ABBREVIATED CLINICAL STUDY REPORT

Study Title:	Phase II Pilot Multicenter Study on Efficacy and Safety of Liposomal Amphotericin B (AmBisome®) at 2 mg/kg/day in the Treatment of Candidemia and Invasive Candidiasis in Non-neutropenic Patients
Name of Test Drug:	Liposomal Amphotericin B
Dose and Formulation:	2 mg/kg/day
Indication:	Treatment of Candidemia and Invasive Candidiasis
Sponsor:	Gilead Sciences Srl via Marostica, 1 20146 Milano, Italy
Study No.:	GS-IT-131-0177 (CRITIC)
Phase of Development:	Phase 2
IND No.:	Not Applicable (non-IND study)
EudraCT No.:	2007-000607-15
Study Start Date:	04 March 2008 (First Subject Screened)
Study End Date:	15 December 2008 (Last Subject Observation)
Principal or Coordinating Investigator:	Name: Claudio Viscoli Address: [redacted] [redacted] PPD [redacted]
Gilead Responsible Medical Monitor:	Name: Luigi Antonio Picaro Telephone: [redacted] PPD Fax: [redacted] PPD
Report Date:	05 January 2010 (Final)

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Gilead Sciences Srl
via Marostica, 1
20146 Milano, Italy

Title of Study: Phase II Pilot Multicenter Study on Efficacy and Safety of Liposomal Amphotericin B (AmBisome®) at 2 mg/kg/day in the Treatment of Candidemia and Invasive Candidiasis in Non-neutropenic Patients
Investigators: Multicenter
Study Centers: 3 enrolling centers in Italy out of 7 active sites
Publications: None
Study Period: 04 March 2008 (First subject screened) 15 December 2008 (Last subject observation)
Phase of Development: Phase 2
Objectives: The primary objective of this study was as follows: • Success at end of therapy (EOT) Success was defined as follows (all 4 of the following criteria must have applied): • Absence of all clinical signs and symptoms present at baseline and absence of any new signs and symptoms observed during the episode of candidemia, OR alternative explanation for persistent or relapsing clinical signs and symptoms present at baseline or during the episode of candidemia, such as clearly detectable bacteria (i.e., positive blood cultures) and eradication for the fungal infection (negative cultures) • Blood (or other normally sterile sites) cultures became negative for *Candida* • Infected deep tissue sites became negative for *Candida* or all clinical signs of local infection resolved • No systemic antifungal agent, other than the study drug, was administered for the episode of candidemia or invasive candidiasis • The secondary objectives of this study were as follows: • Efficacy at the second and fourth week after the EOT • Safety of the 2 mg/kg/day regimen

Methodology: Subjects were enrolled to receive intravenous (IV) AmBisome at 2 mg/kg/day for a maximum of 4 weeks. The EOT time point was reached either at the completion of 4 weeks of therapy or earlier, when success or failure was declared. Treatment was discontinued in case of failure, adverse events (AEs) precluding treatment, or success. In case of success, AmBisome at 2 mg/kg/day was to be administered for at least 5 days after the complete resolution of all clinical findings of an active infection or for at least 8 days after the last positive blood culture or culture from a normally sterile site. It was not recommended to declare failure (and therefore change treatment) before giving at least 5 days of antifungal therapy. Failures in subjects given fewer than 5 days of treatment were well documented (e.g., persistent positive cultures despite catheter removal, clinical deterioration in absence of any explanation other than the fungal infection). Follow-up evaluations were conducted at 2 and 4 weeks after the end of AmBisome therapy. At EOT (time point for success or failure), subjects may have been shifted to oral (not IV) antifungals at the discretion of the local investigator, once a complete response had been achieved, if secondary prophylaxis was deemed necessary.

Number of Subjects (Planned and Analyzed):
Planned: 39
Randomized: 9
No study populations were defined and no data summaries were generated.

