CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208587Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 30, 2017
From	Kathy M. Robie-Suh, MD, PhD
Subject	Cross-Discipline Team Leader Review
NDA	208587
Applicant	Emmaus Medical, Inc.
Date of Submission	September 7, 2016
PDUFA Goal Date	July 7, 2017
Proprietary Name / Established (USAN) names	Endari/ (L-glutamine powder)
Dosage forms / Strength	Oral Powder / 5 grams of L-glutamine powder per paper-foil-plastic laminate packet
Proposed Indication(s)	Endari is indicated to reduce the acute complications of sickle cell disease in adult and pediatric patients 5 years of age and older.
Recommended:	Approval

Cross Discipline Team Leader Review Template

1. Introduction

The Applicant has submitted an original 505(b)(2) NDA application for oral L-glutamine powder for the treatment of sickle cell disease (SCD) in adult and pediatric patients. For this application the Applicant is referencing a previously approved L-glutamine product (NutreStore, NDA 21667) also owned by Emmaus that is approved (6/10/2004) for treatment of Short Bowel Syndrome in conjunction with recombinant human growth hormone. The L-glutamine product is formulated as a white crystalline powder to be mixed in a (b) (4) beverage or food for oral administration. The formulations and manufacture of the proposed product for SCD is essentially the same as that for the approved NutreStore product. For the new indication proposed in the current application the Applicant has submitted results from a completed Phase 3 study (GLUSCC09-01) and a Phase 2 study (Study 10478), conducted in patients with sickle cell disease (SCD) as the pivotal studies. The Applicant's proposed indication is L-glutamine is "indicated for the treatment of sickle cell disease". The proposed dose is a total daily dose of 10 grams, 20 grams, or 30 grams based on weight (divided into two doses, administered twice daily).

2. Background

Sickle cell disease is an inherited hemoglobinopathy affecting 50,000 to 100,000 persons in the United States. It is the most common genetic disease identified as part of the Newborn Screening Program in the U.S. The disease is the first for which a specific molecular defect was identified and is characterized by replacement of glutamic acid, the sixth amino acid from the N-terminal end of the β chain, by valine (hemoglobin S). This substitution results in reversible hemoglobin (Hb) polymerization and sickling of red blood cells (RBC). Sickled RBC become lodged and aggregate in small vessels leading to ischemia and eventual infarction of downstream tissue and causing painful vaso-occlusive crises and/or tissue damage. Common acute vaso-occlusive clinical syndromes include painful sickle cell crisis (most commonly involving bones of the trunk and extremities), cerebrovascular accidents (CVA) (strokes and seizures), acute chest syndrome (involving occlusion of pulmonary vasculature), hepatic crisis, priapism, and acute renal papillary infarction. With repeated cycles of sickling, RBC become damaged with a leaky membrane and may become irreversibly sickled and then be taken up and destroyed by the reticuloendothelial system (RES) resulting in a chronic compensated hemolytic anemia. Patients with SCD have an increased risk of infections, due partly to the occurrence of splenic autoinfarction over time with the disease. Patients with SCD have a reduced lifespan.

Extent of hemoglobin polymerization and RBC sickling in homozygous SS patients is affected by a number of factors and is increased with deoxygenation, dehydration, acidosis, and

presence of certain other mutant hemoglobins (e.g., Hb C and Hb D). Beneficial effects of certain factors, such as presence of fetal hemoglobin (Hb F), are due to their interference with polymerization of hemoglobin in the RBC. Currently, Hydroxyurea (HU) (Droxia) is the only approved drug for treatment of SCD, with the indication, "to reduce the frequency of painful crises and to reduce the need for blood transfusions in patients with sickle cell anemia with recurrent moderate to severe painful crises". The action of HU is via increase in HbF. HU approval is for use only in adults. HU has safety concerns in that it is mutagenic and clastogenic, and causes cellular transformation to a tumorigenic phenotype. Also, treatment of patients with Droxia may be complicated by severe, sometimes life-threatening, adverse effects (which are included in a boxed warning in the labeling).

L-Glutamine is an amino acid (molecular formula C5H10N2O3; molecular weight 146.15). Non-clinical pharmacology studies suggest that supplemental L-glutamine can alleviate intracellular oxidative stress and ameliorate endothelial adhesion resulting in a reduction in the negative effects of oxidative stress in SCD. The Applicant states the data support that increasing intracellular L-glutamine concentration via oral supplementation is likely to increase the rate of NDA synthesis, increasing the intracellular redox potential and reducing oxidative stress and damage in the sickle RBCs. The Applicant also states that data show that RBC adhesion to endothelial cells is less in blood samples from patients with SCD treated with L-glutamine than in samples from untreated SCD controls.

L-glutamine for treatment of sickle cell disease has been studied under IND 53841 which was initially opened 7/28/1997 as an investigator-sponsored IND. L-Glutamine was granted Orphan Drug Designation on 8/1/2001 for treatment of SCD. On 1/7/2005 it was granted fast track designation for the indication to reduce painful crises in patients with sickle cell disease, based on results from a limited number of patients suggesting that it may reduce frequency of crises in patients with SCD with few adverse reactions. (b) (4)

(b) (4)

L-glutamine (NutreStore, NDA 21667) is currently approved (June 10, 2004) for the indication "treatment of Short Bowel Syndrome in patients receiving specialized nutritional support when

used in conjunction with a recombinant human growth hormone that is approved for this indication". On 9/21/2004 the manufacturer ([redacted] (b) (4) had the product moved to the Discontinued Products List in the Orange Book stating it was in the process of looking for a marketing partner. NutreStore is not approved elsewhere in the world, though the most recent Annual Report for NutreStore (submitted 8/8/2016, NDA 21667 [redacted] (b) (4) The product was acquired by Emmaus from [redacted] (b) (4) Based on the Annual Reports filed to NDA 21667, there have been no post-marketing adverse event safety reports received for NutreStore since approval.

In support of the current NDA application for treatment of sickle cell disease the Applicant submitted reports of two main studies, namely, Study GLUSCC09-01, which was a Phase 3 randomized (2:1), double-blind, placebo-controlled study of 48 weeks treatment with L-glutamine versus placebo in adult and pediatric patients with sickle cell anemia (SCA) or sickle β-thalassemia, and Study 10478, which was a Phase 2 randomized (1:1), double-blind, placebo-controlled study of 48-weeks treatment with L-glutamine versus placebo in patients with sickle cell anemia (SCA) or sickle β-thalassemia. Reports and data from additional smaller pharmacodynamic (PD) and safety clinical studies also were included in the application.

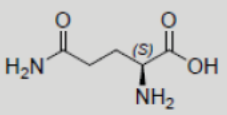
3. CMC/Device

The primary reviews of the Chemistry, Manufacturing and Controls (CMC) aspects of the application were conducted by: Rajan Pragani (Drug Master File/Drug Substance, review signed 2/7/2017), Rajan Pragani (Product Quality, review signed 02/07/2017), Zhaoyang Meng (Process, review signed 6/13/2017), Ephrem Hunde (Facility, review signed 6/13/2017), Rajan Pragani (Environmental assessment, review signed 3/10/2017), and Rajan Pragani (Application Technical Lead – Quality Assessment, Executive Summary signed 6/15/2017). The major findings of these reviews are summarized below.

Drug Substance: The Drug Substance Review OPQ Quality Assessment gives the following chemical name and structure for L-glutamine:

Chemical Name: L-glutamine

Chemical Structure:



The review indicates that the drug substance is a white, crystalline powder or crystals, is soluble in water and is a naturally occurring amino acid. The review states that L-glutamine is a well-characterized amino acid and that the general properties described are consistent with literature and USP monograph criteria.

The review describes that the drug substance manufacture, bulk packaging, and release and stability testing is done by [redacted]. The release testing of bulk drug substance is done per Emmaus' specifications by [redacted]. L-glutamine is manufactured [redacted] The review commented that this manufacturing process is currently being used to supply L-glutamine for the drug product NutreStore (NDA 21667) for short bowel syndrome. The review found control of critical steps and intermediates, process validation studies conducted, and manufacturing process development to be adequate. The review notes that [redacted] originally developed the L-glutamine process at their production sites in [redacted] but transferred the production of L-glutamine to their facility in [redacted] using the processes originating from [redacted] facility. L-Glutamine manufactured at the [redacted] facility was used in the Phase 3 clinical studies and will be used for commercial supply. Characterization of the L-glutamine structure and description of impurities were adequate.

The review found that the analytical test methods were described and validated appropriately and appear adequate for the respective intended uses. The review found the specifications acceptable to ensure the identity, strength, quality, and purity of the drug substance. The applicant demonstrated equivalency between L-glutamine drug substance manufactured at the [redacted] site and the [redacted] site. Each of the reference standards was characterized by well-known techniques, which supported the proposed structures/identity and the identity, purity, and strength of each standard were determined to be adequate. The review commented that no stability or moisture issues have been demonstrated for bulk L-glutamine storage and the proposed container closure system appears adequate to protect the drug substance because of the moisture absorbing [redacted]. The stability data were found adequate to support a retest date of [redacted].

