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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

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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.

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

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

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

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

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

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

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

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

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

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

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

1 Center.

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

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

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

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

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

13 DR. PAZDUR: Richard Pazdur, director, OCE.

14 DR. RINI: For topics such as those being
15 discussed at today's meeting, there are often a
16 variety of opinions, some of which are quite
17 strongly held. Our goal is that today's meeting
18 will be a fair and open forum for discussion of
19 these issues, and that individuals can express
20 their views without interruption. Thus, as a
21 gentle reminder, individuals will be allowed to
22 speak into the record only if recognized by the

1 chairperson. We look forward to a productive
2 meeting.

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

9 We are aware that members of the media are
10 anxious to speak with the FDA about these
11 proceedings, however FDA will refrain from
12 discussing the details of this meeting with the
13 media until its conclusion. Also the committee is
14 reminded to please refrain from discussing the
15 meeting topics during any breaks. Thank you.

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

18 **Conflict of Interest Statement**

19 DR. TESH: The Food and Drug Administration
20 is convening today's meeting of the Oncologic Drugs
21 Advisory Committee meeting under the authority of
22 the Federal Advisory Committee Act of 1972. With

1 the exception of the industry representative, all
2 members and temporary voting members of the
3 committee are special government employees, or
4 regular federal employees from other agencies, and
5 are subject to federal conflict of interest laws
6 and regulations.

7 The following information on the status of
8 this committee's compliance with federal ethics and
9 conflicts of interest laws, covered by but not
10 limited to those found at 18 U.S.C., Section 208,
11 is being provided to participants in today's
12 meeting and to the public. FDA has determined that
13 members and temporary voting members of this
14 committee are in compliance with Federal Ethics and
15 Conflict of Interest laws.

16 Under 18 U.S.C., Section 208, Congress has
17 authorized FDA to grant waivers to special
18 government employees and regular federal employees
19 who have potential financial conflicts when it is
20 determined that the agency's need for a special
21 government employee's services outweighs his or her
22 potential financial conflict of interest, or when

1 the interest of a regular federal employee is not
2 so substantial as to be deemed likely to affect the
3 integrity of the services which the government may
4 expect from the employee.

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

16 Today's agenda involves new drug application
17 208587 for L-glutamine powder, oral solution
18 submitted by Emmaus Medical Inc. The proposed
19 indication/use for this product is for the
20 treatment of sickle cell disease.

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

1 NDA will be discussed. Based on the agenda for
2 today's meeting and all financial interests
3 reported by the committee members and temporary
4 voting members, no conflict of interest waivers
5 have been issued in connection with this meeting.

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

10 With respect to FDA's invited industry
11 representative, we would like to disclose that Dr.
12 P.K. Morrow is participating in this meeting as a
13 non-voting industry representative acting on behalf
14 of regulated industry. Dr. Morrow's role at this
15 meeting is to represent industry in general and not
16 any particular company. Dr. Morrow is employed by
17 Amgen.

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

1 participants need to exclude themselves from such
2 involvement and their exclusion will be noted for
3 the record. FDA encourages all other participants
4 to advise the committee of any financial
5 relationships that you may have with the firm at
6 issue. Thank you.

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

9 **Opening Remarks - Kathy Robie-Suh**

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

14 Sickle cell anemia affects an estimated
15 100,000 adults and children in the U.S., and
16 millions more worldwide. It is one of the most
17 common genetic disorders in the U.S., occurring in
18 about 1 out of every 365 black or African-American
19 births, and 1 out of every 16,300 Hispanic-American
20 births.

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

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

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

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

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

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

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

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

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

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

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

7 Likewise, FDA encourages you at the
8 beginning of your presentation to advise the
9 committee if you do not have any such financial
10 relationships. If you choose not to address this
11 issue of financial relationships at the beginning
12 of your presentation, it will not preclude you from
13 speaking.

14 I now invite the applicant up to start their
15 presentation.

16 **Applicant Presentation - Lan Tran**

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

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

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

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

10 Emmaus is a small company with 19 employees.
11 We are based in California and began as a spinoff
12 from LA BioMed, a non-profit medical research and
13 education institute. The date on our application
14 supports our request that oral L-glutamine be
15 labeled for the treatment of sickle cell disease in
16 children and adults. Our proposed dose is
17 0.3 grams per kilogram, given twice daily, for a
18 maximum total daily dose of 30 grams.