Diagnosis and Main Criteria for Inclusion: Eligible subjects were admitted to an intensive care unit (ICU) with at least one positive culture isolation of *Candida* obtained within 96 hours prior to study entry, and had at least one of the following within 48 hours from the first positive culture:

- Temperature > 38 °C on 2 occasions at least 4 hours apart or one determination > 38.5 °C
- Systolic blood pressure < 90 mmHg, or ≥ 30 mmHg decrease in systolic blood pressure (BP) from baseline
- Signs of inflammation from sterile sites (bone, joint, skin, eye, esophagus, or abdomen), excluding subjects on artificial ventilation with positive bronchoalveolar lavage (BAL)

Duration of Treatment: Subjects were treated for a maximum of 4 weeks; the EOT time point was reached either at the completion of 4 weeks of therapy or earlier, when success or failure (after at least 5 days of therapy) was declared. In case of success, AmBisome was to be administered for at least 5 days after the complete resolution of all clinical findings of an active infection, or for at least 8 days after the last positive blood culture or culture from a normally sterile site.

Test Product, Dose, Mode of Administration, and Batch No.: AmBisome 2 mg/kg/day IV over 1–2 hours (Batch No. 042775A)

Reference Therapy, Dose, Mode of Administration, and Batch No.: Not applicable

Criteria for Evaluation:

Efficacy: Success at EOT, efficacy at the second and fourth week after EOT, time to negative blood culture, resolution of clinical signs and symptoms, microbiological eradication from blood culture or infected sterile site, and duration of study treatment

Safety: Laboratory tests, physical examinations, and adverse events assessment

Statistical Methods:

No data summaries or statistical analyses were conducted for this study. All data were listed by subject.

SUMMARY – RESULTS:

The study did not achieve the planned enrollment. Nine (9) subjects were enrolled over a 10-month period and treated, and 8 of the 9 subjects completed the study. One subject discontinued early due to a serious adverse event (SAE) (death due to cardiac arrest).

Efficacy Results: Six (67%) of the 9 subjects achieved treatment success between Days 10 and 16 (EOT), and the 4 subjects who were assessed at follow-up maintained success at the 2- and 4-week post-EOT follow-up assessments. Two subjects failed treatment: [redacted] at Day 19, and [redacted] at Day 9. [redacted] was positive for *Candida parapsilosis* at baseline and at EOT, and had recurrence of candidemia. [redacted] interrupted treatment for efficacy reasons due to positive urine cultures for *Candida* species on Days 8 and 9 (EOT). One subject, [redacted], had no recorded assessment of response, although his bacterial cultures were negative at Day 4, and candidemia resolved. This subject received 7 days of treatment, and died from cardiocirculatory arrest the day after the last dose.

Safety Results: Adverse events were reported for 2 subjects: [redacted] and [redacted] both experienced Grade 4 (life-threatening) SAEs of cardiocirculatory arrest. [redacted] had already completed an 18-day course of treatment and was declared a failure on Day 19, and SAE onset was on Day 24. For [redacted], SAE onset was on Day 8, the day after the last dose of study drug. Both subjects died on the day of SAE onset. Both events were considered unrelated to study drug or study procedures.

For most subjects, white blood cell (WBC) and differential counts either decreased from abnormally high values or remained low throughout the study. Most subjects also had low values for hematocrit and hemoglobin throughout the study. All subjects had hypoalbuminemia, and most subjects also had electrolyte abnormalities, particularly hypocalcemia (6 subjects) and hypokalemia (5 subjects). Hypocalcemia, hypokalemia, and anemia are known adverse reactions to AmBisome. All subjects with reported results had urine blood detected at one or more time points, and 5 subjects had bacteria detected via microscopic examination.

CONCLUSIONS: Results of this Phase 2, open-label, pilot study of liposomal amphotericin B (AmBisome 2 mg/kg/day) as a treatment for candidemia and invasive candidiasis in non-neutropenic subjects lead to the following conclusions:

- AmBisome treatment was successful in treating candidemia in 6 of 9 subjects after 10 to 16 days of treatment.
- Two subjects died, both from cardiac arrest unrelated to treatment. These were the only AEs or SAEs reported during the study.
- AmBisome was well tolerated, with no drug-related AEs or SAEs reported. Hypocalcemia and hypokalemia were observed frequently; both are known adverse reactions to AmBisome.