2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:

Page:</td><td rowspan="3">(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:</td></tr>
<tr><td>Name of Active Ingredient:</td></tr>
<tr><td colspan="3">Title of the study: “A Phase III Multicentre, Open-Label, Randomized Study of XL119 versus 5-Fluorouracil (5-FU) plus Leucovorin (LV) in Subjects with Advanced Biliary Tumors Not Amenable to Conventional Surgery”</td></tr>
<tr><td colspan="3">Investigators: Investigators in both North America and Europe countries according to the original plan. At the time of early termination, more new sites in existing countries (Germany, Italy, France, Poland, Spain Russia), and in new countries (Argentina, Chile, Romania, India, Korea, Taiwan, Thailand) were planned to be added.</td></tr>
<tr><td colspan="3">Study Centers: Sites initiated/recruiting: 33/21 in North America (28/17 in USA and 5/4 in Canada) and 32/25 in Europe (Belgium 1/1, France 5/4, Germany 10/10, Hungary 1/1, Italy 6/3, Poland 1/1, Russia 1/1, Spain 6/3, UK 1/1).</td></tr>
<tr><td colspan="3">Publication (reference): Not applicable.</td></tr>
<tr><td colspan="2">Study period (years):
FPFV= Sept 04
LPLV= Nov 06</td><td>Phase of development: III</td></tr>
<tr><td colspan="3">- Objectives:
- The primary objective of this study was to compare survival duration for XL119 and 5-FU/LV subjects.
- The secondary objectives were:
- to evaluate clinical benefit for XL119 and 5-FU/LV subjects
- to assess the safety profile of XL119</td></tr>
<tr><td colspan="3">Efficacy and safety variables:
Primary Efficacy variable: overall survival duration, for all cause mortality.
Secondary Efficacy variables:
- Progression Free Survival (clinical or radiologic)
- Measure of clinical benefit (ECOG Performance Status and Functional Assessment of Cancer Therapy–Hepatobiliary -FACT-Hep- Quality of Life subscales.
Other Secondary Efficacy variables:
- Best tumor response (Response Rate) and Disease Control Rate.

Safety variables:
- serious and nonserious adverse events (AEs)
- laboratory evaluations</td></tr>
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Methodology: This was a multicentre, randomized, open-label study to compare safety and efficacy of becatecarin administered i.v. to subjects with bile tract tumors vs 5-FU/LV regimen.

Number of subjects:	Planned:	600 (300 active + 300 comparator arm)	
	Enrolled:	248 (125 active + 123 comparator)	
	Analyzed	Safety set:	225
		FAS:	225
		PP set:	NA

Diagnosis and main criteria for inclusion:

- Male and female subjects with advanced histologically confirmed biliary cancer (gallbladder cancer or cholangiocarcinoma) that was not amenable to conventional surgical approach. If only cytology was available, written approval by medical monitor was required.
- 18 years or older
- Life expectancy of at least 12 weeks
- Eastern Cooperative Oncology Group (ECOG) Performance Status score <3
- Laboratory criteria (within 72 hours of first XL119 treatment): white blood cell count (WBC) > 3000/μL, absolute neutrophil count ≥ 1500/μL; hemoglobin ≥ 9.5 g/dL; platelet count ≥ 100,000/μL, lymphocyte count < 20,000/μL; serum creatinine within ULN, if > ULN, creatinine clearance ≥ 60 ml/min, alanine transaminase (ALT) and aspartate transaminase (AST) within 2.5 times the upper limit of normal; bilirubin < 3 mg/dL
- Willing and able to sign informed consent
- Sexually active men and women had to use an accepted and effective method of contraception (including barrier contraception with spermicide)
- Women of child-bearing age had to have a negative pregnancy test

Main criteria for exclusion:

- Prior chemotherapy (excluding chemotherapy given as adjuvant treatment completing more than 6 months prior to entry into study)
- Unstable angina, or class III or IV New York Heart Association heart disease
- Central nervous system metastases
- Uncontrolled diabetes mellitus
- Uncontrolled seizure disorder
- Major surgery, immunotherapy, biological therapy, or radiotherapy during the 28 days preceding the first study treatment
- Need for concomitant anticancer therapy (chemotherapy, immunotherapy, biological therapy or radiation) or other investigational agents during study participation or 28 days prior to study participation
- Pregnant or breast-feeding
- A known history of human immunodeficiency virus (HIV) infection

Test product: becatecarin (XL119)
Dose: 140 mg/m^2 x day
Batch numbers: [redacted], [redacted], [redacted], [redacted]
Mode of administration: i.v. via central venous catheter.