The application was recommended for approval from a Drug Substance perspective. There were no recommendations for post-approval commitments.

Drug Product: The Product Quality Review (Rajan Pragani signed 02/07/2017) describes the drug product as a sealed packet containing a single-dose of 5 g of L-glutamine powder. The Review comments that the drug product powder is the same as the drug substance powder. The drug product is packaged with the same quantity of L-glutamine (5 g) in the same container closure system as is used for the NutreStore® drug product (NDA 21-667). No overages are reported for L-glutamine packets. There are no excipients in the drug product. The review points out that the drug product packets are not manufactured [redacted]. The container configuration is common for this dosage form. The review found that stability data with this same container configuration is sufficient to support use of the container configuration.

Dosing instruction describe that the drug product is to be administered orally in increments of 5 grams with an upper limit of 30 g/day, administered twice daily. The L-glutamine powder should be mixed immediately before ingestion with water or any [redacted] beverage [redacted]

[redacted] or with any non-heated food such as yogurt, applesauce, [redacted]. Complete dissolution is not required prior to administration. In-use compatibility studies (individual studies with water, apple juice, milk, apple sauce, and yogurt) for the NutreStore® drug product were performed based on the intended dosing instructions. The results from the in-use study showed that oral L-glutamine is stable in the food items studied for at least 4 hours post preparation. The Review found the studies adequate to support the use instructions.

The Review found the quality control specification is adequate for the drug product. Batch analysis was provided for two commercial scale and three pilot scale drug product lots using the commercial process and HPLC tests (assay, related substances) were included in the three most recent commercial scale batches (that have not been packaged yet). The Review noted that the content (L-glutamine) and components of the primary and secondary container closure systems for oral L-glutamine packets are identical (except for text) to those used in the NutreStore® drug product (NDA 21-667), which has not had CMC issues. Seal integrity test was requested to be put in the specification and is expected to be tested in packaged full production commercial lots.

All methods except for appearance, HPLC (for assay, related substances), and seal integrity are compendial and performed according to the Glutamine USP monograph. The Review found the HPLC method was adequately validated for [redacted], [redacted], and additional unknown impurities.

The Review found the container closure information in the application is adequate to establish that the packaging components and materials are suitable for their intended use. The review commented that it should also be noted that the drug product is packaged in single-use foil packets that protect the contents from light (although photostability tests as per ICH Q1B showed no degradation of the L-glutamine drug substance). A tamper proof seal is included in the secondary carton container.

Regarding shelf-life the Review comments, "The applicant requests a 48 month shelf life when the product is stored at room temperature 20°C - 25°C (68°F - 77°F). This proposal is acceptable and supported by the 48 months of long term stability data of two drug product lots (made with [redacted] L-glutamine) and 36 month studies of three drug product lots (made with [redacted] L-glutamine) that shows no signs of degradation, diminished appearance, water content increase, pH change, or microbial growth. Additionally, the 48 month shelf life is supported by the stability data generated for commercial lots produced for NDA 21-667 (NutreStore®), which is the same drug product except for labeling." The Applicant has committed to a post-approval stability commitment to place on stability the first 3 full scale commercial drug product lots, consistent with the recommendations in ICH Guidance Q1A(R2) Stability Testing of New Drug Substances and Products.

The Applicant requested an exemption from an environmental assessment based on the categorical exclusion listed in 21 CFR 25.31(b) because the estimated concentrations of the active moiety at the point of entry into the aquatic environment will be below 1 part per billion (ppb) and to Emmaus' knowledge, no extraordinary circumstance exist that would warrant preparation of an environmental assessment. Also, the Applicant states the EIC is [redacted] ppb,

which is well below the 1 ppb limit set by 21 CFR 25.31(b). L-glutamine does not resemble [redacted] The Review finds the information adequate and recommends that categorical exclusion be granted.

The Quality Assessment, Final Risk Assessments (Rajan Pragani, 6/15/2017)indicates that stability assay, physical stability (solid state), content uniformity, and microbial limits are acceptable with low initial risk ranking. Palatability is found acceptable with medium initial risk ranking.

Process: The Process Review (Zhaoyang Meng, 6/13/2017) stated that the proposed drug product is manufactured by [redacted]

Facilities Review (Ephrem Hunde, 6/13/2017) evaluated the [redacted] manufacturing site in [redacted] that is responsible for manufacturing, release and stability testing, and bulk packaging of L-glutamine drug substance and noted that it was last inspected [redacted] with voluntary action indicated (VAI) outcome and no recalls or FARs. The firm was found to be acceptable. The [redacted] site for manufacturing, in-process testing, packaging and labeling of finished product was inspected [redacted] and found acceptable (status NAI) and [redacted] that is responsible for release and stability testing of finished drug product, and release testing of bulk drug substance was inspected on [redacted]. The [redacted] inspectors recommended withhold of the application due to product specific observations related to stability testing methods. OPF Division of Inspectional Assessment review of the establishment inspection report (EIR), the FDA-483 and the firm's response concluded that the observations did not warrant withhold and the final CDER decision is VAI (acceptable). (See Non Concurrence with withhold Recommendation for NFA 208587 L-glutamine powder Memorandum by Ephrem Hunde, 6/2/2017).

Biopharmaceutics: There is no biopharmaceutics assessment for this application. As stated in the Office of Pharmaceutical Quality (OPQ) Quality Assessment Executive Summary (Rajan Pragani, 6/15/2017), "Because the drug product is just the amino acid L-glutamine powder for oral administration, a biopharmaceutics review was deemed unnecessary."

Overall, the OPQ Quality Assessment recommends approval of NDA 208587 for Endari (L-glutamine oral powder), 5 grams per paper-foil-plastic laminate packet. The Executive

Summary states that as part of this action, OPQ grants a (b) (4) month re-test period for the drug substance for storage at (b) (4). OPQ grants a 48 month drug product expiration period for storage at 25°C ± 2°C/60% RH ± 5% RH in the commercial packaging.

4. Nonclinical Pharmacology/Toxicology

The primary Nonclinical Pharmacology/Toxicology Review of the application was conducted by Shwu-Luan Lee (final signature 6/1/2017 and 6/6/2017) . The major findings of the review are summarized below.

The Review describes that the nonclinical information in this application is derived entirely from pharmacodynamic, pharmacokinetic (PK), and toxicology data in the scientific literature and additional toxicology studies provided by the L-glutamine supplier (b) (4) and other pharmacology/toxicology data used to support this 505(b)(2) NDA were previously reviewed under NDA 21667 (Pharmacology/Toxicology Review by Ke Zhang, 5/7/2004).

For the current application the Pharmacology/Toxicology Review summarizes the review findings as follows:

> The pharmacology data provided comes mainly from published scientific articles, and provides the rationale for using L-glutamine in the treatment of SCD and related complications of the disease, such as severe anemia, frequent vasoocclusive processes, and occlusion which damages tissues.
>
> Increases in the rate of glutamine transport and higher active red cell glutamine affinity may increase glutamine availability, and increase the total nicotinamide adenine dinucleotide (NAD) content in sickle red blood cells (RBCs). Research data suggests that sickle RBCs have decreased NAD redox potential, manifested as decreased NADH/[NAD^++NADH] ratios, when compared with normal RBCs. At the same time, sickle RBCs have higher total NAD content than normal RBCs. Decreased NAD redox potential renders sickle RBCs more susceptible to oxidative damage. Oxidative damage may result in stimulation of inflammatory processes and expression of adhesion molecules in RBCs .Thus L-glutamine may improve the condition of sickle RBCs by increasing the NAD redox potential and NADH levels, thereby preventing some of the oxidative damage they typically experience.
>
> Most of the safety toxicology studies for L-glutamine that support this NDA (205857) were reviewed under NDA 21667. The current review cites excerpts of the review for NDA 21667 where relevant. In brief, the oral LD_{50} values were approximately 20 g/kg in mice and rabbits and approximately 10 g/kg in rats. The potential targets of organs of toxicity include the stomach, liver, and kidney.

Mechanism: The Pharmacology/Toxicology Review states that L-glutamine is an essential amino acid abundant in the body which functions as 1) a precursor of nucleic acids and nucleotides such as the pyridine nucleotides, NAD and its reduced form NADH, 2) a preferred fuel for rapidly dividing cells including hematopoietic cells, and 3) a precursor for glutathione (GSH). Based on literature cited by the Applicant, the rationale for use of L-glutamine in SCD

is based on its ability to increase the activity of NAD synthesis and elevate the NAD redox potential in sickle RBCs to counter the oxidant-dependent pathophysiology of the disease.

Safety Pharmacology: There were no safety pharmacology studies submitted in the NDA.