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

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

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

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

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

19 These observations were expanded in a phase
20 2 study in sickle cell patients and confirmed in a
21 large phase 3 study leading to a new drug
22 application submission in September 2016.

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

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

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

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

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

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

11 **Applicant Presentation - Victor Gordeuk**

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

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

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

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

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

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

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

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

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

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

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

1 avascular necrosis of the bones.

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

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

18 Sickle cell disease has a high mortality.
19 This slide shows life expectancy of sickle cell
20 patients compared to the general American
21 population in the 20th century. For most of the
22 20th century, sickle cell patients died in

1 childhood.

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

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

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

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

1 20 percent in those who experience fewer crises.

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

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

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

1 painful crises.

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

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

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

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

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

5 The second crisis was complicated by bone
6 infarction and a joint effusion, and the
7 hospitalization lasted 5 days. The third crisis
8 was marked by a dramatic deterioration after
9 admission. He developed acute chest syndrome and
10 respiratory failure. He was rushed to the
11 intensive care unit, required intubation, and
12 underwent mechanical ventilation for several days.
13 The duration of the hospital stay was almost
14 3 weeks, and this third crisis was nearly fatal.

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

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

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

5 For instance, this is a lifelong illness as
6 opposed to a recently diagnosed malignancy.

7 Patients with sickle cell disease face the stigma
8 of suspected narcotic-seeking behavior. This
9 differs starkly from the universal compassion for
10 patients with cancer.

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

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

22 Thank you. I would now like to introduce

1 Dr. Niihara who will present clinical efficacy and
2 safety.

3 **Applicant Presentation - Yutaka Niihara**

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

10 We also extend our thanks to the patients,
11 investigators, and study personnel who participated
12 in these trials, and whose efforts have allowed us
13 to bring this to you for consideration. My
14 interest in this disease is longstanding, going
15 back to the days of my medical training in early
16 1990s.

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

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

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

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

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

1 NAD.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

6 We gave patients 0.3 grams per kilogram of
7 L-glutamine twice daily and monitored them for 48
8 weeks. Our primary endpoint was frequency of
9 sickle cell crisis. Looking at the mean, we saw
10 9.6 crises during the observation period for
11 placebo, versus 4.3 in the treatment group. The
12 p-value was 0.15.

13 Looking at hospitalizations, the mean was
14 1.9 for placebo group and 1.4 for the L-glutamine.
15 The p-value was 0.11. These results all trended in
16 favor of L-glutamine.

17 Using Negative Binomial Regression or NBR,
18 we looked at the primary endpoint again, using
19 observed data and exposure time. Rate of ratio was
20 0.47 favoring L-glutamine. The phase 2 clinical
21 trial confirmed L-glutamine's beneficial effect on
22 sickle red blood cells clinically, and provided

1 invaluable data to structure our phase 3 clinical
2 trial.

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

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

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

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

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

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

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

22 Here we see data on patients disposition.

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

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

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

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

22 The primary endpoint was frequency of sickle

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

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

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

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

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

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

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

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

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

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

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

1 hydroxyurea.

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

8 Here we can describe the delay to first
9 crisis using the Kaplan-Meier curve. The hazard
10 ratio was 0.69 or decrease in risk rate by
11 31 percent. Separation of the curves are
12 persistent throughout the observation period.

13 In regard to the time to second crisis, the
14 results again favored L-glutamine group, with
15 hazard ratio of 0.68 or reduction in risk rate by
16 32 percent, p-value 0.026. Again, the curves are
17 separated throughout the observation period.

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

1 of crisis events through the observation period and
2 persistent effect over time. Hazard ratio here was
3 0.79 or risk rate reduction of 21 percent.

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

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

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

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

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

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

7 Blood transfusion is yet another potential
8 burden faced by sickle cell patients. Altogether,
9 47 percent in L-glutamine patient group, and
10 51 percent of patients in the placebo group
11 received simple transfusion therapy during the
12 observation.

