Applicant Presentation – Victor Gordeuk

DR. GORDEUK: Good afternoon. My name's Victor Gordeuk. I am professor of medicine at the University of Illinois in Chicago, and the director of the Sickle Cell Center there. This is the largest sickle cell center in the Midwest.

I have been treating sickle cell disease patients for more than 30 years, and it is a pleasure for me to share a brief background on sickle cell disease.

Sickle cell disease is a homozygous hemoglobinopathy due to a point mutation in the

beta-globin chain of the hemoglobin molecule. It affects about 100,000 Americans, over 95 percent of them African-Americans.

The condition has a complex pathophysiology. It is a chronic hemolytic process, a chronic anemia. It is characterized by continuous oxidative stress. This stress contributes to unpredictable painful vaso-occlusive crises. The cumulative effect of these crises contributes to progressive organ damage and mortality.

Deoxygenation and hemoglobin sickling are fundamental to the pathophysiology of sickle cell disease. May I call your attention to the animation on the screen. The red blood cell is normally a malleable biconcave disc that releases oxygen to the tissues under deoxygenated conditions.

There's a tendency in these conditions for the hemoglobin S molecule to come out of solution and deform the red cell. There is a specific time for this to occur, called the delay time. Under normal circumstances, the abnormal shape will be

assumed in the larger venules, and the cells will return to normal shape as they are reoxygenated in the lungs.

However, under conditions in which there is reduced perfusion of the microvessels, the abnormal shape with be assumed in the microvessels themselves. This will lead to adhesion to the endothelial cells of the microvasculature, vaso-occlusion, and initiation of an inflammatory cascade.

Sickle cell disease is a condition of multisystem organ damage. First, I would like to call your attention to the lower left-hand corner of the slide. Vaso-occlusion in the marrow of the long bones gives rise to the excruciating painful episodes that characterize the clinical course of patients with sickle cell disease.

Many other organs are damaged by vaso-occlusion as well, leading to high rates of chronic kidney disease, hepatic damage, acute respiratory failure, hemorrhagic and ischemic stroke, retinopathy, cardiomyopathy, priapism, and

avascular necrosis of the bones.

Sickle cell disease causes a substantial burden to the patients and their families. There are frequent hospitalizations with severe pain, and these frequent crises interrupt the patients' lives. They limit the ability of these patients to attend school regularly, to maintain regular employment, and to plan for normal daily activities.

These problems start in childhood and become more frequent as the patient grows older. By the time of adulthood, there is a high risk of developing end-stage renal disease requiring hemodialysis, cardiopulmonary complications that require chronic oxygen therapy and that limit exercise capacity, and the disability secondary to avascular necrosis of the bones.

Sickle cell disease has a high mortality. This slide shows life expectancy of sickle cell patients compared to the general American population in the 20th century. For most of the 20th century, sickle cell patients died in

childhood.

There was an increase in survival in the early 1970s when the universal use of penicillin prophylaxis resulted in most children living up to young adulthood, but the life expectancy of patients with sickle cell anemia is still dramatically lower than the general population, and we need a major focus on improving life expectancy.

This graph represents a classic analysis of the relationship between the annual rate of sickle cell pain crises and mortality. It is derived from the comprehensive study of sickle cell disease, a dataset of approximately 3700 patients that were followed for more than a decade.

The blue line shows that mortality in patients who experience three or more crises per year is markedly higher, than those who experience a lower rate of crises, represented by the purple and orange lines.

At the age of 40, the probability of death approaches 50 percent in patients who experience three or more crises per year, as opposed to

20 percent in those who experience fewer crises.

As mentioned earlier, hydroxyurea is the only drug that has been approved by the FDA for sickle cell disease. Approval was granted in 1998, based on a study that was published in 1995. Reduction in the rate of pain crises was the primary outcome variable. This was defined as an emergency room visit or a hospitalization for treatment of acute pain.

The left-hand panel shows the time to first crisis for hydroxyurea compared to placebo. The time was increased by about 1.5 months with hydroxyurea. The right-hand panel shows that the time to the second crisis was even more dramatically improved. The time to the second crisis was increased by 4 months in the patients who received hydroxyurea.

We need new agents to reduce sickle cell crises. Reducing painful crises is the top priority of patients and it results in improved survival. Although hydroxyurea is a great drug, it reduces the frequency, but does not eliminate all

painful crises.

It is not effective for all patients, and it is not tolerated by others. There are fears of infertility, birth defects, and secondary malignancies, both on the part of patients and the doctors who treat them.

Other modalities are available, but are associated with certain limitations and are not recommended specifically for reducing the rate of pain crises. These include simple or exchange blood transfusion, and HLA-matched or haploidentical hematopoietic stem cell transplantation.

In closing, I'd like to tell you about one of my own patients. He is a young man in his 20's, who holds down a full-time job despite having severe complications of sickle cell disease. He has poor compliance with hydroxyurea, due to worries about infertility.

This young man was admitted to the hospital with a vaso-occlusive pain crises 3 times in the past 12 months. Each time he presented with

similar acute pain symptoms, but the hospital course varied considerably. In the first crisis, the pain improved rapidly, leading to his discharge after two days.

The second crisis was complicated by bone infarction and a join effusion, and the hospitalization lasted 5 days. The third crisis was marked by a dramatic deterioration after admission. He developed acute chest syndrome and respiratory failure. He was rushed to the intensive care unit, required intubation, and underwent mechanical ventilation for several days. The duration of the hospital stay was almost 3 weeks, and this third crisis was nearly fatal.

This patient is a good example of why we definitely need new drugs to reduce crises in sickle cell disease. Even a reduction in the rate of one crises per year would be highly significant from the clinical standpoint.

Finally, I would like to make a point about the challenges of studying sickle cell disease based on my experience and being involved in many

clinical trials over the years. The challenges related to studying sickle cell disease are distinct. Quite different from studying other conditions such as cancer.

For instance, this is a lifelong illness as opposed to a recently diagnosed malignancy. Patients with sickle cell disease face the stigma of suspected narcotic-seeking behavior. This differs starkly from the universal compassion for patients with cancer.

Many patients with sickle cell disease have financial difficulties, may need to take long trips on public transportation for their appointment. They made need to change cell phone carriers and phone numbers frequently and have frequent changes in that address.

Nevertheless, we in the field are committed to conducting clinical trials in sickle cell patients to identify new, much needed treatments, and I'm very excited by the success of the present study.

Thank you. I would now like to introduce

Dr. Niihara who will present clinical efficacy and safety.

Applicant Presentation - Yutaka Niihara

DR. NIIHARA: Thank you, Dr. Gordeuk. As the chairman and CEO of Emmaus, I'd like to thank each member of the advisory committee and the FDA for this opportunity to present our findings regarding the robust efficacy and safety profile of L-glutamine.

We also extend our thanks to the patients, investigators, and study personnel who participated in these trials, and whose efforts have allowed us to bring this to you for consideration. My interest in this disease is longstanding, going back to the days of my medical training in early 1990s.

At that time, I chose to devote my life working with sickle cell patients. This decision was reached as I observed their devastating conditions firsthand. What I saw were a series of serious medical complications accompanied by the most severe pain.

Now why L-glutamine? It is one of the most ubiquitous molecules. In this presentation, we will briefly go over how L-glutamine was realized as an effective and safety agent to treat sickle cell patients with clinically meaningful outcomes.

In the summary of clinical data with L-glutamine therapy, we'll describe lower frequency in the number of life-altering and potentially-fatal crisis that sickle cell patients face every day.

In addition, we'll describe the outcome of other conditions related to sickle cell disease with L-glutamine therapy. In pathophysiology of sickle cell disease, oxidant stress plays a major role. In order to counter this effect red blood cells utilizes a molecule, NAD, or nicotinamide adenine dinucleotide, to ameliorate its damaging effect.

The activity of NAD is gauged by a NAD redox potential described here. It is basically ratio of reduced NAD or NADH to total NAD, which is the sum of NAD plus and NADH. NAD plus is the oxidized

NAD.

In the sickle red blood cell, due to increased oxidant stress, this NAD redox potential is significantly decreased. Working through metabolism of NAD, we noted that one of the precursors for NAD, L-glutamine can improve and normalize NAD redox potential if it is applied adequately to sickle red blood cells.

L-glutamine treatment also improved the rate of endothelial adhesion by sickle red blood cells. This cartoon figure of red blood cells is an illustration of the interaction of L-glutamine in NAD synthesis. At the right of the cartoon, you see where glutamine, represented by Gln in a box, enters into the NAD synthesis pathway, resulting in production of NAD.

Our bench research data suggested that supplementation with L-glutamine will improve NAD redox potential in sickle red blood cells. Subsequently, we studied the effect of oral supplementation with L-glutamine with 7 sickle cell volunteers. We studied their blood cells before

and after the treatment. The normal range for NAD redox potential is above 60 percent, whereas sickle cell patients typically have 40 to 50 percent range.

Improvement was evident. Within 4 weeks, all patients improved their NAD redox potential. All but one went from subnormal to normal level. With these changes we predicted a decrease in further damage to sickle red blood cells with L-glutamine supplementation.

Also, we predicted this will lead to decreased adhesiveness of sickle cells, leading to improved transit through microvasculature, thus preventing vaso-occlusive changes.

In terms of peripheral blood smear, we have noted change from baseline where the cells were deformed and clumped, to smooth, round, and less adhesive to each other, with the treatment as seen in these slides.

Although a number of permanently sickle cells in the peripheral smear is not always predictive of the severity of the disease, the

changes we saw were quite dramatic. When we analyzed adhesion rate of red blood cells to endothelial cells, there was consistent improvement in adhesion rate.

Patient 1 through 5 in this figure, received glutamine therapy, and patient 6 was monitored as a control without therapy. Our study have shown consistent improvement in NAD redox potential before and after the treatment.

This study was repeated several times with different volunteers in a blinded fashion with the same results. The decreased adhesion is an indication that sickle red blood cells have smoother transit through small vasculature, with less vaso-occlusive changes, which is a basis for sickle cell crisis.

The animation, which was shown by Dr. Gordeuk as well, this shows sickle red blood cells as it unloads the oxygen in the capillary. The hardening of red blood cells initiate. Now if the transit time is normal before the cells completely harden, it gets to larger venule system where it

will not cause occlusion of vasculature, even though the cells are quite hardened.

However, with increase in adhesiveness, red blood cells will become more likely to cause vascular occlusion. As the transit time increases, what will happen is that as the transit time increases before the cells have chance to get out to the microvasculature, it becomes completely rigid that it can no longer move outside of the microvasculature. This is the mechanism that leads to occlusion. Such occlusion triggers vaso-occlusive crisis, resulting in tissue anoxia, inflammation, pain, and organ damage.

The data you have seen provided the basis to continue on to conduct phase 2 clinical trial. In our phase 2 clinical trial, it was double-blinded, randomized study. It enrolled total of 70 patients, age 5 and up, all had a diagnosis of sickle cell anemia, or sickle beta zero thalassemia.

Use of hydroxyurea was permitted, provided the patients were stable on the medication for at

least 3 months. Please be aware that during the study and before unblinding we discovered scientific misconduct at one of the study sites. Consequently, all of the 11 patients from that site were not included in the analysis.

We gave patients 0.3 grams per kilogram of L-glutamine twice daily and monitored them for 48 weeks. Our primary endpoint was frequency of sickle cell crisis. Looking at the mean, we saw 9.6 crises during the observation period for placebo, versus 4.3 in the treatment group. The p-value was 0.15.

Looking at hospitalizations, the mean was 1.9 for placebo group and 1.4 for the L-glutamine. The p-value was 0.11. These results all trended in favor of L-glutamine.

Using Negative Binomial Regression or NBR, we looked at the primary endpoint again, using observed data and exposure time. Rate of ratio was 0.47 favoring L-glutamine. The phase 2 clinical trial confirmed L-glutamine's beneficial effect on sickle red blood cells clinically, and provided

invaluable data to structure our phase 3 clinical trial.

For our phase 3 clinical trial, we enrolled sickle cell anemia patients and sickle beta zero thalassemia patients 5 years and older. The reason why these two genotypes were chosen is that these two are some of the worst sickle cell patients clinically, and also phenotypes are the same in that neither of them have hemoglobin A.

Patients had to have 2 or more crises verified in the source document during a 12-month period prior to enrolment. Use of hydroxyurea was permitted provided that they were stable on it for at least 3 months, and intended to stay on hydroxyurea throughout the study period.

Transfusions were allowed during the treatment phase. Patients were enrolled at 2 to 1 ratio, L-glutamine to placebo respectively, and they were observed for 48 weeks. The study was stratified by site and hydroxyurea use.

For the primary endpoint we looked at the number of crises during the 48-week treatment

period. A crisis involved a visit to a medical facility with administration narcotics or ketorolac, having acute chest syndrome, priapism, or splenic sequestration.

These crises were formally adjudicated by a Central Adjudication Committee. We also looked at other endpoints including time to first and second sickle cell crisis, as well as recurrent events, number of hospitalizations, cumulative days hospitalized, occurrence of acute chest syndrome, and episodes of blood transfusions.

For statistical considerations, we calculated the sample size to be 220 or greater, to have 80 percent power. For this we used Wilcoxon Test. For the analysis, we used Cochran-Mantel-Haenszel with modified ridits. Our two-sided output was determined to be 0.045 due to an interim analysis. Imputation was utilized for missing data in the primary analysis. With sensitivity analysis various methods, including NBR were used.

Here we see data on patients disposition.

The L-glutamine group enrolled 152 patients; placebo enrolled 78, reflecting the 2 to 1 randomization rate. The discontinuation rate was higher in the L-glutamine group at 36 percent versus 24 percent in the placebo group.

In either group, the majority of reasons for withdrawal were consent withdrawn and other. The demographics of the two groups that enrolled, age, sex, race, use of hydroxyurea, were quite similar between the groups.

