NDA 208587: L-glutamine

FDA Presentation

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May 24, 2017
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Outline

- Introduction
  - L-glutamine: proposed indication
  - Major issues for Advisory Committee

- Clinical Studies supporting NDA
  - Study design
  - Efficacy
  - Safety

- Summary
L-glutamine

Proposed Indication:
For the treatment of sickle cell disease (SCD)

Proposed dose: 0.3 grams(g)/kilogram(kg) body weight, upper limit of 30 g/day, orally twice daily
Two Clinical Trials Conducted

Major Issues:

1. Statistical issues: Impact of incomplete data and imputation methods on efficacy results
2. Clinical meaningfulness of the trial data
Study 1: GLUSCC09-01

- Study Population:
  - Patients with Sickle Cell Anemia (SCA) or sickle $\beta^0$-thalassemia (≥5 years old)
  - 2 or more painful crises in 12 months prior to screening
- Randomized to L-glutamine versus placebo (2:1 ratio)
- Stratified by study site and hydroxyurea (HU) use
- L-glutamine dose: 0.3 g/kg body weight, orally, twice daily, (upper limit of 30 g/day)
- 4-weeks screening, 48 weeks treatment period, 3 weeks tapering, and 2 week follow-up period. Monthly study visits
Primary Endpoint (GLUSCC09-01)

• Number of sickle cell crises (SCC) through Week 48
• SCC defined as:
  – Visit to a medical facility for SCD-related pain; treated with a parenterally administered narcotic or toradol; or
  – Acute chest syndrome (ACS), priapism, and splenic sequestration
• SCC adjudicated by Central Adjudication Committee (CAC)
Secondary Endpoints
(GLUSCC09-01)

• Number of sickle cell crises at Week 24
• Number of hospitalizations for sickle cell pain
• Number of ER visits for sickle cell pain
• Hematological parameters
Demographics
(GLUSCC09-01, N=230)

• Age: Mean 22 years; Range: 5-58 years
• Race/ethnicity: 94% Black, 3% Hispanic, 3% Other
• Gender: 54% Female
• Diagnosis: 90% Sickle cell anemia
  9% - Sickle β⁰ thalassemia
  1% - Sickle β⁺ thalassemia
• Hydroxyurea (HU) use at baseline: 67%
# Subject Disposition (GLUSCC09-01)

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>L-Glutamine n=151</th>
<th>Placebo N=78</th>
<th>Total N=229</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Study</td>
<td>64%</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>Discontinued study*</td>
<td><strong>36%</strong></td>
<td><strong>24%</strong></td>
<td><strong>32%</strong></td>
</tr>
<tr>
<td>Reason for discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consent Withdrawn</td>
<td>15%</td>
<td>11%</td>
<td>14%</td>
</tr>
<tr>
<td>Non compliance</td>
<td>5%</td>
<td>1%</td>
<td>4%</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>3%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Deaths</td>
<td>1%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>8%</td>
<td>8%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Discontinued before Week 48
Study 2: 10478

Study design similar to GLUSCC09-01. Except:

– Randomization 1:1 ratio
– Stratified by study site but not by HU use
– HU use not balanced between treatment arms at baseline
Primary Endpoint - Study 10478

• Number of SCC through Week 48
• SCC defined as:
  – Visit to a medical facility that lasted > 4 hours for acute sickling-related pain; treated with a parenterally administered narcotic
  – ACS, priapism, hepatic and splenic sequestration
• SCC not adjudicated by CAC
Subject Disposition  
(Study 10478)

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>L-glutamine N=37</th>
<th>Placebo N=33</th>
<th>Total N=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Study</td>
<td>49%</td>
<td>36%</td>
<td>43%</td>
</tr>
<tr>
<td>Discontinued study*</td>
<td><strong>51%</strong></td>
<td><strong>64%</strong></td>
<td><strong>57%</strong></td>
</tr>
<tr>
<td>Non compliance</td>
<td>24%</td>
<td>27%</td>
<td>26%</td>
</tr>
<tr>
<td>Consent Withdrawn</td>
<td>8%</td>
<td>15%</td>
<td>11%</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>0%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>5%</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Adverse events</td>
<td>0%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>Deaths</td>
<td>3%</td>
<td>0%</td>
<td>1%</td>
</tr>
<tr>
<td>Other</td>
<td>11%</td>
<td>12%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*Discontinued before Week 48
FDA Analysis