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

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

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

5 In summary, the consistency of L-glutamine
6 therapy were noted to result in clinically
7 meaningful benefit. As Dr. Gordeuk has shown
8 earlier, sickle cell crises are linked to morbidity
9 and mortality, the accumulative damage they cause.
10 In our study, L-glutamine treatment group had
11 significantly lower incidence of sickle cell
12 crises. In terms of time to first crisis there was
13 56 percent delay in the treatment group. Rates of
14 acute chest syndrome were lower by 67 percent.
15 This is a condition that frequently requires ICU
16 care and is a major cause of mortality.

17 Hospitalization rates were lower by
18 33 percent in the L-glutamine group, and cumulative
19 days were also lower in the treatment group by
20 41 percent. Simple blood transfusion events were
21 lower by 39 percent, and relative difference in
22 requirement for exchange transfusion was even

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

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

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

17 Now I'd like to turn to the safety profile
18 of L-glutamine therapy. Please note that our
19 safety evaluation plan integrated studies 10478 and
20 09-01, evaluation included 298 patients. All
21 investigator-reported adverse events including
22 those adjudicated as sickle cell crisis were

1 included.

2 Demographics and disease characteristics
3 were balanced between the two groups. Please allow
4 me to reiterate the differential randomization in
5 two studies; 2 to 1 in study 09-01 or phase 3
6 clinical trial, and 1 to 1 in study 10478 or phase
7 2 clinical trial. So we will generally focus on
8 the proportions of patients rather than the actual
9 number in these tables.

10 The duration of exposure days in L-glutamine
11 group was 268.9 days and 283.3 days for the placebo
12 group. Over 100 patients had exposure greater than
13 48 weeks in the L-glutamine group, compared to 73
14 in the placebo group. The total exposure of
15 L-glutamine was 137.7 patient-years.

16 Adverse events were common and experienced
17 by 96.3 percent of patients in the L-glutamine
18 group, and 97.3 percent of patients in the placebo
19 group. Serious adverse events were experienced by
20 75.4 percent of patients in the L-glutamine arm,
21 and 80.2 percent in the placebo group.

22 Adverse events leading to discontinuations

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

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

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

1 between the two treatment groups.

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

8 A summary of adverse events that led to
9 study discontinuation is presented here. There
10 were 5 patients representing 2.7 percent in
11 L-glutamine group, and one patient representing
12 0.9 percent in placebo group. Please note that
13 with the asterisk, hypersplenism and abdominal
14 pain -- these two events were experienced by the
15 same patient.

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

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

4 **Applicant Presentation - Wally Smith**

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

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

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

1 this devastating disease.

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

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

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

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

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

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

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

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

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

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

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

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

8 But just imagine 10,000 patients on
9 L-glutamine. Let's take the FDA's most
10 conservative estimate of a mean reduction of 0.8
11 crises per year. That 10,000 patients would have
12 8000 fewer crises in the next year. Over 5 years,
13 40,000 fewer crises.

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

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

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

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

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

11 **FDA Presentation - Rosanna Setse**

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

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

1 being sought.

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

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

10 The proposed indication for L-glutamine, as
11 has been mentioned before, is for the treatment of
12 sickle cell disease. The proposed dose is
13 0.3 grams per kilogram body weight, with an upper
14 limit of 30 grams per day, administered orally,
15 twice a day.

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

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

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

3 Study 09-01 is the pivotal study supporting
4 this application. The study population consisted
5 of patients with a documented diagnosis of sickle
6 cell anemia, or sickle beta thalassemia by
7 hemoglobin electrophoresis, who were 5 years of age
8 or older at the time of enrolment, and who had at
9 least two documented crisis episodes in the
10 12 months prior to screening.

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

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

22 As mentioned by the applicant, the primary

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

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

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

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

1 This study included both pediatric and adult
2 patients. The mean age of participants was
3 22 years, with ages ranging from 5 to 58 years.

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

10 The disposition of subjects enrolled in
11 study 09-01 was as follows: 68 percent of the
12 total study population completed the study;
13 32 percent discontinued the study before the end of
14 week 48.

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

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

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

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

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

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

1 from study 10478.