Pediatric representation was significant, and the under 18 group represented about half of the patients enrolled. Hydroxyurea were also represented. Two-thirds of the patients in this study in both arms were being treated with hydroxyurea.

Both groups entered with about 4 sickle cell crises in the previous 12 months. As noted previously, these crises were confirmed by medical records, but were adjudicated, as we did in our trial.

The primary endpoint was frequency of sickle

cell crises which were adjudicated. The p-value was 0.0052, favoring L-glutamine treatment group. The mean number of crises was 3.2 in the L-glutamine group, versus 3.9 in the placebo group. Median was 3 versus 4, respectively, using imputed data.

As was indicated earlier, please note that each crisis is associated with organ damages and are cumulative. Because the primary analysis looked at events over 48 weeks, data were imputed for patients who withdrew early. With pre-defined primary analysis method using imputation, p-value was 0.0052.

In this analysis the data was imputed, based on the greatest of either the mean number of crisis among completers within treatment group or the number of crisis at the time of withdrawal for each individual patient.

With other forms of imputation last observations carried forward and time-adjusted LOCF our p-values were 0.0025 and 0.019 respectively. When we used observed data and exposure time using

Negative Binomial Regression or NBR analysis, we obtained a rate ratio of 0.78, indicating risk rate reduction of 22 percent with p-value of 0.037.

Please note the general consistency in these results in primary analysis and sensitivity analysis. However, based on communication with the agency, we conducted additional exploratory imputation analysis as seen on the next slide.

FDA has kindly informed us that they had conducted some exploratory sensitivity analysis based on multiple imputation methods for checking the robustness of our study primary analysis result. We then conducted analysis with various standard imputation methods as well. This slide provides the forest plots risk reduction rates using L-glutamine.

The black boxes are the risk reduction rate estimates, with corresponding confidence intervals. The results from extensive sensitivity analysis were consistent, demonstrating the robustness of the claim of the treatment from L-glutamine, based on the primary analysis.

The risk reductions from these analyses were between 25 percent and 45 percent in favor of L-glutamine, even when we assume there is no treatment effect between the two arms for imputation. As an example from this table, for the first case please note the plot on the upper-left corner. Here we considered there is no treatment difference and assumed a standard ordinal logistic regression for all the categorical data.

With these data, multiple imputation and analysis showed risk reduction from L-glutamine to be more than 50 percent over the control. This is the forest plot that shows the result of subsets. I'd like to first focus on the use of hydroxyurea, for those patients who were using hydroxyurea, which is the only medication available for sickle cell patients today.

We looked at those who were not on hydroxyurea during the study. The rate ratio favored the use of L-glutamine in both groups and risk reduction rates were almost equal between two groups, whether they were on hydroxyurea or not on

hydroxyurea.

Hydroxyurea patients were noted as HU Yes, and people who were not on hydroxyurea are indicated as HU No. The results for males, females and age groups 18 or younger, and 18 or older, also consistently showed benefit of L-glutamine over placebo.

Here we can describe the delay to first crisis using the Kaplan-Meier curve. The hazard ratio was 0.69 or decrease in risk rate by 31 percent. Separation of the curves are persistent throughout the observation period.

In regard to the time to second crisis, the results again favored L-glutamine group, with hazard ratio of 0.68 or reduction in risk rate by 32 percent, p-value 0.026. Again, the curves are separated throughout the observation period.

This curve demonstrates the difference of mean number of recurring crisis at each time point. Again, we noted the clear separation between the two groups throughout the observation period. The totality of evidence clearly indicates a lower risk

of crisis events through the observation period and persistent effect over time. Hazard ratio here was 0.79 or risk rate reduction of 21 percent.

Hospitalization is a tangible way to look at clinical outcome. The hospitalization rate favored L-glutamine group as well. The p-value was 0.0045. Mean was 2.3 events in L-glutamine group and 3 events for placebo.

In terms of the length of stay in the hospital, it again favored L-glutamine group. Our p-value was 0.022 and the mean difference was 66 days; 12 days in L-glutamine versus 18 days in placebo.

We also found that one of the most devastating complications, acute chest syndrome, was significantly lower among the L-glutamine group with a p-value of 0.0028. The rate was 0.1 in the L-glutamine group versus 0.3 in the placebo group.

The table shows distribution and those who had at least 1 acute chest syndrome, was 9 percent in L-glutamine group versus 23 percent in the placebo group. When we accounted for each acute

chest syndrome, the rate of acute chest syndrome occurrence were more than 60 percent higher in the placebo group compared to L-glutamine group.

Acute chest syndrome is one of the major causes of mortality. It often requires ICU admission with respiratory support.

Blood transfusion is yet another potential burden faced by sickle cell patients. Altogether, 47 percent in L-glutamine patient group, and 51 percent of patients in the placebo group received simple transfusion therapy during the observation.

When we looked at the patients who actually received transfusion in each group, the patients in L-glutamine group received average of 3 simple transfusions during the observation period, whereas placebo group patients received 4.5 transfusions during the observation period.

In sickle cell patients, acute exchange transfusions are provided in extreme cases, such as in acute chest syndrome or in CVA. The data for exchange transfusions similarly favored L-glutamine

group; 6.4 percent of patients had to receive exchange transfusion in the placebo group, whereas only 2 percent had to receive exchange transfusion in L-glutamine group.

In summary, the consistency of L-glutamine therapy were noted to result in clinically meaningful benefit. As Dr. Gordeuk has shown earlier, sickle cell crises are linked to morbidity and mortality, the accumulative damage they cause. In our study, L-glutamine treatment group had significantly lower incidence of sickle cell crises. In terms of time to first crisis there was 56 percent delay in the treatment group. Rates of acute chest syndrome were lower by 67 percent. This is a condition that frequently requires ICU care and is a major cause of mortality.

Hospitalization rates were lower by 33 percent in the L-glutamine group, and cumulative days were also lower in the treatment group by 41 percent. Simple blood transfusion events were lower by 39 percent, and relative difference in requirement for exchange transfusion was even

larger favoring L-glutamine therapy. In total, L-glutamine favorably affected our patients in most major areas of concern today for sickle cell patients.

In conclusion, we observed efficacy of L-glutamine therapy across the endpoints in the study 09-01. Lower frequency of sickle cell crises. Lower frequency of acute chest syndrome. Longer duration to the first and second crisis. Lower frequency of hospitalization. Fewer cumulative days hospitalized. Fewer blood transfusion events.

This was consistent with the trends we have seen in the phase 2 clinical trial. In total, L-glutamine treatment favorably affected our patients in most major areas of concern today.

Now I'd like to turn to the safety profile of L-glutamine therapy. Please note that our safety evaluation plan integrated studies 10478 and 09-01, evaluation included 298 patients. All investigator-reported adverse events including those adjudicated as sickle cell crisis were

included.

Demographics and disease characteristics were balanced between the two groups. Please allow me to reiterate the differential randomization in two studies; 2 to 1 in study 09-01 or phase 3 clinical trial, and 1 to 1 in study 10478 or phase 2 clinical trial. So we will generally focus on the proportions of patients rather than the actual number in these tables.

The duration of exposure days in L-glutamine group was 268.9 days and 283.3 days for the placebo group. Over 100 patients had exposure greater than 48 weeks in the L-glutamine group, compared to 73 in the placebo group. The total exposure of L-glutamine was 137.7 patient-years.

Adverse events were common and experienced by 96.3 percent of patients in the L-glutamine group, and 97.3 percent of patients in the placebo group. Serious adverse events were experienced by 75.4 percent of patients in the L-glutamine arm, and 80.2 percent in the placebo group.

Adverse events leading to discontinuations

were relatively low at 2.7 percent for L-glutamine, and 0.9 percent for placebo. There were a total of 3 deaths during the study, all on L-glutamine. One death was observed in the phase 2 clinical trial; 2 deaths were observed in the phase 3 clinical trial where randomization was 2 to 1 for L-glutamine to placebo respectively. Each of these patients were adults, had serious chronic comorbidities as they entered into the studies, and these deaths were not unexpected. Thus, the investigators did not consider them related to the treatment.

A summary of the adverse events that occurred at greater than 10 percent occurrence rate in the L-glutamine group that was greater than placebo are provided here. Constipation, nausea, headache occurred around 20 percent of L-glutamine patients. Pain in extremities, back and also known cardiac chest pain were noted. These are primarily seen in pediatric patients.

For all other adverse events that did not qualify to be listed here, the proportion of patients reporting events were fairly similar

between the two treatment groups.

Turning to serious adverse events, sickle cell crisis, acute chest syndrome, and pneumonia were among the most common events. The occurrence of serious adverse events were generally higher in the placebo group compared to the L-glutamine group.

A summary of adverse events that led to study discontinuation is presented here. There were 5 patients representing 2.7 percent in L-glutamine group, and one patient representing 0.9 percent in placebo group. Please note that with the asterisk, hypersplenism and abdominal pain -- these two events were experienced by the same patient.

In summary, L-glutamine is well-tolerated both in pediatric and adult patients. Common serious adverse events were generally higher in the placebo group. Adverse events leading to discontinuation were infrequent. Overall, the safety profile was similar to placebo, and the risks of L-glutamine treatment are minimal.

Now I'd like to turn discussion over to Dr. Smith who is going to go over clinical perspective on the data.

Applicant Presentation - Wally Smith

DR. SMITH: Thank you, Dr. Niihara. Some of you know me. I'm Dr. Wally Smith. Take care of sickle cell patients at Virginia Commonwealth University, and I have the privilege of talking with you about my view of the risk-benefit profile of L-glutamine in sickle cell patients, and why I would like to have this become the second ever drug approved for sickle cell disease, so that my patients can have it.

I've been treating patients with sickle cell disease for 32 years, and in that time we have made some progress, as been shown, in treating the disease and extending the lives of our patients.

We've gotten patients with sickle cell disease into adulthood using prophylactic penicillin. In some instances, we've been able to extend life in adults with hydroxyurea. But there is still much to be done to reduce the impact of

this devastating disease.

Pertinent to our discussion today, to reduce the number of sickle cell crises, which may be deadly in our patients. Now many of my patients are in pain all the time. I'm known for talking about that. These patients are dealing with their pain at home and they control it at home, and it's significant.

But when they have a crisis, it's significant in a new way. It's a new level of pain. That means that they have done all that they can do to exhaust and to treat their pain at home, and they are now at the last resort of coming to the hospital, coming to the emergency department.

They describe that kind of pain as if somebody took a baseball bat to their shin and started whamming and whamming, all day, all night, all week, and no matter what they did, the pain would not relent.

So every time somebody comes to the hospital with a crisis, it is significant. It matters. They don't like coming. When a patient presents,

the patient is on alert, the doctors are on alert, the medical center is on high alert, just like we saw with Dr. Gordeuk's patients. We're all trying to ensure that that patient doesn't end up like the last time Dr. Gordeuk's patient came to the hospital.

We don't know if the patient's going to die during that admission. In the emergency department, they have extreme pain, fatigue, disability -- that's usual; we try to treat that. We give high dose opioids. We give oxygen. We give hydration. We try to prevent hospitalization.

For some patients, like in this study, even though they had a crisis, they were able to go home. But for other patients, they're hospitalized, and there everybody wonders, especially the patient, could this be the end?

So you saw the possibilities of what a crisis represents; acute chest syndrome. For some patients, especially children, a possible stroke. The downstream complications from that, altered cognition, altered organ failure, altered organ

function, priapism, other kinds of organ failures. All of this really is what is possible during a crisis.

The length of stay is variable, it's unpredictable. It could be a few days, could be a few weeks. The financial costs can be extreme. The human costs are phenomenal. When the patients go home, they now have to pick up where they left off -- their schooling, their jobs, their families, their social responsibilities, have suffered while they were away from home. They don't know when they're going to have the next crisis, so they try to prepare for that.

For some patients, they have to come out of school, lose their job, lose their spouse. So the demands of living are interrupted every time a patient has a single crisis, a single hospitalization. Having one fewer of those would be welcomed by my patients, and by their families, by their employers. In the event that L-glutamine helps them do that, I'm all for having this drug approved.

Dr. Niihara has shown you what I consider convincing, consistent results that L-glutamine translates to fewer crises, fewer hospitalizations, fewer acute chest syndromes, fewer transfusions. You've heard a lot about statistics, about imputation today -- one fewer, versus 0.9 fewer, versus 0.8 fewer crises.

But just imagine 10,000 patients on L-glutamine. Let's take the FDA's most conservative estimate of a mean reduction of 0.8 crises per year. That 10,000 patients would have 8000 fewer crises in the next year. Over 5 years, 40,000 fewer crises.

Imagine how that would relate to mortality. We already saw that the crisis rate relates to mortality. We already saw that it doesn't matter if you're already on hydroxyurea or not; you're still getting a benefit.

So clearly, this product can be used with or without hydroxyurea, and I'm encouraged by the effect profile. I'm also encouraged by the safety profile. I do not see anything of concern here. I

think it's safe to use in adults and children.

In my mind, the benefit-risk ratio is clear. I would give this drug to just about anybody with sickle cell disease. I would offer it to children and to adults. On behalf of my patients, I'm asking for your support today to recommend for a positive risk-benefit ratio in this drug. Thank you.

DR. RINI: All right. Thank you. We'll now proceed with the FDA presentation.

FDA Presentation - Rosanna Setse

DR. SETSE: Good afternoon. I am Rosanna Setse, a medical officer, the Division of Hematology Products. I'll be presenting FDA's findings from the review of NDA 208587 for L-glutamine.

The FDA review team for this application is shown on the slide. The outline of my presentation will be as follows. I'll start with a few introductory comments, which will include the proposed indication for L-glutamine, as well as the major issues for which advisory committee input is

being sought.

Next, will be a review of the clinical study support in this NDA. I will summarize again, the study designs and present the safety findings from FDA's analysis. Dr. Smith from the Office of Biometrics will present the efficacy findings.

Finally, I will summarize FDA's key efficacy and safety findings, and reiterate the key issues for advisory committee discussion and vote.