• Efficacy:
  – Study GLUSCC09-01

• Safety:
  – Study GLUSCC09-01
  – Study10478
NDA 208,587
Oral L-glutamine For Patients With Sickle Cell Disease
Statistical Review Considerations

May 24, 2017
Oncologic Drugs Advisory Committee
Che Smith, PhD – Statistical Reviewer
Yuan Li Shen, DrPH – Team Leader, Statistics
Thomas Gwise, PhD – Deputy Division Director, Statistics
STUDY 10478

STATISTICAL ISSUES

• Different definition of a sickle cell crisis
• Un-adjudicated primary efficacy endpoint
• Early study dropout
• Primary efficacy result did not meet level of significance
  – Potential misconduct at one study site
  – Heterogeneous study population across treatment arms
STUDY GLUSCC09-01

STATISTICAL ISSUES

• High early dropout rate and differential dropout rates between treatment arms

• Imputation of incomplete sickle cell crisis event counts

• Interpretation of efficacy results based on data impacted by dropouts
Study 0901 Overview

- Randomized, placebo-controlled, multicenter study
- Enrolled 230 patients with SCA or sickle β⁰-thalassemia, ≥ 5 years of age, with 2+ painful crises in previous 12 months
- Randomized 2:1 to L-glutamine or placebo treatment, respectively; stratified by site and baseline HU use
- 48 week treatment period, 3 week taper, 2 week follow up
- Primary Efficacy Endpoint: number of sickle cell crises
- Secondary Efficacy Endpoints: SCC at 24 weeks, hospitalizations, emergency room visits, hematologic parameters
### Statistical Analysis Plan

<table>
<thead>
<tr>
<th>Study GLUSCC09-01</th>
</tr>
</thead>
</table>
| **Sample size specification** | Based on Wilcoxon Rank Sum Test  
Significance level: 0.045  
80% power to detect difference in distributions of the number of sickle cell crises at Week 48 |
| **Pre-specified primary efficacy analysis** | Number of sickle cell crises (SCC) at Week 48, CMH test using Modified Ridit scores |
| **Stratification Factors** | Study center region  
Hydroxyurea use at baseline |
| **Secondary efficacy endpoints** | Number of SCC at 24 weeks  
Number of hospital visits  
Number of ER visits  
Hematological parameters |
| **Interim Analysis** | Number of SCC at 24 weeks  
0.005 significance level |
| **Post hoc sensitivity analyses** | Negative Binomial regression  
Removing one or both stratification factor(s)  
Time-adjusted/ last observation carried forward |
Study Dropout Over Time
By Treatment Group

SOURCE: FDA Analysis
Patient Experiences on Study GLUSCC09-01

- Completed 48 weeks of treatment; at least one crisis recorded
- Completed 48 weeks of treatment; no crises were recorded
- Dropped out before week 48; at least one crisis recorded
- Dropped out before week 48; no crises recorded
Patient Experiences on Study GLUSCC09-01

<table>
<thead>
<tr>
<th>Subset</th>
<th>L-glutamine N = 152</th>
<th>Placebo N = 78</th>
</tr>
</thead>
<tbody>
<tr>
<td>48 week completers; at least one SCC</td>
<td>82 (53.9%)</td>
<td>55 (70.5%)</td>
</tr>
<tr>
<td>48 week completers; no recorded SCC</td>
<td>15 (9.9%)</td>
<td>4 (5.1%)</td>
</tr>
<tr>
<td>Dropped out; at least one SCC</td>
<td>35 (23.0%)</td>
<td>15 (19.2%)</td>
</tr>
<tr>
<td>Dropped out; no recorded SCC</td>
<td>20 (13.2%)</td>
<td>4 (5.1%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>152</strong></td>
<td><strong>78</strong></td>
</tr>
</tbody>
</table>

SOURCE: FDA Reviewer analysis
Comparing Distributions Of The Number Of Sickle Cell Crises By Treatment Group

Histograms of observed data, and observed data with Applicant’s imputation

Reported SCC counts

Reported SCC counts after imputation

Applicant’s imputation rule:
max(crisis experienced up to dropout, mean crises among completers in treatment group)