2 Another difference between study 10478 and
3 09-01 was with respect to the definition of the
4 primary endpoint. In study 10478, a sickle cell
5 crisis was defined as visit to a medical facility
6 that lasted more than 4 hours for an acute
7 sickling-related pain, which was treated with a
8 parenterally administered narcotic.

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

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

20 However, in this study more subjects in the
21 placebo group discontinued the study before week
22 48, compared to the L-glutamine group, 64 versus

1 51 percent respectively. Reasons for dropouts
2 again was similar between the treatment groups with
3 the most frequent reason being non-compliance,
4 consent withdrawn, and other reasons.

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

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

11 **FDA Presentation - Che Smith**

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

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

22 In study 10478, patients experienced between

1 zero and 90 crises within a 48-week treatment
2 period, compared to study 09-01 in which patients
3 experienced between zero and 15 crises across
4 48 weeks.

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

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

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

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

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

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

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

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

1 ridity scores controlling for stratification
2 factors.

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

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

1 Early study dropout occurred at a higher
2 rate than expected, with about 36 percent of
3 patients from the L-glutamine treatment group
4 dropping out of the study early, compared to
5 24 percent of patients randomized to placebo
6 treatment.

7 Additionally, a notable number of patients
8 dropped out of the study before the midpoint at
9 24 weeks. Study narratives on the reasons why
10 these patients dropped out of the study do not give
11 sufficient information as to whether dropout was
12 related to the patients' assigned treatment group
13 or other study characteristics.

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

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

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

5 First, there were patients who completed 48
6 weeks of assigned treatment and had at least 1
7 crisis event recorded. There were additional
8 patients who completed the study and had no crisis
9 events recorded. Among those who did not complete
10 48 weeks of treatment, some patients dropped out
11 having experienced at least 1 recorded crisis
12 event. And finally, there were some patients who
13 dropped out of the study and had no recorded crisis
14 events at the time of dropout.

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

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

1 this case, it is reasonable to assume that these
2 19 patients did not experience any crises, since
3 they were seen at the final visit.

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

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

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

1 introduced bias in the primary and secondary
2 efficacy results.

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

8 Patients randomized to L-glutamine treatment
9 who dropped out of the study with fewer than
10 3 crises, had an imputed 48-week crisis count of 3.
11 Patients randomized to placebo treatment who
12 dropped out with fewer than 4 crises, had an
13 imputed 48-week crisis count of 4. These imputed
14 values represent the mean number of crises among
15 study completers from each treatment group.

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

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

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

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

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

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

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

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

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

1 crisis events for a patient are not necessarily
2 independent.

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

8 Based on this analysis, the proportional
9 rate of sickle cell crises at 48 weeks is estimated
10 to be 3 crises among the L-glutamine patients, and
11 3.8 crises for placebo patients. The FDA obtained
12 a hazard ratio of 0.73 in favor of the L-glutamine
13 treatment group, with a 95 percent confidence
14 interval ranging from 0.55 to 0.99.

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

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

1 treatment period, as well as patients who may have
2 dropped out of the study, but had at least
3 1 recorded crisis event before dropping out.

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

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

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

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

1 sensitivity analysis population, before applying
2 Negative Binomial Regression models.

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

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

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

22 Particularly, a recurrent event analysis

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

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

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

13 **Applicant Presentation - Rosanna Setse**

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

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

22 There was also a lower frequency of serious

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

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

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

19 A total of 298 subjects received at least
20 1 or more doses of L-glutamine, or study
21 medication, during studies 10478 and 09-01. One
22 hundred and eighty seven subjects received

1 L-glutamine for one or more days; 73 percent were
2 treated with L-glutamine for at least 24 weeks, and
3 58 percent received L-glutamine for 48 weeks or
4 more.

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

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

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

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

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

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

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

22 As shown in the highlighted box, the

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

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

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

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

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

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

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

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

12 The applicant's primary efficacy analysis
13 resulted in a median sickle cell crisis counts of
14 3 versus 4, for L-glutamine versus placebo treated
15 subjects at 48 weeks.

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

1 imputations.

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

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

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

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

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

10 **Clarifying Questions to the Presenters**

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

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

1 leading up to study intervention was 3 for each
2 group.

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

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

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

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

1 same.