The proposed indication for L-glutamine, as has been mentioned before, is for the treatment of sickle cell disease. The proposed dose is 0.3 grams per kilogram body weight, with an upper limit of 30 grams per day, administered orally, twice a day.

The applicant conducted two main clinical trials in patients with sickle cell disease, in support of this application. These will be discussed in later slides. FDA requests the advisory committee to discuss the following issues.

First, statistical issues regarding the impact of incomplete data and imputation methods on

the efficacy results; and two, the clinical meaningfulness of the observed efficacy results.

Study 09-01 is the pivotal study supporting this application. The study population consisted of patients with a documented diagnosis of sickle cell anemia, or sickle beta thalassemia by hemoglobin electrophoresis, who were 5 years of age or older at the time of enrolment, and who had at least two documented crisis episodes in the 12 months prior to screening.

Study subjects were randomized to L-glutamine versus placebo in a 2 to 1 ratio, with randomization stratified by study site and hydroxyurea use. Study subjects were treated with L-glutamine 0.3 grams per kilogram body weight, orally, twice a day, or placebo at an equivalent dose.

There was a 4-week screening period, followed by 48 weeks of treatment, then 3 weeks of drug tapering and 2 weeks of follow-up. Study visits occurred monthly.

As mentioned by the applicant, the primary

endpoint in study 09-01 was the number of sickle cell crises through week 48. In this study, a sickle cell crisis event was defined as a visit to a medical facility for sickle cell disease-related pain, treated with a parenterally administered narcotic or Toradol; or the occurrence of acute chest syndrome, priapism, and splenic sequestration, even if these symptoms for these events were not painful enough to require narcotics.

Determination of whether any given crisis episode met the criteria for the primary endpoint, was adjudicated by a Central Adjudication Committee.

The secondary endpoints prespecified by the applicants for this study are listed on this slide. This included the number of sickle cell crises at week 24, the number of hospitalizations for sickle cell pain, and the number of ER visits for sickle cell pain.

A total of 230 patients with sickle cell anemia or sickle beta thalassemia were enrolled.

This study included both pediatric and adult patients. The mean age of participants was 22 years, with ages ranging from 5 to 58 years.

The majority of subjects were black or African-American, and majority had a diagnosis of sickle cell anemia. Sixty-seven percent of the study subjects were being treated with hydroxyurea at baseline, and continued treatment with hydroxyurea throughout the study period.

The disposition of subjects enrolled in study 09-01 was as follows: 68 percent of the total study population completed the study; 32 percent discontinued the study before the end of week 48.

As shown in the displayed table, the proportion of subjects who discontinued or dropped out of the study before the end of week 48 was higher in the L-glutamine group than in the placebo group; 36 versus 24 percent.

The most common reason for study discontinuation, as shown in this slide, in both treatment groups, was consent withdrawn. FDA's

review of the verbatim text for the subjects who dropped out of the study due to consent withdrawn or other reasons revealed a variety of reasons with no particular trends.

Although not shown on this slide, there were no notable differences in the demographic characteristics of subjects who completed the study, compared to those who discontinued the study for both the L-glutamine and the placebo treatment groups.

Study 10478 was also a randomized, double-blind, placebo-controlled study, and was generally similar to study 09-01 with some notable exceptions. In study 10478, randomization to L-glutamine versus placebo was done in a 1 to 1 ratio, and randomization was stratified by study site, but not by hydroxyurea use.

As a result, hydroxyurea use was not balanced between the treatment arms at baseline. The division considers the lack of stratification by hydroxyurea use a confounding factor in the study, which complicates interpretation of findings

from study 10478.

Another difference between study 10478 and 09-01 was with respect to the definition of the primary endpoint. In study 10478, a sickle cell crisis was defined as visit to a medical facility that lasted more than 4 hours for an acute sickling-related pain, which was treated with a parenterally administered narcotic.

Acute chest syndrome, priapism, splenic sequestration, and hepatic sequestration were also considered sickle cell crisis events. However, unlike in study 09-01, the occurrence of a sickle cell crisis event in study 10478 was not determined by an adjudication committee.

The disposition of subjects enrolled in study 10478 is shown on the displayed slide. A total of 70 patients were enrolled. More than half of the study population, 57 percent, dropped out of the study before week 48.

However, in this study more subjects in the placebo group discontinued the study before week 48, compared to the L-glutamine group, 64 versus

51 percent respectively. Reasons for dropouts again was similar between the treatment groups with the most frequent reason being non-compliance, consent withdrawn, and other reasons.

Due to the issues identified with study 10478, FDA's efficacy analysis is focused on study 09-01. Data from study 10478 is however included in FDA's integrated safety analysis.

I'll now hand it over to my colleague, Dr. Smith, to present the efficacy findings.

FDA Presentation - Che Smith

DR. SMITH: Good afternoon. My name is Che Smith and I will briefly review some of the statistical issues identified during the review of this application.

As Dr. Setse discussed there were notable differences between study 10478 and study 09-01. First, sickle cell crises were defined and classified differently in study 10478 and a wider range of crises were experienced by patients, compared to study 09-01.

In study 10478, patients experienced between

zero and 90 crises within a 48-week treatment period, compared to study 09-01 in which patients experienced between zero and 15 crises across 48 weeks.

In both treatment arms of study 10478, more than half of patients dropped out of the study before the full 48-week treatment period, with more patients dropping out from the placebo arm. The primary efficacy result for study 10478 did not meet the prespecified significance level. The study may have been underpowered due to potential misconduct at 1 of 5 study sites, resulting in the removal of that sites data from consideration.

Additionally, this study did not stratify by baseline hydroxyurea use, resulting in a heterogeneous study population between treatment arms. For these reasons, my presentation focuses only on study 09-01.

I will focus on 3 statistical issues identified during the review of this study. First, there was a high early dropout rate, and differential dropout rates between treatment arms.

In previous communication with the applicant, the agency indicated that if this occurred it would be a concern.

Second, since about one-third of patients across both treatment arms dropped out of the study early, these patients had incomplete counts of sickle cell crises over a 48-week period. The methods used by the applicant to estimate the incomplete counts may not be optimal.

Third, the presence of incomplete data and differential dropout rates complicates interpretation of the results of study 09-01.

As presented previously, study 09-01 was a phase 3 study that enrolled and randomized 230 patients in a 2 to 1 ratio to either L-glutamine or placebo treatment, and randomization was stratified by study site and hydroxyurea use at baseline.

The applicant's statistical analysis plan for study 09-01 specify that the primary efficacy analysis would compare sickle cell crisis events through week 48, between treatment groups, using the Cochran-Mantel-Haenszel test, using modified

ridit scores controlling for stratification factors.

The statistical analysis plan included an interim analysis based on sickle cell crisis counts at week 24 to be evaluated at the 0.005 significance level. According to the statistical analysis plan, the number of sickle cell crises for patients who dropped out of the study early was to be estimated by the mean number of crises for subjects in the same treatment group who completed the study, or the number of crises experienced by the patient at the time of dropout, whichever was larger.

The statistical analysis plan indicated that an early dropout rate of 25 percent was expected across both treatment arms over the 48-week treatment period. In a previous review of the statistical analysis plan, the agency emphasized that if the dropout rate ended up higher than expected, then the applicant's proposed method for imputing sickle cell crisis counts would be a concern.

Early study dropout occurred at a higher rate than expected, with about 36 percent of patients from the L-glutamine treatment group dropping out of the study early, compared to 24 percent of patients randomized to placebo treatment.

Additionally, a notable number of patients dropped out of the study before the midpoint at 24 weeks. Study narratives on the reasons why these patients dropped out of the study do not give sufficient information as to whether dropout was related to the patients' assigned treatment group or other study characteristics.

Patients who dropped out early had less exposure to their assigned treatment. Since the dropout rate was higher in the L-glutamine treatment group, this makes it difficult to assess the potential effect of L-glutamine.

The agency has concerns about the methods used to estimate 48-week sickle cell crisis counts for some patients who dropped out of the study before week 48.

This slide summarizes 4 possible patient experiences on study 09-01. Together, these mutually exclusive groups of patients comprise the full intent-to-treat study population.

First, there were patients who completed 48 weeks of assigned treatment and had at least 1 crisis event recorded. There were additional patients who completed the study and had no crisis events recorded. Among those who did not complete 48 weeks of treatment, some patients dropped out having experienced at least 1 recorded crisis event. And finally, there were some patients who dropped out of the study and had no recorded crisis events at the time of dropout.

Of the 230 patients enrolled in the study, there were 137 patients across both treatment groups who completed the study with at least one reported crisis event, and this is represented in the first row of the table.

There were 19 other patients who also completed the study, but did not have any recorded crisis events, represented in the second row. In

this case, it is reasonable to assume that these 19 patients did not experience any crises, since they were seen at the final visit.

In a response to a statistical information request from the agency, the applicant noted, and I quote, "There were no missing data on number of crises." Among the remaining 74 patients who did not complete the study, however, it is not clear from study documentation whether 24 dropouts represented in the fourth row, with no recorded crises, had a crisis count of zero crises unknown or missing.

Displayed in each chart on this slide are the frequencies of sickle cell crisis counts in the L-glutamine treatment group represented by the pink bars on top, and counts for the placebo group represented by blue bars on the bottom.

In the chart on the left, are histograms of reported crisis counts without any imputation. Considering that nearly one-third of patients had incomplete counts of sickle cell crisis events, the imputation method used by the applicant may have

introduced bias in the primary and secondary efficacy results.

Under the applicant's imputation role, crisis counts were not imputed for patients who completed the study or who dropped out with more than the mean number of crises in their assigned treatment group.

Patients randomized to L-glutamine treatment who dropped out of the study with fewer than 3 crises, had an imputed 48-week crisis count of 3. Patients randomized to placebo treatment who dropped out with fewer than 4 crises, had an imputed 48-week crisis count of 4. These imputed values represent the mean number of crises among study completers from each treatment group.

Because the unimputed distributions of crises are skewed in each treatment group, as seen on the left, using the mean crisis count among completers to impute incomplete crisis counts may have introduced bias. When the applicant's imputation method is applied to study data, as seen in the chart on the right, it creates a notable

difference in the appearance of the histograms with a peak at 3 in the L-glutamine group and at 4 for patients in the placebo group. This raises concerns that the applicant's imputation method does not reflect the underlying distribution being estimated through imputation.

As a reminder, the applicant's primary efficacy analysis was performed use imputed data. This analysis estimates that patients treated with L-glutamine experienced a median of 3 sickle cell crisis events across 48 weeks, compared to an estimated median of 4 crisis events in the placebo arm.

Using the prespecified Cochran-Mantel-Haenszel test with modified ridit scores controlling for baseline hydroxyurea and study site region, the applicant's analysis yields a p-value of 0.0052, which falls below the prespecified significance level of 0.045.

The same imputation scheme was used to estimate the number of hospitalizations and emergency room visits for patients who dropped out

of the study. It may have introduced bias as well in the prespecified secondary efficacy endpoint results.

In addition to the FDA's concerns about the imputation method used by the applicant to fill in incomplete data, the Cochran-Mantel-Haenszel test does not account for the varying time spent on the study, and it relies on assumptions about the completeness of study data.

Considering that patients from both treatment arms dropped out the study early with more dropouts from the L-glutamine arm, and that the method used to impute incomplete counts may have shifted the distribution of crises, the agency is concerned that the results of the test could be biased and therefore raise questions that the test results support a claim that L-glutamine reduces the occurrence of sickle cell crises.

To overcome the difficulties caused by dropouts, the FDA performed a recurrent event analysis that incorporated the time a patient spent on the study, and assumes that the times between

crisis events for a patient are not necessarily independent.

In this analysis, there is no need to impute incomplete crisis counts in all observed events, as well as the timing of events are included. The figure displays the mean cumulative number or crises over time in weeks for each treatment group.

Based on this analysis, the proportional rate of sickle cell crises at 48 weeks is estimated to be 3 crises among the L-glutamine patients, and 3.8 crises for placebo patients. The FDA obtained a hazard ratio of 0.73 in favor of the L-glutamine treatment group, with a 95 percent confidence interval ranging from 0.55 to 0.99.

One drawback of this approach is that it requires an assumption of independent censoring, which may not be valid in this case, given the differential dropout rates between treatment arms.

The agency performed additional sensitivity analyses of the primary efficacy endpoint, using an FDA sensitivity analysis population, which consists of the 206 patients who completed the 48-week

treatment period, as well as patients who may have dropped out of the study, but had at least 1 recorded crisis event before dropping out.

Presented here are 3 FDA analyses using Negative Binomial Regression. Like the recurrent event analysis, Negative Binomial Regression takes into account the time a patient spent on the study and it does not require imputation of incomplete crisis counts. Using this approach, one can compare rates of crises per 48 weeks between treatment groups.

In the first analysis, Negative Binomial Regression is applied to the FDA sensitivity analysis population that I just described, where incomplete crisis counts for 24 patients were omitted.

In the second analysis, we assumed the incomplete counts for the 24 patients not completing the study were equal to zero.

Finally, a multiple imputation approach using fully conditional specifications, imputes counts for the 24 patients excluded from the FDA

sensitivity analysis population, before applying Negative Binomial Regression models.

Results of each of the FDA sensitivity analyses using Negative Binomial Regression vary, but together can be interpreted as showing a trend in favor of L-glutamine.

Overall, when incomplete crisis counts are handled different than the applicant's method in the analysis of the primary efficacy endpoint takes time on study into account to compare rates of crises between treatment groups, the results trend in favor of L-glutamine. Although, in some cases, confidence intervals for rate ratios overlap a ratio of 1.

In summary, there were more study dropouts than expected in study 09-01 and an imbalance in study dropout between treatment groups. The agency explored alternative methods of handling dropouts that incorporated relevant study information such as time spent on treatment before dropping out of the study.