Absorption, Distribution, Metabolism and Excretion (ADME): There were no ADME studies conducted by the Applicant. The Review quotes from the Pharmacology/Toxicology Review of NDA 21667 for NutreStore (Ke Zhang, 5/5/2004): "Glutamine level in the body is maintained by dietary intake and synthesis from endogenous glutamate. The typical daily dietary intake of glutamine is ~5-10 g. Oral absorption of glutamine was demonstrated with peak plasma level of glutamine reached at ~1-1.5 hours after dosing in rats. Glutamine was distributed in the liver, lung, kidney, heart, spleen, muscle, and brain following dietary or intravenous administration in rats. Glutamine is formed in the body through the condensation of a glutamate and an ammonia molecule by glutamine synthetase with hydrolysis of ATP. In the reverse process, glutaminase deaminated glutamine to glutamate and ammonia. Approximately 66% radioactivity (15N) of glutamine was recovered in the urine following intravenous administration of radio-labeled glutamine in rats. Majority of the radioactivity (94%) was associated with urinary urea and only ~4% was as ammonia."

Toxicology: The Review includes the following table of toxicology findings from Dr. Zhang's Pharmacology/Toxicology Review of NDA 21667:

Species	Study details	Key Findings/comments
Mice, rats and rabbits	Single maximum tolerated dose (MTD) (Kyowa Kogyo Co., 1974; non-GLP)	LD_{50} values (g/kg) • Mouse: oral (20-22); IV (4.5) • Rat: oral (7.5-10.5) • Rabbit (male): oral (18.8)
Rats	Oral gavage[8]: 4, 6[9] and 10 g/kg/day for 30 days (n=10/sex/group)	• Mortality: Glutamine was lethal in the high dose due to "administration of the test substance suspension in large volumes" ("physical problem"). • Mean body weight: ~7% lower in the high dose males as compared to the control • Catarrh[10] in the stomach was noted in the L-glutamine groups but not in the control

		group.
Rats	Oral gavage: 2 and 4 g/kg/day for 180 days (n=10/sex/group) (non-GLP)	• Mean body weight: ~5% lower in the high dose females as compared to the control. • Slight decrease in hematocrit (10-11%) in the high dose males as compared to the control. • Serum glutamic pyruvic transaminase was significantly increased in the high dose males on Day 180 as compared to the control (26.8 IU and 12 IU, respectively). • Stomach: Catarrh in the stomach and infiltration of inflammatory cell and edema in gastric submucosa were identified in the both glutamine groups but not in control group. The catarrh in the stomach was noted on both Days 90 and 180. On Day 180: • Liver: fatty infiltration in the liver cells (slight, one each in the two dose groups) • Kidney: vacuolation of tubular epithelium (slight, 2 at high dose), protein case (slight, one at high dose)

[8] L-glutamine was suspended in 5% aqueous gum Arabic solution at 25-50% and volume of 0.16-2 ml/100 g body weight was given by oral gavage.
[9] It is noticed that the data from glutamine dose group of 6 g/kg/day were not presented in the tables in the result section.

Mutagenicity: Citing the Pharmacology/Toxicology Review of NDA 21667 the Review describes results from a published sister-chromatid exchange (SCE) study done to determine the effects of excessive amounts of amino acids on SCEs in human lymphocytes which showed a small and concentration-independent increase in SCEs that may not be of any clinical significance and noted no positive control was included in the study.

Pharmacology/Toxicology also reviewed additional toxicology information from literature included in the Carcinogenicity Assessment Document (CAC) submitted on 3/24, 2017 to support the Applicant's request for waiver of the requirement to conduct bioassays in animals to assess for the carcinogenicity of L-glutamine). Key findings reported in the review Memo-to-File (Shwu-Luan Lee, 6/6/2017) are summarized below:

13 weeks oral toxicity in rats:

- L-glutamine administered to rats in feed at up to 5% of the diet for 13 weeks was tolerated (approximating L-glutamine doses of 33-39 g/day for a 60 kg human).
- Slightly decreased body weight gains and increased urinary protein were observed at L-glutamine doses ≥ 2.5 % diet.
- The NOEL is 1.25% diet, which is equivalent to 833 mg/kg/day or 4998 mg/m^2/day in males and 964 mg/kg/day or 5784 mg/m^2/day in females (approximating 8-9 g/day in a 60 kg human).

Oral subchronic study in rats:

L-glutamine in feed levels up to 5% diet (estimated 3832-4515 mg/kg/day for male and female rats, or 38-45 g in 60 kg human subject) for 13 weeks was tolerated. The dose level of 3832-4515 mg/kg/day is also the NOAEL of the study.

Oral subchronic and genotoxicity studies;

- L-glutamine was not mutagenic in the Ames test.
- L-glutamine was not clastogenic in CHL/IU cells.

CHU=Chinese hamster lung

In vitro:

In studies conducted in vitro (CHO cells) or in vivo (rats, bone marrow cells), the treatments with L-glutamine and ascorbic acid (AA) did not induce chromosomal aberrations, while increased frequencies of chromosomal aberrations were observed in the DXR-treated cultures.

DXR=doxorubicin (positive control)

Monosodium glutamate (10 to 20000 μg/plate) was negative when tested in *Salmonella typhimurium* strains TA98, TA100, and TA1538 with and without metabolic activation

- Negative results were observed in peripheral blood samples collected from mice receiving oral doses of L-glutamine (150, 300 and 600 mg/kg) in the micronucleus assay and comet assay.
- Pretreatment of oral L-glutamine significantly alleviated the clastogenic (micronucleus assay) and genotoxic (Comet assay) damages of cisplatin.

Several lines of evidence indicate the carcinogenic potential of L-glutamine is likely low:

- L-glutamine supplementation does not stimulate tumor growth (Bartlett et al. 1995; Buchman 2001)
- L-glutamine can inhibit tumor cell proliferation (Yoshida et al. 1995; Liu et al. 2000), or decrease tumor size (Fahr et al. 1994; Klimberg et al. 1996; Shewchuk et al. 1997; Liu et al. 2000)
- L-glutamine increases natural killer cell (NK) activity against malignant cells (Fahr et al. 1994; Klimberg et al. 1996).

The Review Memo also states that results from several studies in which healthy adult male and female subjects received oral supplemental L-glutamine at daily doses ranging from 3-45 g for up to 10 weeks did not reveal any compound-related adverse effects. The memo recommended for labeling to include the following in Section 13.1:

L-glutamine was not mutagenic in a bacterial mutagenicity (Ames) assay, nor clastogenic in a chromosomal aberration assay in mammalian (Chinese Hamster Lung CHL/IU) cells.

Reproductive and Developmental Toxicology: Citing the Pharmacology/Toxicology Review of NDA 21667 the Review noted that a literature study in pregnant rabbits did not show evidence of teratogenicity, but the study did not cover the entire period of organogenesis and was not considered valid. The current Pharmacology/Toxicology Review comments that the current L-glutamine (NutreStore) label includes the following:

- Long-term studies in animals have not been performed to evaluate the carcinogenic potential of L-glutamine.
- Studies to evaluate L-glutamine's mutagenic potential have not been conducted. Animal reproduction studies and its potential for impairment of fertility have not been conducted with L-glutamine.

- It is also not known whether L-glutamine can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

The Review states, "Given the abundance of L-glutamine in the human body, high levels derived from food products, along with the long clinical history with the Listed Drug, and the proposed SCD patient population, additional nonclinical studies were not needed to support approval of NDA 208587."

The Review summarizes the non-clinical safety review conclusions as follows:

> L-glutamine is well characterized chemically, and considered to be a conditionally essential amino acid. Both NDA 208578 and NDA 21667 rely on publicly available scientific literature to describe key aspects of the pharmacology and toxicology of L-glutamine. Of the clinical studies described in the published literature, of note are a study in very-low-birth-weight infants and intensive care unit (ICU) subjects on renal replacement therapy. A range of L-glutamine doses were used in these studies, including the proposed oral L-glutamine dose of 30 g/day. There is a long history of L-glutamine consumption by and administration to humans. In addition, L-glutamine has been studied in a number of clinical conditions and is currently approved for the treatment of SBS. From the perspective of Pharmacology/Toxicology L-glutamine is reasonably safe for use by patients with SCD, and there are no nonclinical approvability issues.

Conclusions and Recommendations: The review concluded that there are no pharmacology/toxicology issues that preclude approval of L-glutamine for the indication and recommended approval. There were no recommendations for post-marketing studies.

The review states that the label for this product will retain much of the pharmacology/toxicology sections labeling for the Listed Drug (NutreStore) with minor modifications.

5. Clinical Pharmacology/Biopharmaceutics

The Office of Clinical Pharmacology (OCP) primary review of the application was conducted by Yuhong Chen (review signed 5/31/2017). The Review commented that no dedicated clinical pharmacology studies were conducted. The Applicant relied on publicly available data from published literature and the Nutrestore labeling to describe the clinical pharmacology. The Review includes the following summary information:

ADME: The review provides the following findings for L-glutamine ADME in humans:

- Absorption: Following a single oral dose of 0.1 g/kg (~8.5 g), mean peak L-glutamine concentration of 1028 μM (or 150 μg/mL) occurred approximately 30 minutes after administration. An oral glutamine dose of 0.3 g/kg (equivalent of 18 g to 32 g) resulted in a peak plasma concentration of 1328 ± 99 μmol/L at 45 minutes after dosing.
- Distribution: After an intravenous bolus, the volume of distribution is estimated to be ~ 200 mL/kg.