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

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

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

14 DR. RINI: Thank you. Dr. Nowakowski?

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

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

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

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

1 DR. NIIHARA: No, and thank you for good
2 suggestions. Due to the number of patients that we
3 enrolled, and the 230 patients are -- even though
4 230 patient study may not be a large study compared
5 to some other areas, 230 patient study is a fairly
6 large study for sickle cell. Because of this, we
7 could really minimize our stratification.

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

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

16 DR. NIIHARA: No.

17 DR. NOWAKOWSKI: Okay. By the way, I would
18 like to compliment Enmaus Medical for conducting
19 this study in this very much area of medical need.

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

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

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

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

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

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

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

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

15 DR. NIIHARA: Yes, they --

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

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

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

5 DR. NOWAKOWSKI: Okay. Thank you.

6 DR. NIIHARA: You're welcome.

7 DR. RINI: Okay. Dr. Rieley?

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

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

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

1 treatment assignment?

2 DR. NIIHARA: Yes.

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

6 DR. NIIHARA: No, not at all.

7 DR. RIELEY: Okay.

8 DR. RINI: Dr. Menefee?

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

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

21 DR. MENELEE: But what about the patients
22 that were not getting --

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

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

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

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

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

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

22 DR. NIIHARA: Yes, we do not have overall

1 survival data from this.

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

11 DR. NIIHARA: In terms of survival?

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

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

18 DR. MENEFEER: The baseline sickle cell
19 crises.

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

21 DR. MENEFEER: Okay. Thank you.

22 DR. RINI: Okay. Dr. Uldrick?

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

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

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

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

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

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

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

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

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

12 DR. RINI: Dr. Cole?

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

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

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

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

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

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

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

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

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

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

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

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

18 Second, honestly, I don't understand the
19 0.91, how FDA can get this number. We still cannot
20 duplicate FDA was doing, but that's because our
21 limitation, we don't understand.

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

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

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

15 DR. RINI: Dr. Burstein?

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

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

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

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

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

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

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

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

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

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

1 less, just because we reduce the rate of crisis by
2 21 percent, but we reduce the rate of
3 hospitalization by 33 percent.

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

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

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

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

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

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

14 DR. NIIHARA: Oh, yes.

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

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

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

1 DR. NIIHARA: Right.

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

4 DR. NIIHARA: Yes. Thank you.

5 DR. BURSTEIN: Thank you.

6 DR. RINI: Dr. D'Agostino.

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

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

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

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

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

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

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

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

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

20 DR. D'AGOSTINO: But they're confident, I
21 mean their p-values aren't going to come out to be
22 0.0025. I mean they're -- the first one's hovering

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

4 DR. WEI: Sorry, sir --

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

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

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

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

22 DR. D'AGOSTINO: Your sensitivity analysis.

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

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

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

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

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

22 DR. D'AGOSTINO: And these were all

1 prespecified?

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

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

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

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

8 DR. RINI: Ms. Preusse?

9 MS. PREUSSE: Not sure --

10 DR. RINI: We have a comment from FDA?

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

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

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

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

3 DR. SHEN: It is included in the analysis,
4 but we didn't try -- if the patient just at
5 24 weeks, we did not fill that up to 48 weeks. So
6 we led there --

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

9 DR. SHEN: Yes.

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

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

22 I think I read in the package that almost

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

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

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

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

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

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

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

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

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

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

17 I just wanted to bring this out. Could you
18 focus on the rate which is 2.54 for 5 to 12 years?
19 This is the rate of crisis; 3.95 for what we
20 classified as adolescents 13 to 18; and the adult
21 18 and older the rate is -- I mean there is a
22 variability, but essentially the same.

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

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

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

17 DR. NIIHARA: Yes. Thank you.

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

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

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

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

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

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

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

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

4 DR. RINI: Ms. Miller?

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

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

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

17 DR. NIIHARA: Thank you.

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

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

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

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

12 DR. STARK: This study, besides our phase 2
13 and phase 3 trial, we have not gone beyond the
14 48-week period. To your point, the short bowel
15 syndrome, that is used for a 16 week course of
16 therapy, so it's not a long duration. Therefore,
17 we do not have data beyond approximately a one year
18 period of time.