Particularly, a recurrent event analysis

performed by the FDA, estimated sickle cell crisis rates per 48 weeks of 3 crises for patients treated with L-glutamine, versus 3.8 crises for patients treated with placebo.

Other exploratory analyses performed by the agency and the applicant, also show a trend that support a claim that L-glutamine reduces the number of sickle cell crises over a 48-week period. This apparent trend should be considered in the context of L-glutamine safety profile.

I will now refer back to Dr. Setse to review safety findings. Thank you.

Applicant Presentation - Rosanna Setse

DR. SETSE: I will now provide a summary of FDA's safety review findings.

Overall, no major safety concerns were identified. FDA's safety review revealed a similar pattern in frequency of reported common adverse events, and adverse events that led to study withdrawal among subjects in the L-glutamine and placebo treatment groups.

There was also a lower frequency of serious

adverse events related to sickle cell disease manifestations, namely sickle cell anemia with crises and acute chest syndrome in the L-glutamine group compared to the placebo treatment group.

The safety population consisted of all subjects enrolled in study 09-01 and 10478, who received one or more doses of study medication, excluding subjects from the 1 site in study 10478, which was disqualified.

Safety data from 5 smaller studies conducted by the applicant earlier in the clinical development program of L-glutamine are not included in the integrated safety analysis presented here. Adverse event information from these studies were provided to the committee separately in the briefing document and were generally consistent with adverse events from the studies in the integrated safety database.

A total of 298 subjects received at least 1 or more doses of L-glutamine, or study medication, during studies 10478 and 09-01. One hundred and eighty seven subjects received

L-glutamine for one or more days; 73 percent were treated with L-glutamine for at least 24 weeks, and 58 percent received L-glutamine for 48 weeks or more.

This slide shows a summary of all adverse events in the safety population. Treatment emergent adverse events occurred in over 95 percent of study subjects in either treatment group. There was slightly more drug-related adverse events in the L-glutamine group, compared to the placebo group.

Majority of adverse events were serious. The proportion of subjects with serious adverse event was higher in the placebo treatment group than in the L-glutamine group. However, the frequency of drug-related SAEs was comparable between the treatment groups.

Three treatment emergent deaths occurred in the safety population. All 3 deaths occurred in subjects treated with L-glutamine. All 3 treatment emergent deaths occurred in adult patients who had been treated with L-glutamine on study 09-01 for a

considerable duration. The reported causes of death in these patients are listed on this slide. None of the 3 treatment emergent deaths were considered related to L-glutamine treatment by investigators. Autopsies were not done.

There is insufficient information for causality assessment by the FDA regarding the association between L-glutamine use and death in these patients.

Serious adverse events occurred in 2 percent or more of L-glutamine treated subjects in the safety population. Serious adverse events that occurred in 2 percent or more of L-glutamine treated subjects in the safety population are shown in the displayed table.

As expected in this population, the most common serious adverse event occurring in all subjects was sickle cell anemia with crises. These were crisis events that occurred during the study treatment period, but which did not meet the criteria for the primary endpoint.

As shown in the highlighted box, the

frequency of sickle cell anemia with crisis events was higher in the placebo group compared to the L-glutamine group. Acute chest syndrome was also more frequent in the placebo group compared to the L-glutamine group.

Although sickle cell anemia with crises and acute chest syndrome are being evaluated here as safety endpoints, the lower frequency of these disease-related SAEs in the L-glutamine treatment group lend support to the observed efficacy findings in favor of L-glutamine.

Other SAEs which occurred were pneumonia, chest pain, pyrexia and asthma. The majority of these SAEs were considered unrelated to study treatment by study investigators.

Other than sickle cell anemia with crises, common adverse events which occurred in 10 percent or more of L-glutamine treated subjects are shown on this slide, and included constipation, nausea, headache, pyrexia, abdominal pain, and cough.

Overall, FDA analysis did not reveal any notable differences in the reported frequencies of

treatment emergent adverse events or serious adverse events that led to study drug withdrawal by age, race, or sex.

There were also no notable differences in mean changes from baseline to end of treatment for hematology parameters, liver function tests, or serum chemistry results for L-glutamine and placebo treated subjects.

I'll now summarize the key efficacy and safety findings from FDA's review of this application.

The applicant's primary efficacy analysis resulted in a median sickle cell crisis counts of 3 versus 4, for L-glutamine versus placebo treated subjects at 48 weeks.

FDA analysis estimated mean cumulative rates of sickle cell crises of 3 versus 3.8 for L-glutamine versus placebo treated subjects at 48 weeks with a hazard ratio of 0.73 in favor of L-glutamine. These efficacy results should be interpreted with caution. No analytic method is ideal given the magnitude of study dropouts and

imputations.

Safety -- overall there were few notable differences in the percentages of subjects who reported adverse events, or adverse events that led to study drug withdrawal between L-glutamine and placebo treated groups. Serious adverse events were common in both treatment groups. However, the lower frequency of serious adverse event reports of sickle cell anemia with crises and acute chest syndrome in L-glutamine treated patients suggests a possible benefit effect of L-glutamine.

Other than sickle cell anemia with crisis, the most commonly reported adverse events occurring in patients with sickle cell disease treated with L-glutamine are listed here, and include constipation, nausea, headache, pyrexia, abdominal pain, and cough.

The advisory committee input is sought regarding the following. One, the impact of the observed study dropout rates between treatment arms, data imputation methods, and analytic methods used on interpretation of the efficacy findings.

Two, the clinical significance of at best one fewer sickle cell crisis event per year in patients with sickle cell disease.

The question for the advisory committee today is as follows. Based on the available data presented and discussed, is the overall benefit-risk profile for L-glutamine for the treatment of sickle cell disease favorable? Thank you.

Clarifying Questions to the Presenters

DR. RINI: Okay. Thank you. We will now take questions from the committee to the presenters. If you want to ask a question, just give a wave to Lauren, she'll put your name on a list and we'll take them sequentially. Remember to state your name for the record before you speak, and you can direct your questions to a specific presenter.

I'd like to start actually while Lauren is gathering names for Dr. Niihara and this gets to efficacy. On page 18 of the briefing document it says the median number of crises in the year

leading up to study intervention was 3 for each group.

And then on your slide CE-17, your primary endpoint, the median number of crises in the L-glutamine was also 3. I guess I'm wondering, how can we be convinced of efficacy when the median number didn't really change in the year before intervention and the year after intervention.

Could it be that the placebo group just had a bad year if you will? That they went up while the L-glutamine didn't do anything and that group stayed the same?

DR. NIIHARA: Thank you, Dr. Rini. Yes. First of all, we apologize that -- we redid the baseline analysis based on the source documents only, and we found that baseline crisis was 3.9 for the L-glutamine group and 4.1 for the placebo patients. So we apologize for that discrepancy.

Now after saying that, our study was not to compare the results to the baseline, and because the way the baseline was collected, and the way the crisis was adjudicated during crisis are not the

same.

Our study strictly focused on the differential in the distribution between the two groups, L-glutamine treated group, and placebo treated group. To make sure that these -- to minimize the bias, we randomized the patients. Thus, we got the type of profile at baseline.

DR. RINI: Just one quick follow-up. Do you have any data on anything that happened after the intervention period, after week 48 in either of the groups; was there any data collected?

DR. NIIHARA: No, we do not have it at this time.

DR. RINI: Thank you. Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. Greg Nowakowski. This is a little bit of a follow-up question which Dr. Rini already alluded to. The sickle cell disease is characterized by a huge heterogeneity in the presentation. There are patients who have relatively few pain crisis episodes, and patients who suffer from multiple episodes in one year.

This can result in a significant heterogenecity [ph] in the patients entering the clinical study. In your table which was presented with the baseline characteristics, you tried to show some of those characteristics and show that they're equal in both arms of the study.

However, certain characteristics which are frequently used to describe severity of sickle cell disease were not necessarily included. I wonder if you have any data in this regard. One of those would be the number of sickle cell crisis episodes, and there's basically some stratification -- let's say 1 to 3, 3 to 5, more than 5, or more than 6 per year.

The other stratification factors you would consider would be, for example, the frequency of the chest syndrome and the baseline characteristics of those patients prior to entering the study, and then complications like ankle ulcer or avascular necrosis, or another surrogate markers of the severity of the sickle cell disease. Do you have any of this data available?

DR. NIIHARA: No, and thank you for good suggestions. Due to the number of patients that we enrolled, and the 230 patients are -- even though 230 patient study may not be a large study compared to some other areas, 230 patient study is a fairly large study for sickle cell. Because of this, we could really minimize our stratification.

Our stratification was limited to use of hydroxyurea, which we thought was very important from the phase 2 clinical trial. Then also the sites that we collected the data from. However, your point is very well-taken. But we do not have the data at the baseline on those areas.

DR. NOWAKOWSKI: So you don't have the data to it?

DR. NIIHARA: No.

DR. NOWAKOWSKI: Okay. By the way, I would like to recompliment Emmaus Medical for conducting this study in this very much area of medical need.

The other question I guess which comes down to the discontinuation of the patients on the study, which we have been discussing extensively

here, and that the more patients discontinued in the study, the direct arm, L-glutamine arm versus placebo arm.

Usually when we see this discontinuation we worry either about toxicity, which lead to discontinuation. Looking at the toxicity profile, we don't necessarily see any signal here which would suggest that there was some difference there.

Talking to the patients, frequently talking to the patients why they decide to discontinue study, not unusual in other causes, perceived lack of efficacy. If you're being on the study and you don't feel like you're getting clinical benefit, people may withdraw their consent.

I wonder if you have any characteristics, baseline characteristics of those patients who withdrew from the study in the treatment arm, and the placebo arm, and were they similar, or were there any differences at baseline in those patients.

DR. NIIHARA: Yes. Thank you for a very important question. In terms of withdrawal, yes,

in this particular study, 09-01, the treatment group have higher withdrawal rate at the 35 percent or so, compared to placebo group. However, when we did phase 2 clinical trial, although it was much smaller trial, we had a much higher dropout rate in the placebo group. When we looked at the reason for withdrawal, we found a number of sporadic reasons as was kindly presented by the agency and also by us, we couldn't pinpoint to any particular underlying reason to have a rate of withdrawal to be higher on one side or the other.

DR. NOWAKOWSKI: What about baseline characteristics of those patients? Were they the same?

DR. NIIHARA: Yes, they --

DR. NOWAKOWSKI: The patients withdrawing from those arms. Do you have any data to support it?

DR. NIIHARA: Yes, let's see. The baseline data on the patients that withdrew, one that we have is the number of crises that the patient had up to the point. But in terms of baseline crisis,

we have general baseline characteristics, but if you're referring to those patients who were having more crisis or less crisis that you had mentioned in the earlier question, we do not have them.

DR. NOWAKOWSKI: Okay. Thank you.

DR. NIIHARA: You're welcome.

DR. RINI: Okay. Dr. Rieley?

DR. RIELEY: Three relatively quick questions. The secondary endpoints that were described, the other relevant things, it's notable the consistency. Were these endpoints predefined or are these ones that we looked at afterwards?

DR. NIIHARA: Yes. The sickle cell painful crisis was definitely predefined, and the hospitalization was predefined. Acute chest syndrome was predefined in the sense that it was part of an adjudication process for sickle cell painful crisis. Other indications were considered but they were not predefined as a secondary analysis.

DR. RIELEY: Okay. Is the central adjudication committee, were they blinded to

treatment assignment?

DR. NIIHARA: Yes.

DR. RIELEY: Okay. Then my last question, can we assume that the site that had scientific misconduct was not a part of the 09-01 study?

DR. NIIHARA: No, not at all.

DR. RIELEY: Okay.

DR. RINI: Dr. Menefee?

DR. MENEFEE: Thank you. Just a couple of quick questions, two, maybe three. The first relates to the stratification regarding hydroxyurea. It was clear that there was a subset that were not on hydroxyurea when the study started, but were those patients allowed to receive hydroxyurea once the study had started?

DR. NIIHARA: Yes. In our entry criteria, those patients who stayed on hydroxyurea, they had to be on hydroxyurea at least for 3 months prior to entry and had to be stable, with intent to stay on hydroxyurea for the 48-week period of observation.

DR. MENEFEE: But what about the patients that were not getting --

DR. NIIHARA: Oh yes, patients who were not on hydroxyurea were not allowed to start hydroxyurea during the study.

DR. MENEFEE: Even if it was clinically indicated, they would not --

DR. NIIHARA: Yes, they would withdraw from the study.

DR. MENEFEE: Do we know how many patients were withdrawn specifically?

DR. NIIHARA: No, there were none that had to be started on hydroxyurea. However, the other side, we did have one patient who enrolled with hydroxyurea, but because they came off of hydroxyurea, we had to withdraw the patient from the study.

DR. MENEFEE: Okay. Second question relates to the slide you showed earlier, CM-7 that showed the survival data. I think you may have already answered this question from Dr. Rini, but I was curious, did you have any survival data from either study, overall survival?

DR. NIIHARA: Yes, we do not have overall

survival data from this.

DR. MENEFEE: Thank you. When I look at those numbers, and from other data that you've already presented, patients clearly that had greater than 3 crises, you can see it from the slide, had a worse prognosis, worse survival, versus the patients that we don't really see that much difference between 1 or 2. Are you able to show the data specifically for patients that just had 3 or more versus those that had 2?

DR. NIIHARA: In terms of survival?

DR. MENEFEE: No, in terms of the benefit from the L-glutamine for the prespecified endpoints. Can you basically look at a subset of those that had greater than 3?

DR. NIIHARA: May I -- are you referring to the baseline crises?

DR. MENEFEE: The baseline sickle cell crises.

DR. NIIHARA: Yes. We don't have that data.

DR. MENEFEE: Okay. Thank you.

DR. RINI: Okay. Dr. Uldrick?

DR. ULDRICK: Thanks. I had some questions about how you dealt with dropouts and some of the secondary analyses that were presented -- started on slide 21. I guess for the time to event for first and second crisis, how did you deal with the dropouts?