- Metabolism: Endogenous L-glutamine participates in various metabolic activities, including the formation of glutamate and the synthesis of proteins, nucleotides, and amino sugars. Exogenous L-glutamine is anticipated to undergo similar metabolism.
- Elimination: After an intravenous bolus, the terminal half-life is ~ 1 hour. L-glutamine is eliminated by glomerular filtration, but it is reabsorbed by the renal tubules.

Drug Interactions: No drug interaction studies have been conducted.

Clinical Pharmacokinetics: Review referred to NutreStore labeling. The Review also noted the PK following multiple oral doses has not been characterized. The effect of food on L-glutamine has not been evaluated. The effect of body weight, organ impairment or other intrinsic factors on the PK or PD has not been evaluated.

Major Issues: The Clinical Pharmacology Review examined data from the randomized, placebo controlled phase III trial (GLUSCC09-01)), with additional data from a smaller, randomized phase II trial (Study 10478). The major issue identified during review centered on justification for the dosing and related to concern that the lower daily doses of L-glutamine (10 grams or 20 gram daily) may not provide optimal benefit. The Review based this on the following observations:

- These dose levels [10 and 20 grams daily] did not increase the ratio of NADH to total NAD levels from the baseline in adult patients based on the results of the dose finding study (Study 8288), and the increase in the ratio of NADH to total NAD levels from baseline is the foundation of the Applicant's hypothesis that L-glutamine maybe a promising treatment for SCD.
- The Applicant did not provide justification for a weight based dose as compared to the flat dose used in the dose finding study.
- The efficacy data from the phase III trial suggests that patients with body weight ≤ 65 kg and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day may not benefit from L-glutamine compared to placebo [Rate of sickle cell crises per 48 weeks: L-glutamine 2 vs. placebo 2.5; hazard ratio: 0.87 (95% CI: 0.63, 1.19)]. Comparatively, the relative risk of 0.56 [95% CI: 0.41, 0.77] was estimated for patients administered a total daily dose of 30 grams.
- A subgroup analysis in pediatrics similarly suggests that pediatrics patients may not receive similar benefit as compared to adult patients and most pediatric patients were administered 10 grams or 20 grams per day.
- No PK and PD data was collected during the phase III trial or the phase II trial to support the proposed dose.

Because of these concerns regarding dosing, the Clinical Pharmacology Review recommended a post-marketing commitment (PMC) that the Applicant should conduct a study to optimize the dose in adult and pediatric patients with body weight ≤ 65 kg. The changes in the ratio of NADH to total NAD levels from the baseline should be measured in this study to support the dose optimization along with measures of efficacy and safety. The study population should reflect the typical population of patients with SCD in the United States, especially regarding renal and hepatic function.

The Review concluded the following:

> "L-glutamine oral powder reduced the mean frequency of crises compared to placebo in the total population [L-glutamine 3 vs. placebo 3.8 crises in 48 weeks; relative risk: 0.73 (95% confidence interval (CI): 0.55, 0.99)]. A subgroup analysis suggested patients with body weight ≤ 65 kg and treated with L-glutamine at dose levels 10 grams per day or 20 grams per day may not benefit from L-glutamine compared to placebo [L-glutamine 2 vs. placebo 2.5 crises in 48 weeks; relative risk: 0.87 (95% CI: 0.63, 1.19)]. Pediatric patients were included in this subgroup analysis and may show poorer response. The most common adverse reactions, sickle cell anemia with crisis and acute chest syndrome, occurred less frequently in patients administered L-glutamine oral powder vs. placebo."

Key review issues and recommendations were summarized as follows in the Clinical Pharmacology Review:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The results of the randomized phase III trial demonstrated fewer sickle cell crises in favor of L-glutamine oral powder relative to placebo in the total population. The results of the phase II trial similarly showed that the median number of crises in the patients administered L-glutamine oral powder was lower compared to patients administered placebo. Pharmacokinetic (PK) and pharmacodynamic (PD) samples were not collected during these trials.
General dosing instructions	The proposed total daily dose based on actual body weight is as follows: 10 grams (less than 30 kg), 20 grams (30 kg to 65 kg), or 30 grams (greater than 65 kg). The oral powder is to be mixed with cold or room temperature beverage or food. The effect of temperature or food on the bioavailability of L-glutamine was not evaluated.
Dosing in patient subgroups (intrinsic and extrinsic factors)	Dose individualization is recommended based on actual body weight. The effects of organ impairment or other factors were not evaluated. A trial to determine an appropriate dose for patients with body weight ≤ 65 kg will be recommended based on subgroup analysis that suggests less benefit for patients who received a dose of 10 grams or 20 grams, including patients ≤ 18 years.
Labeling	Generally acceptable. The review team made recommendations for specific content and formatting changes.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed drug product was administered in the phase III and phase II trials.

Overall, the Review recommended approval of the NDA from a clinical pharmacology perspective.

6. Clinical Microbiology

n/a

7. Clinical/Statistical- Efficacy

The primary Joint Clinical and Statistical Review of the application was completed by Rosanna Setse and Che Smith, final signature 6/7/2017. Following is a description of the major trials and a summary of the efficacy results based on the Joint Clinical and Statistical Review. Refer to the Review for more detailed description of the studies and study results.

Study GLUSCC09-01:
GLUSCC09-01 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter, U.S. study to evaluate the long-term safety and efficacy of Endari (L-glutamine) for the treatment of SCD in patients with sickle cell anemia and sickle β^0-thalassemia at least 5 years of age. Patients were randomized in a 2:1 ratio (Endari: placebo) and randomization was stratified by investigational site and prior hydroxyurea usage (HU; yes/no). The primary objective was to determine the efficacy of oral L-glutamine as a therapy for sickle cell anemia and sickle β^0-thalassemia as evaluated by the number of occurrences of sickle cell crises. The secondary efficacy objectives were to assess the effect of oral L-glutamine on the frequency of hospitalizations for sickle cell pain; frequency of emergency room/medical facility visits for sickle cell pain; and hematological parameters (hemoglobin, hematocrit, and reticulocyte count). The study population consisted of patients with SCD documented by hemoglobin electrophoresis who were at least 5 years and older and who had had at least 2 episodes of painful crises within 12 months prior to screening. Patients being treated with an anti-sickling agent within three months of the Screening Visit must have been continuous for at least three months with the intent to continue for the duration of the study. Study treatments were Endari (L-glutamine) approximately 0.3 mg/kg (total daily dose) or placebo (100% maltodextrin) taken orally twice daily for 48 weeks. After 48 weeks of treatment, the dose was tapered gradually to zero over three weeks and a final evaluation visit occurred two weeks after last dose. Study drug (L-glutamine and placebo) was supplied as packets containing 5 grams powder to be mixed with water or (b) (4) beverage or food such as yogurt, applesauce or cereal.

The primary efficacy endpoint was the number of sickle cell crises through Week 48 and prior to start of taper. A sickle cell crisis was defined as a visit to an emergency room/medical facility for SCD-related pain that was treated with a parenterally administered narcotic or parenterally administered Toradol (ketorolac). The occurrence of chest syndrome (acute clinical pulmonary findings corroborated by findings of a new pulmonary infiltrate on chest X-ray films), priapism, and splenic sequestration were considered sickle cell crises even if the symptoms were not painful enough to require narcotics or Toradol (ketorolac). Splenic sequestration was defined as an increase in spleen size associated with pain in the area of the organ along with a decrease in the hemoglobin concentration of at least 2 g/dL within a 24-hour period. Sickle cell crisis events were centrally adjudicated.

Study 10478:
Study 10478 was a multicenter, U.S., double-blind, randomized, placebo-controlled study of the long-term safety and efficacy of Endari compared to placebo for the treatment of SCD in patients with sickle cell anemia and sickle β^0-thalassemia who were at least 5 years of age.