SOURCE: Applicant’s Integrated Summary of Efficacy, Table 1.2; FDA Reviewer analysis
## Applicant’s Efficacy Results

### Primary Efficacy Analysis

<table>
<thead>
<tr>
<th>L-glutamine (N = 152)</th>
<th>Placebo (N = 78)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median number of sickle cell crisis events at 48 weeks (min, max)</strong></td>
<td>3 (0, 15)</td>
<td>4 (0, 15)</td>
</tr>
</tbody>
</table>

### Secondary Efficacy Analysis

<table>
<thead>
<tr>
<th>L-glutamine (N = 152)</th>
<th>Placebo (N = 78)</th>
<th>Nominal p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median number of sickle cell crisis events at 24 weeks (min, max)</strong></td>
<td>2 (0, 8)</td>
<td>2 (0, 7)</td>
</tr>
<tr>
<td><strong>Median number of hospitalizations at 48 weeks (min, max)</strong></td>
<td>2 (0, 14)</td>
<td>3 (0, 13)</td>
</tr>
<tr>
<td><strong>Median number of emergency room visits at 48 weeks (min, max)</strong></td>
<td>1 (0, 12)</td>
<td>1 (0, 15)</td>
</tr>
</tbody>
</table>

**SOURCE:** Applicant’s Integrated Summary of Efficacy, Table 14; Applicant’s Study GLUSCC09-01 Study Report

All analyses adjusted for region and baseline hydroxyurea use; CMH = Cochran-Mantel-Haenszel; CMH test using modified ridit scores
FDA Analysis: Proportional Rate Of Sickle Cell Crisis Events By Treatment Group

L-glutamine
N = 152
3.0 SCC per 48 weeks

Placebo
N = 78
3.8 SCC per 48 weeks

HR (95%CI) : 0.73 (0.55, 0.99)
Patient Experiences on Study GLUSCC09-01

- Completed 48 weeks of treatment; at least one crisis recorded
- Completed 48 weeks of treatment; no crises were recorded
- Dropped out before week 48; at least one crisis recorded

FDA Sensitivity Analysis Population
N = 206
## FDA Exploratory Analyses
Comparing Rates Of Sickle Cell Crisis Events Per 48 Weeks Using Negative Binomial Regression

<table>
<thead>
<tr>
<th>FDA strategy for handling incomplete crisis counts</th>
<th>Rate of crises/48 weeks L-glutamine vs Placebo</th>
<th>Rate Ratio [95% CI] Based on Negative Binomial model</th>
</tr>
</thead>
<tbody>
<tr>
<td>FDA sensitivity analysis population N=206</td>
<td>3.3 v 4.1</td>
<td>0.80 [0.64, 1.01]</td>
</tr>
<tr>
<td>ITT population, assuming incomplete crisis counts for 24 patients are “0”, N=230</td>
<td>3.3 v 4.2</td>
<td>0.77 [0.61, 0.99]</td>
</tr>
<tr>
<td>Multiple Imputation (FCS)* for 24 patients with incomplete crisis counts, N=230</td>
<td>3.9 v 4.3</td>
<td>0.91 [0.73, 1.12]</td>
</tr>
</tbody>
</table>

**SOURCE:** FDA Reviewer analysis
All analyses adjusted for region and baseline hydroxyurea use; using time on study as offset
*FCS = fully conditional specification; The multiple imputation approach adjusts for treatment group study site, baseline hydroxyurea use, age, baseline crisis count, and time spent on study to impute crisis counts for 24 patients.

www.fda.gov
Summary

- FDA explored alternative imputation and analytic methods to assess the impact of study dropout.
- An FDA analysis estimated cumulative rates of crises at week 48:
  - 3.0 vs. 3.8 for L-glutamine vs. Placebo [HR: 0.73, 95%CI: (0.55, 0.99)]
- All other exploratory analyses show a trend in favor of L-glutamine to reduce the number of SCC over 48 weeks; this trend should be considered in the context of the product’s safety profile.
SAFETY

Rosanna Setse, MD, MPH, PhD.
Medical Officer, Division of Hematology Products
SAFETY OVERVIEW