DR. NIIHARA: I would like to ask Ms. LaMoreaux to answer this statistical question. Excuse me, Dr. Wei will answer the question.

DR. WEI: Lee Jen Wei from Harvard, and I'm a professor at School of Public Health. Sir, may I ask are you interested second event or the entire recurrent event.

DR. ULDRICK: I guess I'm asking did you censor the patients at time of dropout to do these curves or were there other methods to develop these curves here?

DR. WEI: Yes. As usual, the patient dropout, we treat it as a censored observation. It's most like a cancer study; exactly the same way.

DR. ULDRICK: Then a follow-up on a similar

question on the secondary outcomes for hospitalizations and for acute chest syndromes. Did you impute rates for patients who had dropout or were these actual rate? How did you deal with the missing patients for these secondary analyses?

DR. NIIHARA: Ms. LaMoreaux, would you --

MS. LAMOREAUX: We used the same imputation as for the primary, except for acute chest syndrome, and that one, there was so many zeros that it would have been the same if we had imputed or not imputed.

DR. RINI: Dr. Cole?

DR. COLE: I'd like to ask the sponsor about one of the slides, CE-19. I wanted to ask about the detail regarding these analyses, where you say imputation method and then you put multiple -- is that multiple imputation; is that what that means?

DR. NIIHARA: Yes. Professor Wei, would you be able to elaborate?

DR. WEI: Professor Cole, the multiple imputation means you build the model first, then you actually starting imputing the incomplete, each

patient, many, many times. So each time you complete observation and you complete a -- say, for example, 230 patients, that's 1 dataset. So we're imputing 300 dataset in fact, then combining the results all together. That we call a multiple imputation.

DR. COLE: I was wondering if that multiple imputation model, what variables were used to do that prediction you talked about. In particular, was the baseline SCC variable used to predict --

DR. WEI: No, sir. We didn't. We only use HU usage and also the region, because that's two factors weren't prespecified. So we didn't use other baseline variables in the imputation model.

DR. COLE: In contrast, if I could ask for the FDA slide 27. This FDA slide lists a multiple imputation model at the very bottom row of the table, and this one clearly talks about what adjustment factors were used, and they included the baseline crisis count.

This analysis is the one I think is probably most conservative, but I wonder if inclusion of

these other covariates or predictors could explain the fact that this analysis is quite different from the other ones that were shown in your slides.

DR. WEI: Professor Cole, you want to ask me my opinion or --

DR. COLE: Well I'm just wondering why the results of the multiple imputation analysis done by FDA differ so much from the multiple imputation analysis done by the sponsor?

DR. WEI: Okay. This is my opinion. I cannot speak on behalf of FDA. I wish I could. Professor Cole, if you look at the dataset, it is not a large dataset. If you actually build a model with so many variables, I'm not so sure the model is stable. I have no idea we're seeing those -- so many variables included, how the model fit the data. That's the first.

Second, honestly, I don't understand the 0.91, how FDA can get this number. We still cannot duplicate FDA was doing, but that's because our limitation, we don't understand.

DR. COLE: Just to follow-up on that, the

point was asked about baseline characteristics and whether they differ between dropouts and non-dropouts and completers. One of the variables I think is probably predictive, is this baseline SCC, but it was noted that we don't know whether there was a difference between dropouts and non-dropouts on that particular variable, and it could be very important to include that kind of variable in a multiple imputation model, and that might completely explain why there's a different result here from the FDA imputation model.

I just wanted to make that point, that it might be more important to include those kinds of variables in the imputation.

DR. RINI: Dr. Burstein?

DR. BURSTEIN: First I want to congratulate the investigators. I don't take care of sickle cell anemia on a daily basis, but I clearly remember being a house officer caring for these young people who were so desperately sick, and they would show up in the emergency room and they would tell me how to manage them, because they'd been

there so often, they would say, "You need to put on oxygen and hydration, and pain medications, and give a transfusion," and I was grateful for their help and I'm glad to see that there may be some progress here.

I had a really silly question, which I will start with. How is this L-glutamine different from the stuff you buy at Whole Foods or GNC centers? I mean obviously the dose looks to be a lot bigger. Is it otherwise the same physical product?

DR. NIIHARA: No, it is not, but I'll have Dr. Stark to elaborate on this.

DR. STARK: I certainly hope that this will answer your question, but if our drug is FDA approved, our L-glutamine will be a prescription drug with an Rx label per se, and would be produced under the same regulations as any given prescription drug, and it will not be an over the counter type drug, nor will it be a nutritional supplement.

DR. NIIHARA: If I may add one more point to this in terms of quality of this L-glutamine, in

order to produce what we call drug master file grade glutamine, it has to go through several more process than just to incubate bacteria with sugar to produce glutamine. This purification process is quite difficult. Because of this, the quality -- the product that we are providing, it would be quite different than what you may have at a nutritional supplement store.

DR. BURSTEIN: Different question then. You show very compelling data I think on frequency of hospitalization and number of hospital days. Are there data on the acuity of the hospitalization? We talked a little about ICU stays. There's lower data of transfusions.

Is that just a function of how many hospitalizations they get, I guess is really the question, or is actually that their faring better during the hospitalization episode?

DR. NIIHARA: Yes. When I took the data all together and look at them together, it seems like -- there appears to be even if a patient does have crisis, the chance of being hospitalized are

less, just because we reduce the rate of crisis by 21 percent, but we reduce the rate of hospitalization by 33 percent.

When it comes to ICU, we don't have direct data on ICU, but acute chest syndrome is almost always sent straight from emergency room to ICU. Acute chest syndrome, although relatively speaking there are fewer events, there was over 66 percent difference in the occurrence. By reducing from this, most likely the ICU stay is going to be less.

So even if they had to be hospitalized, the chance of going to ICU, based on this data only, is likely to be less. But other than that, we have not looked into these data together. We collected these data completely separately.

DR. BURSTEIN: And finally, as it relates to slide CE-21 and CE-22, I want to understand the second crisis episode. Just to be clear in my own mind, the patients who had 1 crisis continued on this product post-hospitalization or recovery, and then still in the 48 week window or afterwards had a delayed time to the second; is that correct?

They did not stop the product. In cancer studies, we usually stop the product at progression or event, but that would not have been the case here.

DR. NIIHARA: Yes. Thank you for the question. Yes, exactly correct. The patient stayed on the medication whether they had crisis, or hospitalized, or had acute chest syndrome, if they can continue.

DR. BURSTEIN: For the clinicians amongst you, is the implication of the CE-22 data, which is time to second crisis, does that mean that in the real world you would be recommending this well beyond the 48 weeks --

DR. NIIHARA: Oh, yes.

DR. BURSTEIN: -- were there to be a label. I mean this would be essentially an indefinite course of therapy for these patients.

DR. NIIHARA: Yes. Just like hydroxyurea is recommended chronically for indefinite period of time, that is our intention.

DR. BURSTEIN: The 48 weeks was the study structure --

DR. NIIHARA: Right.

DR. BURSTEIN: -- but not what you would expect in routine clinical practice.

DR. NIIHARA: Yes. Thank you.

DR. BURSTEIN: Thank you.

DR. RINI: Dr. D'Agostino.

DR. D'AGOSTINO: Somewhat continuing Dr. Cole's question, I was very struck by the sensitivity analysis, and I wasn't, as was mentioned a moment ago, I wasn't clear on what was driving in terms of the variables for the sensitivity analysis. Was there a discussion before the data was collected or in the protocol with the FDA on what would make a sensitivity analysis, or what a sensitivity analysis should include? Oftentimes, I'm on the other side of the table. We anticipate missing data and we'll have the FDA tell us, you put the worst value in as the value of variable of the sensitivity analysis and you go back and forth.

These are such different results, that it looks like you must be handling different data as

opposed to -- so was there no discussion? Well, the FDA sees what they did. Is there any discussion or any mention from the FDA in terms of what was done by the sponsored in terms of acceptability for variables, because it's just so striking that these results are so different.

DR. NIIHARA: Yes. First of all, I want to recognize FDA for helping us throughout two decades to work on this, and they have given us a number of guidance, which you can see in our documents. In order to accommodate the stratification and the probable missing data, we had agreed on this CMH modified ridit.

Beyond that, we did discuss about having different ways of looking at this, without dependency on the missing data. Therefore, we had used NBR, and of course, FDA had gone further for us during this whole process after new drug application was submitted, and we followed some of those things that they had done to analyze our data, including multiple imputational method. Dr. Wei, would you --

DR. D'AGOSTINO: What's driving the difference or what's generating the big difference between what the FDA has and what you've submitted?

DR. WEI: Professor D'Agostino, first allow me to say this. In the NDA, the sponsor indeed has so-called a two specified imputation methods, which we notice the results are pretty consistent.

Then after the sponsor submit NDA, FDA was very kind to inform us they have done some exploratory imputation, and particularly emphasize the multiple imputation. That's what we -- our group actually did some, so-called, sensitivity analysis.

But sir, if you really look at the results, only one sensitivity analysis done by FDA, which is different, right, 0.91. Otherwise, the other two actually is very consistent with ours. Sorry to say this, the third one, we call the bad one for us, 0.91, we still don't know what's going on.

DR. D'AGOSTINO: But they're confident, I mean their p-values aren't going to come out to be 0.0025. I mean they're -- the first one's hovering

with confidence interval of 0.64 to 1.01, and then the second one to 0.99. I mean these aren't going to be --

DR. WEI: Sorry, sir --

DR. D'AGOSTINO: The p-values you get for your sensitivity analysis are strikingly different than what I think with p-values that the FDA would be getting.

DR. WEI: Well, look at this so-called risk reduction, right -- 0.80, first one 0.77, the last one 0.91, right? The confidence intervals that's no surprise, because our study size wasn't thousands of patients. If you look at this point estimating, only the last one, it's a little inconsistent.

DR. D'AGOSTINO: But do you think your confidence intervals would be hovering around 1, if you made the analyses -- presented them as confidence intervals also?

DR. WEI: You're talking about our sensitivity analysis?

DR. D'AGOSTINO: Your sensitivity analysis.

DR. WEI: Our sensitivity analysis are very impressive. If you allow me to pull the slide up again, the forest plot. Professor D'Agostino, if you look at the confidence interval, everything on the upper bound is on the left-hand side of 1.

Look at the right-hand side, the negative binomial, the upper bound also less than 1. That means they're okay.

We did this as 300 sets of imputation. Our result is actually very consistent. They're pretty much around 0.7 risk reduction, whatever you want to call, odds ratio.

DR. D'AGOSTINO: It's just that you're getting results different than the FDA. You have the same set of data, so you're doing something different, bringing in different variables or something else.

DR. WEI: Professor D'Agostino, if you'll allow me to just have 30 seconds here. What we did is a very simple idea. It's a very standard multiple imputation.

DR. D'AGOSTINO: And these were all

prespecified?

DR. WEI: It was not. It's all exploratory, including FDA's. Yes, those are all exploratory.

DR. D'AGOSTINO: Keep searching, you'll --

DR. WEI: No. Well, we didn't search that much I mean.

DR. D'AGOSTINO: I follow this. Thank you.

DR. RINI: Ms. Preusse?

MS. PREUSSE: Not sure --

DR. RINI: We have a comment from FDA?

DR. SHEN: This is Yuan-Li Shen, statistical team lead for this application. I just want to make one comment about FDA's sensitivity analysis. For those non-completer, we did not try to fill that with data. The only thing we did, is just do the multiple imputation for those non-completers with missing data. I guess our analysis are different from the applicant's analysis.

DR. D'AGOSTINO: Could you say that again? What are you doing different?

DR. SHEN: Our analysis, we did not try to fill up the data for those non-completers.

DR. D'AGOSTINO: Non-completers -- so you ignored the non-completers.

DR. SHEN: It is included in the analysis, but we didn't try -- if the patient just at 24 weeks, we did not fill that up to 48 weeks. So we led there --

DR. D'AGOSTINO: You took whatever they had at that point?

DR. SHEN: Yes.

DR. RINI: Vali, you have a follow-up question?

DR. PAPADIMITRAKOPOULOU: I actually have a follow-up question and comment, because this discussion came up. It is a different analysis, because you're excluding the 24 patients, the FDA does. They have an N of 206. And what is also remarkable, and maybe I would like to hear the sponsor's comment on this, the group that is dropping out preferentially from the L-glutamine arm, is the patients that didn't receive hydroxyurea.

I think I read in the package that almost

half of the patients who were not taking hydroxyurea at baseline, withdrew from the L-glutamine arm. That can mean a number of things, and maybe I would like to speculate. Is this a less risk group? Is this a less severe disease? Is this by choice? Does this mean something about the population that is dropping out, and would that affect the results?

DR. NIIHARA: Thank you for the comments, and I would like to make many speculations on the patients who were not on hydroxyurea. It could be due to patient's choice, or likely in some cases, yes, the providers like us, we tend to recommend more emphatically to the patients who have a larger number of crisis, so that may be a factor.

However, when we looked into the hydroxyurea issue on the L-glutamine arm, are we really looking at the subset of subsets, and the difference in the dropout rate with hydroxyurea, on either glutamine arm or placebo arm, we really cannot make out any major difference between them. I mean, although what you said is absolutely correct.

DR. RINI: Okay. Ms. Preusse, did you have a comment?

MS. PREUSSE: I have a quick question. Courtney Preusse, patient representative. I heard the FDA say that there were no noticeable differences in SAEs by demographics, but I heard Dr. Niihara, excuse my pronunciation, say when looking at slide CS-6, that AEs occurring more frequently in those who received L-glutamine were primarily in the pediatrics groups, and those adverse events are more frequent than those who received placebo.

Then to add to that point, if you look at slide CE-20 -- sorry, to hop around -- but I also notice that those less than or equal to age 18, so minors, also the whatever you call it, the dot that is closest to the null effect, closest to 1.0 is in that group.

I'm just wondering if the company has considered dose modifications by age or that perhaps those who are not adults are experiencing more adverse events.