The study design was similar to that of Study GLUSCC09-01 with notable differences including in Study 10478:

- Patients were randomized in a 1:1 ratio (rather than 2:1)
- Randomization was stratified by investigational site but not by HU use.
- A painful sickle cell crisis was defined as a visit to a medical facility that lasted more than 4 hours (from the date/time of registration to the date/time of departure) for an acute sickling-related pain; treated with a parenterally administered narcotic (except for facilities in which only orally administered narcotics were used). The occurrence of acute chest syndrome (chest-wall pain in association with findings of a new pulmonary infiltrate on chest x-ray films and fever), priapism, and hepatic or splenic sequestration (a sudden increase in liver or spleen size associated with pain in the area of the organ, a decrease in the hemoglobin concentration of at least 2 g/dL, and, for liver sequestration, abnormal change in liver function tests not due to biliary tract disease) was to be considered a crisis; the occurrence of hematuria and exacerbations of pain was not considered a crisis.
- Sickle cell crisis events were classified by a programming algorithm

Study results: In Study GLUSCC09-01, a total of 230 patients were enrolled across 31 study sites, with 152 patients randomized to treatment with Endari compared to 78 patients randomized to placebo treatment. Patient characteristics at baseline were mostly similar between arms in each study. Patient age at baseline ranged from 5 years to 58 years. At study entry in Study GLUSCC09-01 about 67% of patients in both the Endari arm and the placebo arm had been taking hydroxyurea for at least three months prior to enrollment. In Study GLUSCC09-01 the mean number of sickle cell crises per protocol per patient during prior year at study entry was 3.9 in the Endari arm (median, 3.0; range 0-16) and 4.1 in the placebo arm (median, 3.0; range 0-18). Overall, about 32% of the 230 enrolled patients dropped out of Study GLUSCC09-01 before the full 48-week treatment period, with a higher dropout rate among patients randomized to the Endari arm (36%) compared to the placebo arm (24%).

In Study 10478, a total of 81 patients were enrolled at 5 study sites, with 42 patients randomized to treatment with Endari compared to 39 patients randomized to placebo treatment. One study site was suspected by the Applicant of potential misconduct; as a result, data for 11 patients enrolled at this site are omitted throughout this review, leaving 70 patients. Patient characteristics at baseline were mostly similar between arms in each study. Patient age at baseline ranged from 9 years to 58 years. At study entry in Study 10478 about 62% of patients in the Endari arm compared to 39% in the placebo arm had been taking hydroxyurea for at least three months prior to enrollment. The lack of stratification for HU use in the study is considered a major flaw which confounds interpretation of the study results. In Study 10478 the mean number of sickle cell crises per protocol per patient during prior year at study entry was not documented as a number but rather noted only as a yes/no answer to question 'Has the patient had at least two episodes of painful crises within the last 12 months?' In Study 10478, overall, about 57% of the 70 enrolled patients dropped out of the study before the full 48-week treatment period, (Endari, 51%; placebo, 64%).

The large dropout rate and differential dropout rates between treatment arms complicated interpretation of the study results. The Review states: "Although reasons given for study

withdrawal are not sufficiently informative, the fact that dropout differs by treatment group in both studies suggests that missing data are not missing at random. This assumption has a wide impact on the choice of approach used to handle incomplete data (e.g., imputation), as well as the choice of analytic method to assess the treatment effect. Most analytic methods are asymptotically valid under the 'missing at random' assumption, but not under the assumption that data are "missing not at random".

Regarding analysis and interpretation of the efficacy results of these studies, the Review comments:

> Efficacy results from Studies 10478 and GLUSCC09-01 are not considered to be comparable, due to differences in the definitions and classification of the primary endpoint, the number of sickle cell crises experienced through Week 48 of treatment. Patients in Study 10478 experienced a wider range of crises within the 48-week treatment period (0 to 90 crises) compared to patients in Study GLUSCC09-01 (0 to 15 crises). Study GLUSCC09-01 randomized patients in a ratio of 2:1 to Endari vs. placebo treatment, while Study 10478 randomized patients to assigned treatment groups in a 1:1 ratio. Randomization in Study GLUSCC09-01 was stratified by study site and baseline hydroxyurea use; in Study 10478, randomization was stratified only by study site. Additionally, early study dropout was high and differential between treatment arms in both studies; more than half of patients enrolled in Study 10478 dropped out of the study before the full 48-week treatment period. For these reasons, the Agency reviewed efficacy results separately for each study.

The Applicant's table showing the Primary Efficacy Analysis results is reproduced below from the Joint Clinical and Statistical Review:

Table 11: Primary Efficacy Analysis, Number of sickle cell crises, by Study and Treatment group

Parameter	Study 10478		Study GLUSCC09-01	
	Endari (N = 33)	Placebo (N = 29)	Endari (N = 152)	Placebo (N = 78)
Primary Analysis				
Mean (SD)	4.5 (5.37)	10.8 (18.74)	3.2 (2.25)	3.9 (2.53)
Median (min, max)	4 (0, 27)	5 (0, 90)	3 (0, 15)	4 (0, 15)
p-value (controlling for study center)	0.072		---	
p-value (controlling for region and HU use)	---		0.0630	
p-value (Applicant re-analysis*)	---		0.0052	

*In the Integrated Summary of Efficacy, the Applicant submitted a "re-analysis" of the primary efficacy endpoint in Study GLUSCC09-01

SOURCE: Table 14 of Applicant's Integrated Summary of Efficacy

The Applicant's primary efficacy analysis of Study 10478 did not meet its prespecified significance level.

In assessing the analyses the review discusses the Applicant's pre-defined mode for handling missing data by imputation. The review comments:

Because of high and differential dropout rates in Study GLUSCC09-01, the CMH test is not the optimal analytic method to compare the distribution of sickle cell crisis counts between treatment groups. The Applicant's imputation method assigned a crisis count of 3 to any patients from the Endari treatment group who dropped out of the study early having experienced fewer than 3 crises, and a crisis count of 4 was assigned to placebo patients who dropped out of the study early having experienced fewer than 4 crises. These imputed values represent the rounded average crisis count among patients in the assigned treatment group who completed the 48-week treatment period. Any patients who dropped out of the study early with more than the average crisis count among completers from their treatment group did not have an imputed value; their crisis count at time of dropout was carried forward as their count through 48 weeks. This method of imputation may have introduced bias in the primary and secondary efficacy results.

As an alternative to the Applicant's imputation method the FDA Statistical review team conducted alternate sensitivity analyses which made use of the actual data available for patients who had at least one crisis reported but did not complete the entire treatment duration. The following table from the Joint Clinical and Statistical Review shows the numbers of patients by study experience.

Table 12: FDA Exploratory Analysis: Patient Experiences on Study GLUSCC09-01, Number (%) of patients by study experience

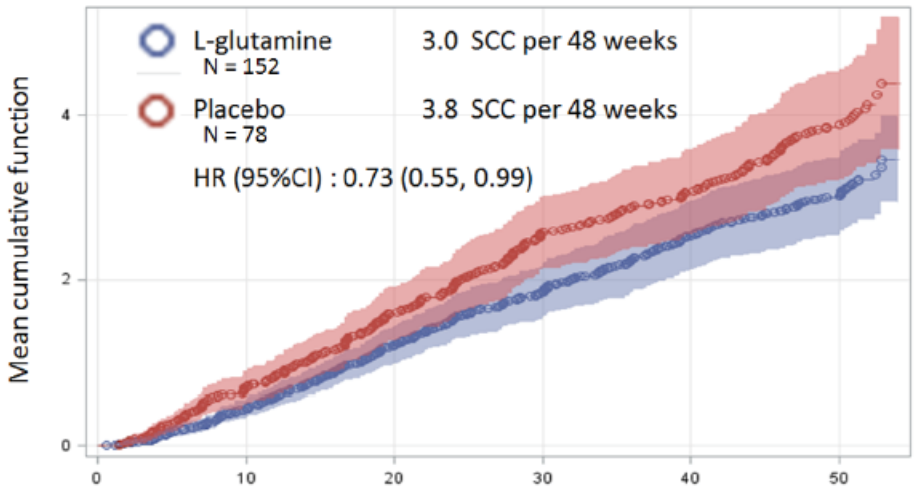
Study Experience	Endari (N = 152)	Placebo (N = 78)
Completed study; at least one crisis recorded	82 (53.9)	55 (70.5)
Completed study; no crises recorded	15 (9.9)	4 (5.1)
Did not complete study; at least one crisis recorded	35 (23.0)	15 (19.2)
Did not complete study; no crises recorded	20 (13.2)	4 (5.1)
Total	152	78

SOURCE: FDA Reviewer Analysis

The Review explains the FDA approach to the data assessment as follows:

An alternative analysis was performed by FDA in an effort to overcome the difficulties caused by the incomplete data records. A recurrent event analysis based on the proportional rate regression model (Lawless and Nadeau, 1995; Lin et al., 2000) was performed by FDA to incorporate information on patients' time spent on study and to take into account the fact that times between crisis events for a patient are not necessarily independent. Covariances for the estimators of the regression parameters $\hat{\beta}$, accounting for the dependence structure of the recurrence times, can be computed using a robust (or sandwich) estimator. In this analysis, there is no need for imputation of incomplete crisis counts and all events (as well as timing of events) are included. Patients without any events were censored at their last visit. Based on this analysis, FDA obtained a hazard ratio of 0.73 (95% CI: [0.55, 0.99]) in favor of the ENDARI treatment group. In the figure below, mean cumulative numbers of crises up to time t (in weeks) is plotted (Nelson, 2003), which is analogous to the Nelson-Aalen estimator for the cumulative hazard function of time to event data. The estimated SCC counts at 48 weeks are 3.8 (95% CI: [3.1, 4.5]) and 3.0 (95% CI: [2.5, 3.4]) for patients in the placebo and Endari and treatment groups, respectively.