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

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

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

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

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

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

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

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

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

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

18 **Open Public Hearing**

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

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

1 decision making. To ensure such transparency at
2 the open public hearing session of the advisory
3 committee meeting, FDA believes it's important for
4 you to understand the context of an individual's
5 presentation.

6 For this reason, FDA encourages you, the
7 open public hearing speaker, at the beginning of
8 your written or oral statement to advise the
9 committee of any financial relationship that you
10 may have with the sponsor, its product, and if
11 known its direct competitors.

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

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

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

6 That said, in many instances and for many
7 topics, there will be a variety of opinions. One
8 of our goals today for this open public hearing is
9 to be conducted in a fair and open way where every
10 participant is listened to carefully and treated
11 with dignity, courtesy, and respect.

12 Therefore, please speak only when recognized
13 by the chairperson, and thank you for your
14 cooperation. If we could have speaker number 1
15 step up to the podium and introduce yourself.
16 State your name and any organization you're
17 representing, for the record.

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

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

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

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

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

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

22 The briefing documents from the company and

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

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

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

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

1 explanation.

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

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

14 Thank you.

15 DR. RINI: Thank you. Speaker number 2?

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

1 Emmaus.

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

10 Shortly after I started, I was called for a
11 20-year-old young lady with sickle cell anemia SS,
12 just admitted to the medical floor. Her mother was
13 crying loudly, and said, "This may be the time
14 she's going to leave me." Her daughter was in
15 severe pain.

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

22 I told her about the clinic, and following

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

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

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

22 We should not forget iron overload, one of

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

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

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

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

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

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

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

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

20 Thank you.

21 DR. RINI: Thank you. Speaker number 3?

22 MS. GOUGIS: Hello. My name is Juanita

1 Gougis. The applicant has paid for my travel, but
2 I have no financial ties to the company. I am
3 28 years old and I was diagnosed with sickle cell
4 disease when I was two. It has been very difficult
5 for me to come to terms with my reality that I
6 would be in pain and hospitalized very frequently
7 and would never have a normal life.

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

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

1 pain crisis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

17 DR. RINI: Thank you. Speaker number 4?

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

1 financial ties with the applicant.

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

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

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

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

1 the ethnicities in the United States.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

19 (Video played - unclear audio.)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 be alive.

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

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

13 MS. VALENTINE: Thank you.

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

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

22 I am an advocate, and today I bring the

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

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

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

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

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

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

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

22 As an example, if the crisis started in

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

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

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

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

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

3 DR. RINI: Thank you. Speaker number 7?

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

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

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

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

1 patients with sickle cell disease. For almost
2 25 years, I've been working with children and
3 adults with sickle cell disease on clinical trials,
4 and also serving as newborn screening coordinator.

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

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

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

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

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

9 I have seen good. This past Tuesday I
10 received a call from a mother, inviting me to her
11 22-year-old son's college graduation, which will be
12 held on the 28th of May. I've known this young man
13 since his birth. I was the one who informed his
14 mother that her child had sickle cell disease. I
15 can still remember her tears.

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

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

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

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

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

17 **Questions to the Committee and Discussion**

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

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

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

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

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

17 (Pause.)

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

1 continue to flash even after you have entered your
2 vote.

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

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

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

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

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

3 (Vote taken.)

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

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

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

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

1 were receiving.

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

9 DR. RINI: Thank you. Dr. Fitzhugh.

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

17 DR. RINI: Thank you. Ms. Miller.

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

1 time.

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

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

11 DR. RINI: Thank you. Ms. Preusse?

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

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

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

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

9 DR. RINI: Thank you. Dr. Uldrick.

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

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

1 dropout.

2 DR. RINI: Thank you. Dr. Cole?

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

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

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

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

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

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

10 DR. RINI: Thank you. Dr. Burstein.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

9 DR. RINI: Thank you. Dr. Rieley?

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

17 DR. RINI: Thank you. Dr. Klepin?

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

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

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

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

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

1 drug.

2 DR. RINI: Thank you. Vali.

3 DR. PAPADIMITRAKOPOULOU: Vali

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 because of what we heard today.

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

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

17 Did the FDA have any further comment?

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

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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.)