DR. NIIHARA: Thank you. The adverse events that I referred to for pediatric patients were events that really did not require any medical intervention. These were reported as mild pain in arms or legs type of things. That's what I meant by this.

Yes, it is very important that you did note the adolescent group to have rate ratio to be slightly toward 1.0 compared to the other group. This group is a difficult group to study. We did look into many factors, because it just appeared that this group had many different factors.

Nothing really helped us really explain this, except for this one fact. Could you get the slide up on the efficacy on the adolescent group? Not the forest plot, but efficacy by the rate.

I just wanted to bring this out. Could you focus on the rate which is 2.54 for 5 to 12 years? This is the rate of crisis; 3.95 for what we classified as adolescents 13 to 18; and the adult 18 and older the rate is -- I mean there is a variability, but essentially the same.

But then you look at the rate on placebo side, 4.85 for very young group, and then older group is 5.14, but when we look at the adolescent, it's 2.70 and the only thing I can say is that this is right now, as far as we're concerned, it's an anomaly and we cannot come up with any explanation.

Then when you take all these numbers and do the rate ratio, because rate ratio in 5 to 12 years is 2.54 divide by 4.85, it's going to favor L-glutamine. But you do the rate ratio on adolescent group, then it actually essentially reverses. But the rate of response or the rate of crisis stays about the same. Well, I will stop here. Thank you.

DR. SETSE: I'd like to make a comment about that, please.

DR. NIIHARA: Yes. Thank you.

DR. SETSE: For the safety review done by the FDA, there were some adverse events which occurred at a higher frequency in patients less than 18, compared to greater than 18 in the L-glutamine group. However, overall we did not

think this was significant, especially also because the same trend was seen in the placebo group where a greater number of adverse events occurred in the less than 18, compared to greater than 18.

DR. RINI: Dr. Fitzhugh, do you have a question?

DR. FITZHUGH: Yes. This was not presented today, but my understanding from what I read before, was that one of the investigators reported one of the crises as being related to glutamine, and I just wondered if you had any comments about that?

DR. NIIHARA: Yes. I am not aware of this. Would you repeat the question for Dr. Stark?

DR. FITZHUGH: Yes. From what I read, my understanding was one of crises was reported as being related to the glutamine. I was just wondering if you had thoughts about that. I can try to find it.

DR. STARK: That was taken directly from the case report form. It was an investigator assessed adverse event and once it's checked that way, we

have taken that record and carried it over to our data. We do not have any more additional information on that.

DR. RINI: Ms. Miller?

MS. MILLER: Did you find that in the non-compliant group that it could have been the ones that who were supposed to stay on their hydroxyurea, that they got off of it because they didn't understand that they were supposed to stay on it and they might have gone into the hospital because of that?

DR. NIIHARA: That's a possibility, but I do not have an exact explanation on this one, but thank you for the thoughts. Dr. Stark has --

DR. STARK: That patient elected to come off of hydroxyurea. That was an elective.

DR. NIIHARA: Thank you.

DR. RINI: Okay, are there other questions or comments for the presenters? Dr. Menefee?

DR. MENEFEE: Just a question and a comment. One building on a comment that Dr. Burstein mentioned a few moments ago regarding the potential

use of this drug chronically, beyond the parameters in the study. Do we have any long-term toxicity data for patients that have been on this agent for years? I know there's an improved indication already for short bowel syndrome, so I don't know if we have data available that we can see, is there any difference in safety signal for individuals that have been on it for longer periods of time? Is it also the same dosing in both populations?

DR. NIIHARA: Yes. Dr. Stark, would you be able to --

DR. STARK: This study, besides our phase 2 and phase 3 trial, we have not gone beyond the 48-week period. To your point, the short bowel syndrome, that is used for a 16 week course of therapy, so it's not a long duration. Therefore, we do not have data beyond approximately a one year period of time.

DR. MENEFEE: Okay. Thank you. The second is really just for my edification. I also do not treat patients with sickle cell with any regularity, but I know there have been improvements

in the use of opioids and other analgesics in this patient population over the years, and there could probably be a great deal of variability in the use of these agents among different centers and practitioners.

First, and maybe this is best answered by Dr. Gordeuk and Dr. Smith, in your practices has the more aggressive use of these analgesics reduced hospitalizations and ER visits? If so, do you think that could have impacted one of the endpoints of the study?

DR. SMITH: Thank you for making that observation. There has been a slow uptake, but a steady uptake of the use of opioids more often, and for longer periods of time in patients with sickle cell disease. That has happened in one observational study. More often for patients who are on hydroxyurea; those patients are using opioids more. So it's a confounding for indication by treatment.

Other than that, for this particular study, I don't believe that there would have been a

differential effect, because of differential use of opioids between arms, and I don't believe that in this particular study the use of opioids would have been significant enough to have reduced a hospitalization or two because of use.

DR. MENEFEE: Was that data recorded in terms of opioid use in each patient?

DR. SMITH: There was no data on opioid use recorded in this study.

DR. RINI: Are there any other questions for the sponsor? There's no other questions, we'll take a 15-minute break now. I'd like to remind the committee to not discuss any part of this application during the break, and we will resume at 3:25. Thank you.

(Whereupon, at 3:11 p.m., a recess was taken.)

Open Public Hearing

DR. RINI: If people could take their seats, we are going to get started.

Both the FDA and the public believe in a transparent process for information gathering and

decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes it's important for you 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 the sponsor, its product, and if known its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance to this 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.

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 for this open public hearing is 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, and thank you for your cooperation. If we could have speaker number 1 step up to the podium and introduce yourself. State your name and any organization you're representing, for the record.

MS. FOX-RAWLINGS: Thank you for the opportunity to speak today. My name is Dr. Stephanie Fox-Rawlings. I am a senior fellow at the National Center for Health Research. Our research center analyzes scientific and medical

data to provide objective health information to patients, providers, and policy makers.

We do not accept funding from drug or device companies, so I have no conflicts of interest.

Sickle cell disease can cause serious health crises. Patients deserve and need new treatments. This requires high quality clinical trials to demonstrate whether new treatments are effective and safe.

When many patients that start a study, drop out before it is completed, it is impossible to accurately evaluate the benefits compared to the risks. The sponsors used an excellent study design. It was randomized, double-blind, placebo-controlled, and multicenter.

However, the difference in the number of sickle cell crises between drug and placebo arms may be modest, this could still be a meaningful improvement, but the disproportional dropout rate makes it difficult to be confident whether the drug is effective.

The briefing documents from the company and

FDA do not discuss the methods that the sponsor used for patient retention. There are many reasons why patients drop out of studies, but it usually comes down to one issue. The incentives don't outweigh the disincentives for patients to participate.

Disincentives can be adverse events or they could be lack of benefit, or they can be logistical. Maybe participation is too time consuming, requires going somewhere that is inconvenient, or perhaps the participants need childcare for children or family.

Often participation may be expensive if it requires arranging transportation, paying for parking, paying for childcare, or taking time off from work.

To make a study successful, sponsors need to make it easy for patients to participate and have incentives that are attractive enough to encourage participation. Most of the patients who dropped out did not say that adverse events were the reason, but the data presented don't provide a good

explanation.

Perhaps they dropped out because their sickle cell symptoms were worse. Perhaps financial incentives were insufficient. We don't know and that means we can't conclude whether the drug has a meaningful benefit.

FDA should approve new treatments based on clearly demonstrated evidence of efficacy and safety. This requires high quality clinical trials where most patients stay in the trial. FDA should not approve a drug with questionable benefit when the poor retention rate raises concerns about safety or efficacy.

Thank you.

DR. RINI: Thank you. Speaker number 2?

DR. BELLEVUE: Good afternoon. My name is Rita Bellevue. I am a physician, adult hematologist, who also had training in pediatric hematology. I retired recently from New York Methodist Hospital. I have no financial relationship with the company to disclose, although my travel expenses for this trip were paid for by

Emmaus.

I was a principal investigator for the L-glutamine study. My first hematology attending position was at Interfaith Medical Center where I had my training. I was a staff physician in the division and I was responsible of the sickle cell clinic, which was a combined program for newborns, children, adolescents, and adults with sickle cell disease.

Shortly after I started, I was called for a 20-year-old young lady with sickle cell anemia SS, just admitted to the medical floor. Her mother was crying loudly, and said, "This may be the time she's going to leave me." Her daughter was in severe pain.

I went to speak with her and tried to reassure her without much success. The next morning I sat with her and learned she did not have a hematologist for her daughter, who had repeated admissions. All she knew about sickle cell was that people do not live beyond the second decade.

I told her about the clinic, and following

discharge her daughter began coming regularly, receiving complete care with psychosocial support and education about sickle cell. Her mother sometimes came along where she took the opportunity to learn more about the disease.

Patients with sickle cell disease face many problems. The frequency interval of a pain crisis are unpredictable with periods of pain and periods of normalcy. I can recall many times seeing a patient in the emergency department, very often a young teen appearing well-groomed from head to toe. They were ready to go to church, a wedding, or to a party, when the pain started. I cannot count how many times a young patient missed high school graduation or even a family or friend wedding.

There are many complications and comorbidities associated with the disease. Chronic fatigue, stroke, leg ulcers, acute chest syndrome, chronic back pain, hip and shoulder pain, and other progressive organ damage to kidneys, lungs, and eyes, just to name a few.

We should not forget iron overload, one of

the many complications of repeated blood transfusion. Our world as care providers is very important, and individuals with sickle cell disease have to be seen in the context of their life and their interaction with other people.

Often there is emotional stress in the family. So many times I have seen patients admitted for a pain crisis, which appeared simple, and which in a few hours they were transferred to intensive care because of severe acute complications. Sometimes he or she didn't make it.

Often I have seen patients who fear death with each admission; reassurance and words are important. It is very difficult to understand the burden of sickle cell for our patients and their families. Some of the young patients develop anxiety, because they are missing school, or they try to hide their disease and they don't people to know, even their friends.

Patients and their families are very eager to know about any progress made in the field of sickle cell disease, including clinical trials. It

is important that we make every effort to improve the quality of life of our patients, help with their stress, and negative thinking.

Inadequate management results in decrease in quality of life, early mortality, missed school, or other life activities; disability from chronic pain, and misuse of opioids. Many patients particularly young adults, do not have access to comprehensive care, and use the emergency department for care.

Many patients are reluctant to go to emergency department because of the attitudes of some physicians and nurses towards patients with frequent or recurrent pain. Our patients are looking, not only for a cure, but for a treatment which will stop the pain and the progression of the disease.

Something that can prevent one less trip to the emergency room will mean so much to them. Thank you.

DR. RINI: Thank you. Speaker number 3?

MS. GOUGIS: Hello. My name is Juanita

Gougis. The applicant has paid for my travel, but I have no financial ties to the company. I am 28 years old and I was diagnosed with sickle cell disease when I was two. It has been very difficult for me to come to terms with my reality that I would be in pain and hospitalized very frequently and would never have a normal life.

Nobody even knows about sickle cell. The sickle cell community is small. Two of my friends that I've known for a very long time recently died. One of them, Courtney, was about to graduate UC Berkeley, and now she is no longer here. It was shocking to me. We are trying to look forward to the future and there's nothing to treat us, just medications that damage our organs and we are suffering.

Emotionally and socially, it has been a struggle. I felt like no one understood what I was going through and couldn't relate. Growing up I would try to avoid questions about my disease, but it was very hard for me to hide it when I would miss school once a month because I was having a

pain crisis.

I've seen the hospital too many times. Most people have been to the hospital once, when they were born. For me, it's about 12 times a year. Every three or four weeks, I have to put my entire life on hold. It's always unexpected, yet the same.

I go to the hospital, wait three or four hours to be seen by a doctor in excruciating pain. Then I stay in a room staring at three walls in a tremendous amount of pain. I feel like there's no relief. It's depressing. It makes me feel like I want to give up, and I feel defeated.

After a week or more, once released from the hospital, I can go to work and do normal things. I love swimming. I also recently took up drawing. Both bring me joy and are stress relievers, but I can’t do those things in a pain crisis or after release from the hospital. The pain medication makes me unable to even sketch.

I feel like I'm in a daze, unmotivated to eat, walk, go the restroom, do anything. Things

that most people take for granted and do with ease is a hassle. I rely on my mom and sisters to get through recovery day. Sometimes I think I could function, but I can't.

Even back at work, I feel like I really can't get anything done. At my job, I'm the head lifeguard and help my boss with projects. When I'm sick for a week or two, I can't do those things. If I have a swim meet, I have to pretend things are normal, but I'm quiet, distant, and I have to be an actor for a while, and not let my team know I'm in pain or just got out of the hospital.

I tell myself mentally to shake it off. I coach a swim team and they don't know I have sickle cell, and I don't know how they would react to their coach being sickly and unhealthy.

In April, I went to Canada with some friends. It was supposed to be a nice enjoyable time for me, but I had a pain crisis. I was in another country, I needed to go to the hospital because things were getting really bad. This time, I had to stick it out. We spent all this money to

go away and I had a pain crisis. I had to sit on a long plane ride in pain. I look normal on the outside. I have a good poker face, but inside, I felt like my organs were falling apart.

When I got to the airport, I couldn't go home, or lie in bed, or unpack. I had to go directly to the hospital. I thought, seriously, I can get away from away from the hospital. I'm back here again. I can't escape my disease.

I am very blessed to have found Dr. Yutaka and participate in a clinical trial of L-glutamine that improved my life in so many aspects. I felt myself living a life I didn't think was possible. It gave me so much hope. When I was on the trial I had a lot of pain free days where I felt like a normal person. I took fewer medications and I didn't have to go to the hospital for almost a year. I even took up a sport that I've heard doctors say from a young age that I couldn't do, and that sport was swimming.