Figure 3: FDA Analysis: Mean cumulative functions for sickle cell crisis events by treatment group



SOURCE: FDA Reviewer Analysis

Figure 4: FDA Analysis: Estimated 48-week sickle cell crisis event count by treatment group, recurrent event analysis, ITT population (N = 230)

	Endari (N = 152)	Placebo (N = 78)
Estimated sickle cell crisis event count (95% CI)	3.0 (2.5, 3.4)	3.8 (3.1, 4.5)
Hazard Ratio, Endari vs. Placebo (95% CI)	0.73 (0.55, 0.99)	

SOURCE: FDA Reviewer Analysis

In commenting on the analysis the review states, "The FDA analysis of sickle cell crises as recurrent events takes relevant study information into account to compare the number of crises between treatment groups at Week 48 without requiring imputation of incomplete data, although the analysis requires an assumption of independent censoring. Overall, the result favors Endari treatment over placebo."

Additional exploratory sensitivity analyses in the Review using negative binomial regression (NBR) showed trends in favor of Endari.

Table 15: FDA Exploratory Analyses: Rates of sickle cell crisis counts per 48 weeks between treatment groups, Negative binomial regression

FDA Analysis Set	Endari (N = 132)	Placebo (N = 74)	Rate Ratio for Endari vs. Placebo [95% CI]
FDA sensitivity analysis population (data consisting of rows 1-3 of Table 12 above) (95% CI), N=206	3.3 (2.8, 3.8)	4.1 (3.3, 4.9)	0.80 [0.64, 1.01]
ITT population, assuming crises counts for row 4 in Table 12 are "0" (95% CI), N = 230	3.3 (2.7, 3.9)	4.2 (3.4, 5.1)	0.77 [0.61, 0.99]
Multiple imputation for crises counts in row 4 of Table 12 using fully conditional specification*, ITT population (95% CI), N=230	3.9 (3.3, 4.5)	4.3 (3.2, 5.4)	0.91 [0.73, 1.12]

All analyses use time on study as an offset and control for study stratification factors (region of study site and baseline hydroxyurea use)
*Multiple imputation approach imputes crisis counts for 24 patients using information on treatment group, study stratification factors, time on study, baseline age, and baseline crisis count
SOURCE: FDA Reviewer Analyses

The applicant's NBR sensitivity analyses similarly showed trends in favor of Endari.

The Review cautions, "It is important to note that there is no ideal post-hoc analysis that can overcome the amount and differential nature of study dropout in Study GLUSCC09-01. There is no optimal imputation approach or analytic method that can estimate the true 48-week sickle cell crisis counts of patients who dropped out of the study early. The analyses presented here represent a spectrum of assumptions that can be made about the observed data. They are mean to show that, when incomplete crisis counts are handled differently than the Applicant's method and analysis of the primary efficacy endpoint takes time on study into account to compare rates of crises between treatment groups after 48 weeks of treatment, the results trend in favor of Endari. However, in some cases, upper limits of confidence intervals for rate ratios comparing treatment groups include a ratio of 1."

Trends for prespecified secondary efficacy endpoints for both studies, including number of sickle cell crises through Week 24, number of hospitalizations through Week 24, number of emergency room visits through Week 24, number of hospitalizations through Week 48, and number of ER visits through Week 48 by-and-large were consistent with an efficacy benefit of Endari.

The Review also comments that there were additional endpoints for which unplanned analyses were performed – Incidence of ACS, Time to First Sickle Cell Crisis and Cumulative Time in Hospital through Week 48. There were 2 occurrences of ACS in Study 10478, so no analyses were performed on this endpoint. Results for the unplanned secondary endpoints of ACS in Study GLUSCC09-01 are summarized in the table below from the Joint Clinical and Statistical Review. Results of additional unplanned endpoint analyses are included in the Review.

Table 18: Unplanned secondary efficacy endpoint: Incidence of Acute Chest Syndrome in Study GLUSCC09-01, by Treatment Group

Endpoint	Study GLUSCC09-01	
	Endari (N = 152)	Placebo (N = 78)
Incidence of Acute Chest Syndrome		
Mean (SD)	0.1 (0.37)	0.3 (0.63)
Median (min, max)	0 (0, 2)	0 (0, 3)
Nominal p-value (controlling for region and HU use)	0.0028	

SOURCE: Applicant's Integrated Summary Efficacy Table 21

Efficacy results among various population subsets were examined and are shown in the table below. The review comments, "All subgroup analyses should be interpreted with caution since none were pre-specified; these analyses may generate additional hypotheses about the efficacy of Endari among specific subpopulations, but should be considered confirmatory of the primary efficacy result."

Table 21: Efficacy results among subgroups in Study GLUSCC09-01 by treatment group; rate of sickle cell crises per 48 weeks*

	Estimated sickle cell crisis count per 48 weeks (95% CI)		Rate ratio [Endari vs. Placebo] (95% CI)
	Endari (N = 132)	Placebo (N = 74)	
Age group			
≤18	3.3 (2.7, 4.0)	3.5 (3.4, 5.4)	0.95 (0.69, 1.29)
>18	3.6 (2.8, 4.5)	5.5 (4.1, 7.4)	0.67 (0.48, 0.94)
Sex			
Female	3.4 (2.7, 4.2)	3.9 (3.1, 5.0)	0.86 (0.63, 1.17)
Male	3.1 (2.5, 4.0)	4.4 (3.2, 6.0)	0.71 (0.50, 1.02)
Race/Ethnicity			
Black	3.4 (2.9, 4.0)	4.3 (3.6, 5.3)	0.79 (0.62, 1.00)
Hispanic/Other	1.6 (0.4, 6.1)	1.8 (0.5, 6.8)	0.89 (0.28, 2.83)
Hydroxyurea Use at Baseline+			
Yes	3.4 (2.8, 4.1)	4.3 (3.4, 5.4)	0.79 (0.59, 1.06)
No	3.2 (2.4, 4.1)	3.8 (2.8, 5.1)	0.83 (0.58, 1.21)
Region of Study Site^			
Midwest	4.3 (2.9, 6.6)	4.3 (2.8, 6.6)	1.01 (0.59, 1.73)
Northeast	2.3 (1.7, 3.2)	4.4 (3.1, 6.3)	0.53 (0.33, 0.84)
South Atlantic	3.5 (2.5, 5.0)	2.7 (1.8, 4.1)	1.29 (0.82, 2.05)
South Central	2.9 (2.0, 4.3)	3.9 (2.5, 6.3)	0.74 (0.41, 1.34)
West	3.6 (2.6, 4.8)	4.9 (3.4, 7.1)	0.73 (0.45, 1.17)
Dose Level			
<30 g	3.5 (2.9, 4.3)	3.9 (3.0, 5.1)	0.90 (0.66, 1.22)
30 g	2.9 (2.3, 3.7)	5.0 (4.0, 6.4)	0.58 (0.43, 0.79)

*Based on negative binomial regression model, controlling for study stratification factors
+Model controls for region of study site only
^Model controls for baseline hydroxyurea use only

SOURCE: FDA Reviewer Analysis

Regarding efficacy of Endari the Joint Clinical and Statistical Review concludes:

In summary, there were more early study dropouts than anticipated in Study GLUSCC09-01, with more dropouts from the Endari treatment group. The Applicant used imputation to fill in incomplete sickle cell crisis event counts in Study GLUSCC09-01; due to high and differential dropout rates between treatment groups, the imputation method used by the Applicant may have introduced bias in the primary and secondary efficacy analyses. FDA analyses considered alternative methods of handling incomplete crisis event counts that did not rely on imputation of incomplete counts and incorporated relevant study information such as the time spent on treatment before dropping out of the study. Particularly, a recurrent time-to-event analysis performed by FDA estimated sickle cell crisis rates per 48 weeks of 3 crises for patients treated with Endari vs. 3.8 crises for patients treated with placebo (HR: 0.73, 95%CI: [0.55, 0.99]). Other exploratory analyses performed by FDA and the Applicant yielded results in favor of Endari, though the magnitude of benefit was modest compared to the Applicant's primary efficacy analysis using the CMH test. In the presence of high and differential study dropout, no imputation approach or analytic method is ideal since there is no way to know what the true 48-week crisis counts would have been for patients who dropped out of the study early. This apparent trend of an Endari benefit should be considered in the context of the product's safety profile.

8. Safety

The primary Joint Clinical and Statistical Review of the application was completed by Rosanna Setse and Che Smith, final signature 6/7/2017. Following is a description of the major findings of the safety review of the application based on the Joint Clinical and Statistical Review. Refer to the Review for more detailed description of the safety results.

The safety of Endari in this application was based primarily on review of safety data presented in clinical studies GLUSCC09-01 and Study 10478. Additional safety information was sought from the Legacy studies (Studies 8288, 8822, 8775, 10779, and 10511) conducted early in the clinical development program of L-glutamine, and from a review of the published literature.