• No major safety issues
• Review findings:
  – Overall, similar pattern and frequency of common TEAEs and TEAEs that led to study withdrawal between treatment groups
  – Lower frequency of SAE reports of SCA with crisis and ACS among L-glutamine treated patients supports efficacy findings
Safety Population

• Integrated safety database:
  – All subjects from Studies 10478 and GLUSCC09-01 who received ≥ 1 dose of study medication

• Data from studies 8288, 8822, 8775, 10779 and 10511 not included in integrated safety review
  – Early stage, different methodologies
  – Adverse events not as explicitly defined
Summary of Drug Exposure (Safety Population, N= 298)

• 187 subjects received L-glutamine for ≥ 1 day
  – 73% treated for ≥ 24 weeks,
  – 58% treated for ≥ 48 weeks

• Total exposure
  – L-glutamine = 138 subject-years
  – Placebo = 86 subject years
## Summary of Adverse Events
(Safety Population)

<table>
<thead>
<tr>
<th>Subjects with at least 1:</th>
<th>L-glutamine N = 187</th>
<th>Placebo N = 111</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEAE*</td>
<td>96%</td>
<td>97%</td>
</tr>
<tr>
<td>Drug-related TEAE</td>
<td>19%</td>
<td>13%</td>
</tr>
<tr>
<td>SAE**</td>
<td>75%</td>
<td>80%</td>
</tr>
<tr>
<td>Drug-related SAE</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>Deaths (all)</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>TE*** Deaths</td>
<td>2%</td>
<td>0%</td>
</tr>
<tr>
<td>Deaths due to drug-related TEAEs</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*TEAE = treatment emergent adverse event; **SAE = serious adverse event
***TE = Treatment emergent
Treatment Emergent Deaths

• Three treatment emergent deaths
  – Patients aged 37, 45, and 46 years
  – All occurred > 300 days on study GLUSCC09-01

• Cause of death
  – cardiac arrest; respiratory failure, sickle cell crisis; severe anemia; severe hypoglycemia

• None considered treatment related. No autopsies done

• Insufficient information for causality assessment
## Serious Adverse Events*  
(Safety Population)

<table>
<thead>
<tr>
<th>Condition</th>
<th>L-glutamine (n=187)</th>
<th>Placebo (n=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA§ with crisis</td>
<td>66%</td>
<td>72%</td>
</tr>
<tr>
<td>Acute chest syndrome</td>
<td>7%</td>
<td>19%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3%</td>
<td>4%</td>
</tr>
<tr>
<td>Asthma</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Occurring in ≥ 2% of L-glutamine-treated subjects

§SCA = Sickle cell anemia
Common Adverse Events (≥10%) in L-glutamine patients:

Constipation (21%), nausea (19%), headache (18%), pyrexia (17%), abdominal pain (16%) cough (15%), URTI* (14%), pain in an extremity (13%), vomiting (13%), back pain (12%), chest pain (12%) and arthralgia (12%)

*URTI = Upper respiratory tract infection
No notable differences in TEAEs or SAEs by demographic variables
No notable differences in changes in hematology parameters, liver function test or serum chemistry between treatment groups
SUMMARY
Efficacy Summary

• Primary efficacy analysis for Study GLUSCC09-01
  – Applicant: Median SCC counts at 48 weeks of 3 vs 4 for L-glutamine vs placebo (p = 0.0052)
  – FDA: Estimated mean cumulative rates of SCC at 48 weeks of 3 vs 3.8 for L-glutamine vs placebo [HR: 0.73, 95% CI: (0.55, 0.99)]

• No ideal analytic method given magnitude of drop-outs and imputations
Safety Summary

• Overall, similar frequency of TEAEs or TEAEs that led to study drug withdrawal among L-glutamine and placebo treatment groups

• Lower frequency of SAEs (SCA with crisis, ACS) among L-glutamine treated subjects suggests benefit

• Common Adverse events:
  – constipation, nausea, headache, pyrexia, abdominal pain, cough, URTI, pain in an extremity, vomiting, back pain, chest pain and arthralgia
Major Issues for the ODAC

Discuss:

- The impact of study drop-out rates, data imputation and analytic methods on interpretation of efficacy findings
- Clinical significance of one fewer median sickle cell crises/year in patients with SCD
Question for ODAC

Vote:

- 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?