Every day when I go to a swim meet, I wonder about little things that most people take for

granted, like being able to take care of themselves. I wonder what it would be like to not worry about another pain crisis. I wonder about a life without the stigma that sickle cell patients face. I wonder what it would be like to be healthy in general. How is it to not have in the back of your head, or carry the weight that you're going to the hospital because you're going to be in unbearable pain.

When I go swim, I have to think about my health. When I eat something, I have to think about am I putting myself and health at risk. What is it like to not feel like you're a burden on the family, to not be pitied. It must be wonderful just to be normal, just to live. We need treatment now. Thank you.

DR. RINI: Thank you. Speaker number 4?

MS. VALENTINE: Hi. My name is Ashley Valentine and I have a Masters in Applied Sociology. I'm a clinical research coordinator for sickle cell disease at Children's National, and previously I was a policy researcher. I have no

financial ties with the applicant.

A little background. Sickle cell is the most common genetic disorder in the United States. It was discovered over a hundred years ago and the mortality rate since 1990 has decreased for pediatrics, but has increased by 1 percent each year for adults. That's contributed to the fact that we have limited care for adult patients.

We have drastic gaps in research, drug development, and therapies for people with sickle cell disease. As a comparison point here, people with cystic fibrosis affect about 30,000 people in the United States and worldwide it's about 70,000.

Between the years of 2010 and 2013, five drugs were approved for cystic fibrosis. During that time, three and a half times more funding was released.

In contrast, sickle cell disease affects about 100,000 people with the actual disease in the United States. Whereas 1 in every 13 African-Americans are carriers of sickle cell disease and we don't have numbers for the rest of

the ethnicities in the United States.

Across the world, over 250 million people are carriers or have sickle cell disease, and to date there are no drugs that have been approved specifically for sickle cell disease, except for hydroxyurea, which was designed for leukemia. That's over a hundred years. Researchers contribute that cystic fibrosis is a more fluent group than the sickle cell disease groups and we're riddled with burden and stigma.

Some stigmas we face are that in the emergency department, sickle cell disease patients have uncommonly symptoms when they come in with high pain. They have been guidelines released saying that you should be treating sickle cell patients when they present to the emergency department at the same level as you treat people with gunshot wounds to the head.

However, when we present to the emergency department, we wait 25 percent longer than the general populations and when controlled for just black people, we wait about 50 percent longer.

It's also been reported when surveyed the medical staff, that people believe that sickle cell patients are lying; that we're exaggerating the discomfort and that we're abusing drugs or manipulating the system, when in reality when people report these symptoms, it's because the patients are undertreated and undermedicated.

This is an example. This sign, we've all seen zero to 10, but in these pictures -- this is my brother, Marques, he's 33 and has sickle cell hemoglobin SS. He woke up with an 8 out of 10 this day, and in this picture he has a 6 out of hand pain.

I did primary research in the U.K. and I did qualitative research and interviewed 20 patients with sickle cell disease and out of my analysis, these are all the stigmas and stereotypes that they run into when participating in research, when going to the hospital, when going to school, when talking to family members.

One patient that I interviewed, she actually lost her brother from sickle cell and she developed

breast cancer later. She said, switch it from sickle cell to cancer and now everyone understands. Oh, she missed school because she's going through chemotherapy. It's a different label. When a label's understood, you're experiences are better, rather than when it's not understood, and this impacts our quality of life and is an extremely expensive disease.

In 2004, approximately $488 million were spent on sickle cell disease, and 70 percent of our population is on Medicaid and Medicare, because we can't work when our family members are sick, or when people with sickle cell are sick themselves.

In 2010, sickle cell had the highest readmission rates and there's severe unemployment in the sickle cell disease population, because adults can't maintain jobs and neither can their caregivers.

How this plays out in real life -- in 2015, my brother had one crisis, just one. He became sepsis in the hospital. He was hospitalized for six weeks. I came home from Europe. The cost of

his hospitalization was over $400,000. My mom blew through $480 of her FMLA and nearly lost her federal job. My dad was laid off. I came home from my professional job and worked remotely from his hospital room, to make sure no one killed him.

During that time, he was accused of being a drug addict twice, even though we were seen by the pain specialist and every single specialist in that hospital, so he discharged himself and we had to continue palliative care for four weeks after this one crisis.

Our house went into foreclosure. We pooled together all of our finances so we save our house, and our family was able to survive this crisis. This was one crisis and we're a middle income family and we all are working professionals.

This is very important to know, because sickle cell is one of the most misunderstood diseases. It's arguably the most common genetic disorder in the United States. We're here today discussing the first ever specifically drug designed for sickle cell disease, but this disease

has been around since 1910, and there has been no development or really much improvement for care in this patient population.

This is contributed, research says, to racialization of medicine, ethnicity, and stigma of this patient population. I thank you for the time to present today.

DR. RINI: Thank you. Speaker number 5 is --

MS. VALENTINE: Marques. My brother Marques was not able to attend and we have a bunch of medical professionals here. He has avascular necrosis in his hip and femoral had collapsed, but because he has open leg ulcers, he can't be operated on. So he recorded his presentation. I'll just be here doing the slides for him. So we can start that; I don't know who's controlling the audio.

(Video played - unclear audio.)

MR. VALENTINE: [Inaudible] attend today's meeting. I have no financial ties to the applicants. I'm 33 years old and live with sickle

cell anemia [inaudible]. Over the course of my life I've had multiple complications from sickle cell. I've also had multiple [inaudible] with bone and [inaudible] graft in the right knee, a [inaudible] in the left, and caught blastomycosis due to a weakened immune system caused by hydroxyurea and sickle cell.

I've had multiple hospitalizations for pain crisis. I've taken hydroxyurea to treat the sickle cell. It's other medications treating the complications from sickle cell, and not the disease itself. Blood transfusions are the only treatment that stop the sickling from happening.

However, I'm [inaudible] concerned about the stress and my heart. I [inaudible] blood transfusions, and had a total of five ports [indiscernible] over the course of my life. Two ports got infected, and one nearly killed me due to sepsis, not to mention transfusions consume [inaudible].

At my age and with my severity of sickle cell, I don't have many options to slow the

progression of the disease. I rely heavily on blood transfusion and hydroxyurea. However, I need more therapeutic options to treat the sickle cell.

When I am hospitalized because of a pain crisis, the world around me and my family doesn't stop. Each hospitalization requires a family effort to ensure I receive the best care. When we were young, not only did I leave school when I had a sickle crisis, my older brother and younger sister were leaving school, too.

My parents were just starting out and could not always find babysitters for Kevin and Ashley. My dad was fired repeatedly for missing work to care for them. My mom missed promotions and was threatened to be fired from her federal job because she stayed with me in the hospital.

Prior to the hydroxyurea and transfusions, I would stay in the hospital for weeks at a time. My mother would rarely leave me alone for fear that untrained medical professionals could end my life.

She even taught me that if a nurse tried to re-stick me with the same needle to roll on my

tummy and wait for her to leave work and access my Port-a-Cath.

We celebrated birthdays, Thanksgivings, Easter, and many other holidays at the hospital, which sometimes turned into a second home. Ashley even stopped by to take prom pictures at the hospital.

Apart from the medical struggle in sickle cell, I've run into a lot of social implications. When a medical professional doesn't believe in pain and accuses you of being a drug addict when you're sick and vulnerable, it affects your psychological well-being.

We don't want to be on the excessive opioid pills that make you sleepy and make your stomach hurt. I sometimes fight in pain until I can't sit upright anymore. I'd rather be at home, burdened with my dignity, than being accused of drug addiction in a hospital.

My parents struggle with these stigmas, too. My mother was actually removed from my bedside while I was admitted and was unknowingly brought to

a meeting with a family psychiatrist to be evaluated by Munchausen syndrome by proxy disorder, which is a form of child abuse that involves the exaggeration or fabrication of illness or symptoms by your primary caretaker.

In that situation, the medical professionals had not reviewed my medical records and accused my mother of being mentally ill and creating my complications from sickle cell disease.

During kindergarten, I only attended a month of school because of repeated sickle crises. Every time I had a crisis, I missed opportunities to learn to make friends. Ultimately, the school held me back a grade because of it.

My sickle cell progressed during my transition from pediatric care to adult care. I developed seizures from strokes and couldn't complete college. I also lost my license because of seizures. I only had one job due to repeated sickle crises and currently collect SSI and [inaudible]. People with sickle cell are told we won't live past age 30, but now I'm 33 and happy to

be alive.

I sat on a panel at the FDA sickle cell hearing in February of 2014. There I hoped that the pharmaceutical industry would develop a drug to treat sickle cell, not just the complications that break down our bodies.

It's a tough thing to acknowledge when your brain and spirit want to achieve so much, but your body won't allow it. I stay positive because I feel grateful for opportunities like this one, to advocate for sickle cell disease. We need more interest in our disease. Thank you.

MS. VALENTINE: Thank you.

DR. RINI: Okay. Thank you. Speaker number 6?

MS. BROWN: Good afternoon. My name is Mary Brown. I'm the president and CEO of the Sickle Cell Disease Foundation of California. The applicant has paid for my travel and lodging to attend this meeting today. However, I have no financial ties to Emmaus.

I am an advocate, and today I bring the

voices of thousands of individuals with sickle cell disease. We know that the identification of sickle cell disease in the United States, there has been only one FDA-approved drug, hydroxyurea.

We also know that this therapy is severely underutilized. Frankly, many adults are scared of taking it, because it is a chemotherapeutic agent, and they fear the unknown. Right now, there are no other options. L-glutamine may be that option and people with sickle cell disease deserve to be able to have other choices.

In a recent workshop with our sickle cell families, we asked, "How would your life be different if you had one less crisis a year?" Overwhelmingly they responded, it could mean life or death, and they meant that literally.

More specifically they expressed fewer days out of work, which would equal more job security. Fewer days out of school, which could mean graduating on time. Less anxiety about traveling and preparing and participating in other activities.

But the loudest statement that we heard was that they would have one less negative experience in the emergency room and dealing with providers that one, don't know much about sickle cell disease or anything at all; two, think they are drug seeking; three, and will not listen to them about their treatment and care.

Hospitalizations can be extremely stressful anyway, but for a person with sickle cell disease who has to fight for his or her medication, it's exhausting. We also know that when a crisis is over, there is a considerable amount of time to recover.

Being released from the hospital doesn't mean you are ready to go back to school or work right away. The recovery time can take days. For some, there is lingering effects from the pain medications, such as headaches and nausea. For others, there is a complaint of soreness in various parts of the body where the crisis may have started or traveled.

As an example, if the crisis started in

their legs, it may be difficult to walk for several days. Again, delaying a person's ability to get back to their normal routines. One less crisis may not seem like much for a person, but for a person with sickle cell disease, it could be life changing.

I ask you today to consider L-glutamine as an option for persons with sickle cell disease. If there are no harmful side effects, what would it hurt? And if there is a possibility that this therapy could bring a greater quality of life, why not?

Our families ask constantly, why aren't there any other medications we can take? But more importantly they ask, how close are we to a cure? People with sickle cell disease have been suffering, struggling, and dying in the United States for 107 years with only one therapy.

Now there is a possibility that L-glutamine may bring some relief, and positively impact the lives of people sickle cell disease. I ask yours consideration of L-glutamine to be an option.

To quote one of my clients, "One less crisis would be a gift from God." Thank you.

DR. RINI: Thank you. Speaker number 7?

MS. BLACKWOOD: Good afternoon. My name is Miren Blackwood and I work as coordinator for Interfaith Medical Center's sickle cell program in Brooklyn, New York. I also worked on the L-glutamine study.

I'd like to thank the committee to taking time out just to listen to and consider my story today. While Emmaus has paid for my travel and lodging, I have no financial relationship with the company.

Most people do not realize that it's very hard to convince patients already so burdened with their devastating chronic disease to get involved in clinical trials. Clinical trials in themselves demand more from the patient, such as additional visits, diaries, and phone calls.

Asking to do more work on top of an already difficult life, is sometimes asking a bit too much sometimes. I've spent my career working with

patients with sickle cell disease. For almost 25 years, I've been working with children and adults with sickle cell disease on clinical trials, and also serving as newborn screening coordinator.

I've seen these patients at their best, and I've seen them at their absolute worst. After working for such a long time with this population, these patients are now like family to me. I've been there with them, and their families, from birth to the grave.

I really struggled with which story I should share with you today. I didn't know where to start. I didn't know which story I should tell. How do I choose? I've seen these patients at their worst, when they're in the hospital in crisis, screaming out in pain, just asking, just not to let them die.

Just last week a 12-month old baby, who has been diagnosed at birth, was admitted with priapism. I'm not a physician, but I've never seen this in my 25 years. It was one of the most difficult things that I ever had to experience,

just watching that baby in excruciating pain. The baby had to endure a blood transfusion.

This was not just another child entering our hospital. This was a child of a 24-year-old woman, who also is a patient, who I have known since her birth, but she was not the one who brought her child in on this day, because she, herself, was in crisis and had to be admitted.

I have seen good. This past Tuesday I received a call from a mother, inviting me to her 22-year-old son's college graduation, which will be held on the 28th of May. I've known this young man since his birth. I was the one who informed his mother that her child had sickle cell disease. I can still remember her tears.

I remember his yellow eyes and his mother telling me he would get teased at school. I have witnessed firsthand, his struggles with sickle cell disease. This young man has received a full scholarship to NYU School of Medicine.

While I'm joyed to know that he has achieved all of this, I ask myself, will he become a doctor?

Will he make it? There are no guarantees. I'm happy, but I'm also concerned. I dream of what it would mean for these patients just to have just one less crisis. I'm left with these questions. Where do these patients go from here? What treatment or cures will be available for them?

After the L-glutamine study was unblinded, we had patients coming to us asking, "Where can I get this? When are we going to see it approved? When are they going to approve it?" It has clearly made a difference to some of the patients who participated in this trial.

I urge this committee and the FDA to consider treatment options that can prolong and improve the quality of our patients' lives. Thank you.