Duration of treatment: Days 1 through 5 of a 28-day cycle

Reference therapy: 5-Fluorouracil (5-FU) + Leucovorin (LV)
Dose: 375 mg /m^2/day + 25 mg/m^2/day
Batch number: Not available, marketed drug
Mode of administration: i.v. via central venous catheter or alternative i.v. administration.

Duration of treatment: Days 1 through 5 of a 28-day cycle

Criteria for evaluation:

Efficacy evaluation (primary):

The primary efficacy variable was overall survival duration.

Efficacy evaluation (secondary):

Secondary efficacy variables were (1) Progression Free Survival (clinical or radiologic) and (2) measure of clinical benefit (evaluated using ECOG Performance Status and Functional Assessment of Cancer Therapy–Hepatobiliary -FACT-Hep- Quality of Life subscales). An additional measure of efficacy in subjects with measurable disease was best tumor response (Response Rate) and Disease Control Rate. Determination of best-tumor response was based on objective tumor assessments made according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) system of unidimensional evaluation.

Safety:

Safety variables were: (1) serious and nonserious adverse events (AEs) and (2) laboratory evaluations. An Independent Data Monitoring Committee (IDMC) was established to periodically review serious adverse events (SAEs), abnormal laboratory tests, and to assess futility and efficacy at two interim analysis meetings. Two interim analyses were planned to be performed after 33% (172) and 50% (258) of the total deaths (516) were reported.

Statistical methods:

The primary treatment group comparison was based on an intent-to-treat analysis of the survival distributions using the stratified log-rank test. The size of the treatment effect was estimated by the difference in median survival, using the Kaplan-Meier method (median survival for XL119 group – median survival for control group). The incidence of SAEs was tabulated by treatment group, system organ class, and preferred term. Shifts from baseline in laboratory test results obtained at Day 1 and at the final measurement were also summarized.

Summary

Efficacy results:

According to the original plan, the interim analyses were to be performed when data was available for 172 (50%) and 258 (50%) deaths, respectively, of a total of 516 deaths in the primary efficacy cohort.

During the first face to face meeting, held in New York City on September 1st, 2006, the IDMC detected safety signals and concerns, prompting for the execution of an earlier interim analysis. This was performed on November 5th, 2006, when data was available for 225 subjects (111 on becatecarin arm and 114 on 5-FU/LV arm), with 109 deaths occurred. This data showed 94 discontinuations on becatecarin compared to 80 on 5-FU/LV, with 60 deaths in becatecarin arm as opposed to 49 deaths in the control arm.

The stopping rule that had been defined in the protocol was applied and another one was added to see if this latter stopping rule would reduce the power of the study (see paragraph 10.6.2.1). By adding the extra analysis, the power of the study was reduced by only 0.1%, which was

considered to be quite insignificant. The question was then posed of the probability that the study would produce statistically significant results. Using the current confidence intervals, there was a 16% chance that the study would be significant if the hazard ratio was at 1.2. Currently, the hazard ratio was at 1.5, so there was no chance that the results would become statistically significant.

Safety results:

A full safety evaluation was not conducted due to study early termination. Analytical descriptions of laboratory toxicities for hematology and serum chemistry are reported in paragraph 11.2.1 and 11.2.2, respectively.

Details on types and amount of Serious Adverse Events are depicted in paragraph 11.1.3.1, table 11.3. More than 50% of subjects in the becatecarin arm reported serious adverse events compared to approximately 36% of those in the control arm.

Conclusions:

The study was planned to enroll 600 patients. The original study plan foresaw the involvement of an Independent Data Monitoring Committee (IDMC), whose role was to evaluate safety and efficacy data during the study. This committee was scheduled to perform two interim analyses for efficacy when data were available for 172 (33%) and 258 (50%) deaths, respectively, of a total of 516 deaths in the primary efficacy cohort. The IDMC was to recommend to the Helsinn Healthcare SA Directors of Research and Development that the study be discontinued: a) for efficacy, b) for futility.

Due to safety signals and concerns detected during the first face to face meeting, an additional, unplanned interim analysis was performed when data were available for 109 deaths (108 deaths considered). The outcome of the analysis showed a Hazard Ratio at 1.5, so there was no chance that the results would become statistically significant. Based on the evidence provided, the IDMC unanimously decided that the study be stopped for safety, futility and lack of benefit to subjects randomized to becatecarin. The Sponsor terminated the study giving formal notice to the participating sites and all concerned parties. Thereafter, the Sponsor made the decision to suspend the clinical development of the compound becatecarin.

Date of report: December 11, 2008