The Safety population in Studies GLUSCC09-01and 10478 consisted of 298 subjects (187 subjects treated with Endari and 111 subjects treated with placebo) who received at least 1 oral dose of Endari or placebo equivalent to 0.3 g/kg administered twice daily, resulting in daily doses of 30, 20, or 10 g based on subject body weight. Median age was 22 years (range 5 to 58 years), 57% of patients were age >18 years, about 54% of patients were females, 97% of patients were Black, about 90% of patients had sickle cell anemia, and 63% of patients had hydroxyurea use at baseline. Generally, these characteristics were similar between treatment arms except for HU use which was 66% in the Endari patients and 59% in the placebo patients. A summary of drug exposure from these is shown in the following table from the Review.

Table 22: Summary of Drug Exposure (Safety Population)

	Endari N = 187	Placebo N = 111	Total N = 298
Duration of exposure* (days) Mean (SD)	268.9 (126.92)	283.3 (121.63)	274.3 (124.96)
Subjects with exposure, n (%)			
≥ 1 day	187 (100.0)		
≥ 12 weeks	161 (86.1)	98 (88.3)	259 (86.9)
≥ 24 weeks	136 (72.7)	89 (80.2)	225 (75.5)
≥ 48 weeks	109 (58.3)	73 (65.8)	182 (61.1
Number of subject-years**	137.7	86.1	223.8

FDA generated table
Data Source: Applicants ISS Table 3

Four deaths occurred in the safety population. Three deaths occurred in Study GLUSCC09-01. One death occurred in Study 10478. All 4 deaths occurred in Endari-treated subjects. Three deaths were treatment emergent. One death occurred more than 30 days (120 days) after the last dose of study medication and was not considered treatment emergent. No deaths were considered related to study treatment by the investigator. The treatment emergent deaths included:

- A 46 year old woman receiving Endari 15 grams twice daily who after approximately 41 weeks of treatment presented to the emergency room with "acute sickle cell crisis" and CPR in progress and died. Cause of death was listed as cardiopulmonary arrest. The patient had had 1 SCC during the study. There were no significant abnormal physical or laboratory findings. There was no autopsy.
- A 45 year old man with sickle cell anemia receiving Endari 10 grams twice daily for about 49 weeks suffered an acute infarct/transient ischemic attack with sequelae, acute/chronic renal failure, and cardiac arrest during the study. He died on Study day 349 due to cardiac arrest.
- A 37 year old woman with sickle cell anemia receiving Endari 15 grams twice daily died on Study Day 331 of multiple medical problems including respiratory failure, cardiopulmonary arrest and severe hypoglycemia.
- A 10 year old boy died of cause listed as "cardiopulmonary arrest secondary to SIRS, DIC, septic shock, questionable acute abdomen, and HbSS 3 months after completing Study.

Sufficient data is not available for any of the on-treatment deaths to definitively evaluate relationship to Endari. In discussing these cases the Applicant compared the mortality rate observed in the Endari safety population to safety data from published studies that evaluated the effect of Hydroxyurea on mortality and morbidity in adult sickle cell anemia patients using data from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH) trial with 9 years of follow-up and found a rate of 3.1 deaths per 100 patient-years for patients originally randomized to hydroxyurea, 3.6 for patients originally randomized to placebo, and 3.3 for the overall population. The Applicant stated that these rates are all higher than the mortality rate per 100 patient-years seen in the Endari safety population and thus provides evidence that the mortality rate observed in the Endari population is not greater than the expected mortality rate in this population. The Clinical Reviewer commented that the

mortality rate per 100 patient-years and the crude mortality rate observed with Endari in the overall safety population were 2.2 and 1.6% respectively, and while the role of Endari treatment in causing these fatal SAE cannot be categorically ruled out (and noting than Endari treatment may be life-long) , a causal role does not seem likely due to apparent safe use of L-glutamine as a nutritional supplement, mortality rate of patients receiving Endari being similar to published rates in studies of similar patients with sickle cell disease, and known overall decreased life expectancy associated with sickle cell disease.

The most common serious adverse events (SAEs) reported during the studies are summarized in the following table from the review:

Table 26: SAEs occurring in ≥ 2% of Endari-treated Subjects, by PT (Safety Population)

PT	Endari (N = 187)		Placebo (N = 111)	
	Number of subjects	(%)	Number of subjects	(%)
Sickle cell anemia with crisis	124	66.3	80	72.1
Acute chest syndrome	13	6.9	21	18.9
Pneumonia	9	4.8	10	9.0
Chest pain	5	2.7	2	1.8
Pyrexia	5	2.7	4	3.6
Asthma	4	2.1	3	2.7
Pregnancy	4	2.1	3	2.7

Source: FDA Reviewer analysis

As discussed under the Efficacy section above, there was a high rate of study discontinuation in both treatment arms (37.6% overall for the safety population). However, discontinuation rates due to adverse events were low (2.7% for Endari and 0.9% for placebo) and numbers of patients for adverse event withdrawals were small. The events that led to these withdrawals are summarized in the following table.

Table 28: TEAEs leading to study drug withdrawal, Safety Population (N=298)

	Endari N = 187 n (%)	Placebo N = 111 n (%)
Subjects with ≥1 TEAE that led to study withdrawal	5 (2.7)	1 (0.9)
Hypersplenism*	1(0.5)	0 (0.0)
Abdominal pain*	1(0.5)	0(0.0)
Dyspepsia*	1(0.5)	0(0.0)
Burning sensation	1(0.5)	0(0.0)
Pregnancy	1(0.5)	1 (0.9)
Hot flash*	1(0.5)	0

*Drug related TEAEs
FDA generated table

Examination of clinical laboratory data: Potentially clinically significant changes in liver function tests for potential drug-induced liver injury (DILI) [defined by an ALT >3 times ULN, total bilirubin > 2 times ULN, and alkaline phosphatase < 2 times ULN] were noted for five subjects in the Endari arm and 2 subjects in the placebo arm of Study GLUSCC0901and no patients in Study 10478. Of these potential DILI cases, all had possible other causes

including 3 with some LFT elevations at baseline or screening and one with viral hepatitis. However, the Clinical reviewer comments: "*Patients with uncontrolled liver disease or renal insufficiency were excluded from both studies 10478 and GLUSCC09-01. Overall, there was minimal change in the values of BUN and creatinine among Endari treated subjects over the study duration. However, since renal disease is common among patients with sickle cell disease, and Endari is eliminated at least in part by the kidneys, this reviewer agrees with the clinical pharmacology reviewer recommendation for conducting renal impairment studies for Endari in patients with severe renal abnormalities.*"

Explorations of occurrence of adverse events in various subgroups noted that although some TEAES occurred at a much higher frequency in pediatric vs adult patients treated with Endari [ACS (16.3% vs 5.6%), constipation (31.3% vs 14.0%), pyrexia (27.5% vs 9.3%), pain in extremity (22.5% vs 6.5%), back pain (21.3% vs 5.6%), and cough (25.0% vs 8.4%)], a similar pattern was observed in placebo treated patients.

The most common SAE among patients in both treatment groups was sickle cell anemia with crisis (82.1% of Endari patients and 88.7% of placebo patients). There were no notable differences in occurrence of treatment emergent AEs by sex. Analysis of adverse reaction occurrence by race was limited by small number of non-Black patients.

Analysis of adverse events by hydroxyurea use is summarized in the following table from the review. Patients with HU use tended to have slightly higher rates of adverse events in both Endari and placebo treatment arms:

Table 48: AEs by Hydroxyurea (HU) use

	Endari N = 187		Placebo N = 111	
Subjects with at least 1,	HU use at baseline n=124	No HU use at baseline n=63	HU use at baseline n=65	No HU use at baseline n=46
TEAEs, n (%)	122 (98.4)	58 (92.1)	65 (100.0)	43 (93.5)
TEAEs leading to withdrawal from study, n (%)	2 (1.6)	3(4.8)	1 (1.5)	0
SAE, n (%)	100 (80.6)	41 (65.1)	57 (87.7)	32 (69.6)
Sickle cell anemia with crisis	107 (86.3)	45 (71.4)	60 (92.3)	37 (80.4)

Source: FDA analysis

No drug-drug interaction studies with Endari were conducted.

9. Advisory Committee Meeting

This application was presented and discussed at a meeting of the Oncologic Drugs Advisory Committee on May 24, 2017. As summarized in the Joint Clinical and Statistical Review:

The main issues with the application for which AC input was sought were:

- The impact of incomplete data and imputation methods on efficacy results
- Clinical meaningfulness of the observed effect size

The advisory committee vote was requested for the following question:

- Based on the available data presented and discussed, is the overall benefit/risk profile of L-glutamine for the treatment of sickle cell disease favorable?

The Applicant presented the disease background and medical need, a summary of the efficacy and safety results and the Clinical Risk- benefit summary from the Applicants perspective. FDA reviewers presented statistical review considerations and overall findings from the review of this Application.