Questions to the Committee and Discussion

DR. RINI: Thank you. The open public hearing portion of this meeting is now concluded and we'll no longer take questions from the audience. The committee will turn its attention to address the task at hand; that is the careful

consideration of the data before the committee, as well as consideration of all the public comments we just heard.

We'll now proceed with the question to the committee and discussions of that question. I'd like to remind the public observers that while the meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

The question at hand today is: based on the available data presented and discussed, is the overall benefit-risk profile of the L-glutamine for the treatment of sickle cell disease favorable?

I'll ask the committee if they need any clarification of the question or just discussion of the question in general.

(Pause.)

DR. RINI: If there is not further discussion on this question, we can now begin the voting process. We'll be using an electronic voting system for this meeting. Once we begin the vote, your buttons will start flashing, and will

continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked in. The vote will then be displayed on the screen. The designated federal officer will read the vote from the screen into the recorded.

Next, we will go around the room and each individual who voted will state their name and vote into the record, and you can also please discuss and state any reason why you voted, if you did, if you want to, which is encouraged.

Please press the button on your microphone that corresponds to your vote. You have approximately 20 seconds to your vote. Press the button firmly. The lights will continue to flash. Again, if you're unsure of your vote or wish to

change, please press the corresponding button before the vote is closed.

(Vote taken.)

DR. TESH: For the record, the voting result is 10 yes, 3 no, zero abstentions, zero no votes.

DR. RINI: Now that the vote is complete, we'll go around the table and have everyone who voted state their name, their vote, and if you want to, please state the reason why you voted as you did. We will start with Dr. Menefee.

DR. MENEFEE: Michael Menefee. I did vote no. This was a very difficult vote for me. Again, would like to echo comments made earlier in terms of commending the study sponsor for doing the study in this disease that is undertreated in a patient population that has been historically underserved.

That being said, I still have significant concerns regarding the statistical analysis. Others will probably speak to that in greater detail. I was also bothered by some of the confounding factors, which made it unclear to me whether or not the drug was providing the benefit that some of the patients

were receiving.

I think there was a clear signal of activity with this agent, but I also think that there can be better design studies that answer the question more definitively. There were also questions regarding potentially longer, more chronic use of this drug and implications of that, that neither study addressed. Those were my concerns.

DR. RINI: Thank you. Dr. Fitzhugh.

DR. FITZHUGH: I take care of sickle cell patients every day, and so I know what they've gone through and I completely support everything that's been said. I have some minor concerns about the statistical part of it, but all of the data went toward the potential benefit, and the risks seem very low to me. That's why I voted yes.

DR. RINI: Thank you. Ms. Miller.

MS. MILLER: Because I know that 48 weeks is a long time to not have any complications or to have to go into the hospital, and I understand that some of the non-compliance could be because of patients going in and out of the hospital in that 48-week

time.

Because I know a lot of times patients will go into the hospital saying it's a pain crisis, but it might be avascular necrosis, it could be problems in their liver, their kidney, but they all say it's pain to them, and it's a crisis to them.

So I believe that this time is needed to have something else for these patients. They've been waiting too long. I've been waiting too long. I think it's time, and that's why I voted yes.

DR. RINI: Thank you. Ms. Preusse?

MS. PREUSSE: I also voted yes. I noted during the earlier discussion that there were differences in the statistical analyses, and the perceived benefit from this particular treatment when comparing the FDA analysis to the drug company's analysis, but both showed benefit. I didn't hear anyone say that there wasn't a benefit.

The very first presenter said, every life improved by this medication makes such a difference in this patient population, because treatment options are so few and far between. That really stuck with

me. He said it in the first five minutes, the very first presenter, and that really -- it struck me.

It was further driven home by all of the anecdotal stories and I just want to thank the audience members for having the courage to share their very personal stories and teach us more about this disease, and those who suffer silently with it. Thank you for everybody who stood up; thank you.

DR. RINI: Thank you. Dr. Uldrick.

DR. ULDRICK: Thomas Uldrick. I also voted yes. I think that, again, I'd like to commend the sponsor for taking on this study. It's an important study in an undertreated disease, and I believe the decreased number of crises is an important endpoint.

It was a very difficult vote for me, because of the issue of differential dropout between the study arms. What led me to vote yes was the positive effect by both the sponsor and the FDA's proportional rate of sickle cell crises supported by the exploratory endpoints of differences in time to first and second outcome, and also differences in acute chest syndrome, which did not seem to be affected by

dropout.

DR. RINI: Thank you. Dr. Cole?

DR. COLE: Bernard Cole. I voted no, for many of the same reasons that Dr. Menefee mentioned. The limitations resulting from the differential dropout -- as a result of those limitations, it's not clear whether patients at higher risk of an SCC event might have disproportionally dropped out of the L-glutamine arm. I saw this as kind of a severe limitation.

We heard a lot about imputation analyses and many different imputation analyses were provided, but it's not clear whether any of them -- or at least it wasn't clear to me -- whether any them is actually adequate for dealing with the possibility that the dropout might have artificially shifted the risk profile of patients on the study in favor of the L-glutamine arm.

I note on the positive side that under relatively strong assumptions about the missing data mechanism, the observed benefit with L-glutamine is robust to the analytical techniques that were used.

The benefit persists across a variety of secondary endpoints. That made the vote very difficult for me.

I especially appreciate as well the sponsor's commitment to address the critical unmet medical need that sickle cell disease presents. My hope is that the sponsor can more thoroughly address the limitations of this pivotal trial with the FDA.

I would also like to thank the public speakers for sharing their very moving stories.

DR. RINI: Thank you. Dr. Burstein.

DR. BURSTEIN: I voted yes, and I'm struck by several things. First, there was no concern over toxicity with use of this agent, which means that all I needed to do was convince myself there was reasonable likelihood of clinical benefit, which I thought there was.

Secondly, there were two randomized trials that they could present; a randomized phase 2 study and a randomized phase 3 study. Methodologically, the existence of a corroborative randomized trial is one of the strongest overall supporters of data validity that I am aware of. The fact that these

showed qualitatively very similar results, I thought was extraordinarily robust under the circumstances, and warranted strong consideration of approval.

Third, I thought that what I took away as a one fewer hospital visit per year was a clinically compelling benefit for any individual or family or hospital that might be caring for patients with sickle cell disease.

I couldn't follow the complex statistical analyses to the degree I wished I could have, but with regard to the dropout rate, I'm really struck that this is a group of individuals who are chronically ill, who are young people, teens and 20s, who are spending a hugely disproportionate amount of their life in the medical care system, and who have had a tremendous burden imposed on them by their diseases, as well as by widely understood socioeconomic differences in who gets sickle cell disease in America.

In contrast to our discussion this morning of a group of people who were perfectly healthy, I thought that -- and without known disease recurrence

at that time, though understandably concerned about recurrence -- I thought that the fact that there was some dropouts without evidence of toxicity concern could be accepted. I felt comfortable with that -- even in a way that 25 percent of the missing consents this morning didn't leave me quite so comfortable for those contrasting reasons.

I again, would add my commendation to the investigators. I do remember how hard it is to care for these patients, and how compelling their medical need was. To have conducted two randomized trials in this setting is an extraordinary accomplishment and hopefully sets the stage for more innovations to come in sickle cell disease.

DR. RINI: Okay. Thank you. I'll go last. Dr. Nowakowski.

DR. NOWAKOWSKI: Greg Nowakowski. I voted no. This was quite a difficult decision for me, and I must say looking at the votes, my heart is happy that other people voted yes. I am scientific side was for voting no, however. The reasons for this -- I had no concerns about the toxicity. The drug,

L-glutamine, appears to be safe and relatively non-toxic.

I did have significant concerns about the efficacy of this treatment. Some of the limitations were discussed with the imputation of the data, of the missing data. The other big part of this is the potential imbalance between the treatment arms. Unfortunately, with this relatively small study, we cannot stratify for important factors, and as you all are aware, this is extremely heterogeneous disease, and relatively small imbalance between the patients and severity of the disease between the arms, could result in significant differences seen in the study.

Of course when you're making a decision like this where the drug is of relatively little toxicity and potential benefit -- or there might be questioning benefit -- that question is why not, because the risk is relatively low.

There are some risks to it. One of the risks is that the potential components, which there's less activity, could be displacing ones which are quite active, like hydroxyurea, and could be also taking

our focus from supporting patients on hydroxyurea treatment and improving current care.

For those reasons, I voted no. I need to compliment all the public speakers as well, and again, the sponsor of the study for conducting this study. We clearly have a lot more work to do in sickle cell disease, and I hope that this study will provide additional momentum for studying sickle cell.

DR. RINI: Thank you. Dr. Rieley?

DR. RIELEY: Greg Rieley. I voted yes. To add to what everybody else has said, I think the thing that really hit me was the consistency of efficacy endpoints. There are questions about any of the individual analyses, but the uniformity of benefit for all of them, was to me the overwhelming thing.

DR. RINI: Thank you. Dr. Klepin?

DR. KLEPIN: Heidi Klepin, Wake Forest. I voted yes, and I'll just go through the logic very quickly, very similar to what others have said, but first considering the outcome being, I thought, incredibly clinically meaningful in a setting that

clearly is an area of need as was eloquently discussed. The efficacy outcomes that were reported, I agreed were meaningful. That's where I started.

I felt that the toxicity data presented, did not appear to give us a red flag that there would be an expectation of excess toxicity. Then with respect to the limitations discussed with differential dropout, my other question was, is that a fatal flow and was there enough reason to believe that the efficacy data could not be supported adequately.

I think while that is a significant limitation, as has been discussed, I still felt that there was enough reason, based on both the sponsor's and the FDA analyses to believe that there is an effect here, and for those reasons, I voted yes.

I do want to comment that I do think, as others have said, that there are additional information I think that can be learned with the dataset that you have, with respect to differential dropout and baseline characteristics that would be useful to know going forward, to better understand who's benefiting and who's at risk for not taking the

drug.

DR. RINI: Thank you. Vali.

DR. PAPADIMITRAKOPOULOU: Vali Papadimitrakopoulou. I voted yes for all the reasons that were listed by others before. I'm not sure that we can perform clinical studies in this population without a dropout rate. I think the company and the patients that participated and stuck with it should be congratulated. I think that opens the door for more progress. I don't see a safety signal, and there is benefit -- maybe not very robust in all analyses -- but benefit across the different endpoints. I think for that, yes.

DR. RINI: Thank you. Dr. D'Agostino?

DR. D'AGOSTINO: Ralph D'Agostino. I voted yes. There were a lot of statistical questions, obviously, and I raised a number of them. But in looking at the data, there's this missing data, the differential dropout. You have the sensitivity analysis, the imputation.

But if you look at it, and I've been spending the last half hour saying what if this, what if that,

and there's a robustness to the sensitivity analysis, even if you push it and go to the analysis similar to what the FDA was doing, and you come up with a margin that gets pretty big, and isn't statistically significant, but it's pushing the data and it's still very consistent with the positive effect.

I think that there's a lot in this data that gives a positiveness to the study and to the data that was presented in their presentations. I'm always -- I've been on a number of advisory committees over the years and I realize that when we give a vote, that's not the end of the game.

I wanted to give an endorsement as part of a voting consultant, that I think that there's a lot here, and I throw it back to the FDA to hear our arguments and in particular, things I'm saying. There's a tremendous consistency in the data. I think that the more that you look at it, the more that comes out, and it comes up, as I say, in a positive direction for the drug.

DR. RINI: Okay. Thank you. I'm Brian Rini. I voted yes, and I'll just summarize what I heard

from around the table and interlay some of my own comments. I think my yes, like many of the yeses and nos, was difficult. I think this one could have gone either way. As with others, I'd like to give the sponsor a lot of credit for doggedly pursuing this indication, it sounds like over many years, maybe many decades. They're to be given a lot of credit for that in a disease that it sounds like from the advocates, maybe not a lot of people have cared enough about.

This is clearly a bad disease. It's worse than cancer in many ways. I think probably mostly from a stigmas standpoint, it has a desperate need, and it is very difficult to do studies. I get that. To do two randomized studies, just to complete them is a major accomplishment.

I would say, however, that despite this desperate need, our job is to recommend approval of drugs, not based on desperate need, but based on good data. I thought that there was a lot of data -- the data points that weren't known that could have been or should have been.

A lot of the questions that were asked of the committee about baseline use of narcotics, baseline number of crises affecting efficacy of drug -- you have the data; it's all there in your dataset. I would encourage you, as somebody else said, to really look at that, because I think it might be helpful clinically in how do we apply this drug, clinically, if it's FDA approved.

There were concerns about differing methodologies and different hazard ratio outcomes between FDA analysis and sponsor analysis, and different imputation methods, and that's a little bit above my head to discuss the specifics of that, but clearly there was some concern, although it all seemed to come down in favor of the agent.

I think on the positive side there was a modest, but consistent benefit of the agent. I think one thing that's strikingly clear is even any modest benefit in this community, given the sequelae of crises, is significant. It doesn't take much to produce a clinical impact, and that should be motivation to study more drugs in this disease,

because of what we heard today.

A lot of people said there was modest benefit, and that is balanced against really very minimal risk. Had this been a very toxic product, I don't think this committee would have voted for approval. But it's, in essence, a natural product with low risk.

I would, as others have done, just encourage more studies; not just mining the data you have, but more studies about duration of therapy and really quality data collection and maybe trying to borrow a little bit from the cancer world, if you will, in terms of the rigor of data collection, which I think was perhaps a little bit lacking here. But on balance, those are the reasons that I voted yes, and I think summarize the thoughts of the committee.

Did the FDA have any further comment?

DR. FARRELL: No, we appreciate the discussion and we're going to take all your comments into consideration, as well as the speakers from the open public hearing. We want to thank you for a very good discussion.

Adjournment

DR. RINI: Okay. Thank you. We'll now adjourn the meeting. Panel members leave your name badge here, so they can be recycled and take all your personal belongings. Thank you.

(Whereupon, at 4:19 p.m., the afternoon session was adjourned.)