The committee acknowledged the statistical concerns identified by FDA as well as the modest benefit of Endari demonstrated in the pivotal study, but also recognized the favorable safety profile of Endari and the huge unmet need for new treatments for SCD. After detailed discussions and deliberations, the committee voted 10 (Yes) to 3 (No) in favor of approval of Endari for the treatment of sickle cell disease.

10. Pediatrics

As noted in the Joint Clinical and Statistical Review, since L-glutamine has orphan designation for the treatment of SCD, this submission is exempt from the requirements of the Pediatric Research Equity Act (PREA).

Pediatric patients age 5 years and older were included in t both clinical Studies 10478 and GLUSCC09-01 for the indication and efficacy and safety in the pediatric population are included in the discussion under sections 7 and 8 above.

11. Recommendations/Risk Benefit Assessment

The Joint Clinical and Statistical Review provides the following Overall Benefit-Risk summary:

SCD is a serious and life-threatening condition associated with recurrent vaso-occlusive pain or crises episodes and chronic hemolytic anemia. The cumulative effect of recurrent vaso-occlusive episodes and sustained hemolytic anemia result in multiple end-organ complications and a decreased life expectancy. Hydroxyurea is the only drug approved for reducing the frequency of sickle cell crises in adult patients with SCD. There is a huge unmet medical need for new drugs for the treatment of SCD.

In a multicenter, randomized, double-blind, placebo- controlled study (Study GLUSCC09-01), patients with sickle cell anemia and sickle β^0-thalassemia ($\geq$ 5 years of age) who had 2 or more painful crises in the 12 months prior to enrollment were treated with Endari or placebo and evaluated for efficacy and safety through Week 48. FDA analysis estimated the mean cumulative rates of SCC of 3 vs 3.8, for L-glutamine vs placebo group at 48 weeks [HR 0.73, 95% CI: (0.55, 0.99)]. Per the Applicants analysis, the median number of SCC at Week 48 was 3 vs 4 for the Endari vs. placebo groups respectively (p=0.0052). Treatment with Endari also resulted in fewer hospitalizations due to sickle cell pain at Week 48, cumulative days in hospital and a lower incidence of acute chest syndrome across the 48-week treatment period.

The statistical analysis was complicated by a high and differential rate of patient discontinuation from the study before completion of the full 48-week treatment period, which necessitated invocation of imputation methods. FDA sensitivity and exploratory analyses showed a trend in favor of L-glutamine.

The safety review revealed no significant safety concerns overall. Three treatment emergent deaths occurred in L-glutamine-treated subjects. None of these deaths were considered related to L-glutamine treatment by Investigators. The proportion of subjects with SAEs, TEAEs, drug related SAEs, drug related TEAEs and TEAEs that lead to study withdrawal was comparable between the treatment groups. The lower frequency of SCA with crisis and lower frequency of acute chest syndrome in Endari treated subjects suggest a beneficial effect. As expected for this population, the most common adverse event in study subjects was SCA with crises. Other common adverse events in L-glutamine treated subjects were: constipation (21.4%), nausea (19.3%), headache (18.2%), pyrexia (17.1%) and cough (15.5%).

Although some caution is warranted in interpretation of the primary efficacy results from Study GLUSCC09-01, in both the Applicants' and FDA's analysis, Endari treatment was associated with fewer sickle cell crises at Week 48 compared to placebo treatment. This finding is supported by the observed fewer hospitalizations due to sickle cell pain, cumulative days in hospital and a lower incidence of ACS in Endari treated patients across the 48-week treatment period. The lower frequency of disease related SAEs (SCA with crisis and ACS) in Endari treated subjects provides further support for a beneficial effect of Endari treatment in patients with SCD. Considering the observed favorable safety profile of Endari in safety population, the potential benefit from treatment with Endari appears to outweigh the risks in patients with SCD.

I concur with the recommendation of the Joint Clinical and Statistical Review that Endari should be approved for treatment of patients age 5 years and older with sickle cell disease

(b) (4)

The proposed total daily dose of Endari is 10 grams, 20 grams, or 30 grams orally, in two divided doses based on body weight as was administered in the clinical studies. However, the Joint Clinical and Statistical Review notes that In Study GLUSCC09-01, subgroup efficacy analysis suggested a lower benefit of Endari in patients with baseline body weight of $\leq$ 65 kg treated with 10 grams per day or 20 grams per day of L-glutamine compared to placebo [Endari 2 vs. placebo 2.5 crises in 48 weeks; relative risk: 0.87 (95% CI: 0.63, 1.19). In subjects who received a total daily dose of Endari of 30grams, the relative risk was 0.56 [95% CI: 0.41, 0.77] in favor of Endari. Also, treatment with Endari may be life-long and consideration should be given to studying Endari in patients with renal and hepatic impairment, since these disorders are not uncommon in patients with sickle cell

disease. The clinical reviewer agrees with the Clinical Pharmacology Review recommendation that the Applicant should conduct a 24-week clinical trial in adult and pediatric patients with SCD to identify an effective dose of Endari in patients with body weight ≤ 65 kg that increases the ratio of NADH to total NAD levels from the baseline as compared to a dose of 30 grams per day in patients with body weight > 65 kg. This study should also be designed to demonstrate comparative efficacy and safety of Endari at the effective dose in patients with body weight ≤ 65 kg. The study population should reflect the typical population of patients with SCD in the United States, and should include patients with renal and hepatic impairment.

12. Other Relevant Regulatory Issues

As noted in the Combined Clinical and Statistical Review, the applicant provided certification on FDA Form 3454 to indicate that there were no financial arrangements between the Applicant and Investigators which could be affected by the outcome of Study 10478 and GLUSCC09-01; however, the Chairman and CEO of Emmaus Inc., the Applicant, was the Principal Investigator at one of the study sites for Study 10478, an investigator-initiated study.

Office of Scientific Investigations (OSI) inspection (Clinical Inspections Summary by Min Lu, 5/2/2017) of three clinical sites from Study GLUSCC09-01 found two sites no action indicated (NAI) and one site voluntary action indicated (VAI). Inspection of one clinical site from Study 10478 found the VAI site no action indicated (NAI), two sites pending interim classification – NAI and one site pending interim classification – voluntary action indicated (VAI). The inspection summary concluded that the data submitted by each of the clinical sites inspected appear acceptable in support of this specific application.

Proprietary name review (Leeza Rahimi, final signature 2/27 2017) found the proposed proprietary name Endari acceptable. A letter indicating conditional approval of the proprietary name was issued to the Applicant on 2/27/2017.

13. Labeling

The Applicant included proposed labeling in the submission.

Final wording for the labeling for the proposed indication has been developed by the DHP review team with discussion and consideration of the recommendations from each of the review disciplines and consulting review divisions and with negotiation with the Applicant.

Notable recommendations from the Joint Clinical and Statistical Review (primary review completed by Rosanna Setse and Che Smith, final signature 6/7/2017) are as follows:

- Revise the indication statement to provide the goals of therapy and clearly identify the patient population for whom treatment with Endari is indicated.
- Revise section 6.1 of the label to include demographics of the safety population and specify the number of subjects enrolled in the phase 2 and phase 3 studies.
- Include a description of serious adverse events and deaths that occurred in patients treated with L-glutamine in the text of Section 6.1.
- Include all adverse reactions that occurred in L-glutamine treated subjects in the label regardless of causality
- Combine all abdominal pain preferred terms in a grouped term analysis and define the terms that are grouped as a footnote to the table describing adverse events in Section 6.1.
- Include the safety results from pediatric subjects studied in Study 10478 and Study GLUSCC0901 in Section 8.4.
- Include the definition of the primary endpoint- sickle cell crises in Section 14.

Recommendations for labeling from the Clinical Pharmacology Review included that: (a)The Dosage and Administration section should include instructions consistent with the conduct of the phase II and phase III trials regarding administration with food or beverage; (b) (4) (c) the Pharmacokinetics section should include a description of pharmacokinetics of L-glutamine oral powder following a single oral or intravenous dose and a statement indicating that no studies have been conducted to assess the potential for drug interactions or the effect of various intrinsic factors on the PK or PD of L-glutamine powder as described in the NutreStore labeling.

Recommendations for labeling were provided by the Office of Prescription Drug Promotion (OPDP)(Rachel Conklin, 6/20/2017). Among the recommendations was that the data presentation in section 14 be revised to include the absolute risk data in order to adequately qualify the presentation of the relative risk in the label. The review commented that, "This is necessary in order to avoid promotional claims that may exaggerate the benefit of the drug by citing only the relative risk percentages without the accompanying absolute risk reduction (which is often much smaller)."

Recommendations for the carton and container labeling were made by the Division of Medication Error Prevention and Analysis (DMEPA) (Idalia Rychlik, reviews signed 1/24/2017 and 6/12/2017).

Final wording for the labeling is being developed in discussion with the entire review team and should be agreed upon with the Applicant.

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/s/

KATHY M ROBIE SUH
07/07/2017