2. JGDH Synopsis

Approval Date: 18-Jun-2013 GMT

Clinical Study Report Synopsis: Study I5B-IE-JGDH

Title of Study: A Phase 2 Study of a Human Anti-PDGFRα Monoclonal Antibody (olaratumab) in Previously Treated Patients with Unresectable and/or Metastatic Gastrointestinal Stromal Tumors (GIST)	
Number of Investigators: This multicenter study included 11 principal investigators.	
Study Centers: This study was conducted at 11 study centers in six (6) countries.	
Publications Based on the Study: None at this time.	
Length of Study: Date of first patient entered screening phase: 29 August 2011 Date of first patient entered treatment: 15 September 2011 Date of last patient completed entire study incl. survival follow-up: 13 November 2012 Date of early study termination: 27 September 2012	**Phase of Development:** 2
Objectives: Primary objective of this study was the evaluation of tumor response of stable disease, partial response, or complete response at 12 weeks (according to Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST 1.1] criteria) in two separate cohorts representing molecularly distinct subsets of previously treated patients with GIST when treated with olaratumab: Cohort 1 includes patients with GIST harboring platelet-derived growth factor alpha (PDGFRα) mutations (D842V and any others), while Cohort 2 includes patients with GIST not harboring PDGFRα mutations. Secondary objectives were the evaluation of: the progression-free survival (PFS), the safety profile of olaratumab in patients with GIST, the radiographic objective response rate (ORR), and disease control rate (DCR) determined by RECIST 1.1, the overall survival (OS), and the pharmacokinetic (PK) profile and immunogenicity of olaratumab.	
Study Design: Patients in this open-label, two-stage, multicenter, multinational, Phase 2 trial, received intravenous olaratumab 20 mg/kg every 14 days (one cycle). Patients were assessed for tumor response every 6 weeks (± 3 days). All patients continued to receive treatment until there was radiographic documentation of disease progression, death, or intolerable toxicity, or other withdrawal criteria were met. Olaratumab was made available after conclusion of the study to patients who were still receiving and benefiting from study treatment. The study utilized a Simon two-stage optimal design with two cohorts. During Stage I, in each cohort (1 and 2), patients were planned to be enrolled until eight evaluable patients have been enrolled. If two or fewer (of eight evaluable) patients in a cohort had a response of stable disease (SD), partial response (PR), or complete response (CR) (per RECIST 1.1) at 12 weeks following the first dose, then that cohort was discontinued. It was planned that, if three or more of the first eight evaluable patients in a cohort would have a response of SD, PR, or CR at 12 weeks, this would be interpreted as a sign of activity and a second stage would have been started with an accrual of an additional 24 patients to a minimum total of 32 evaluable patients per cohort. If more than 15 patients with a response of SD, PR, or CR would have been observed at 12 weeks in this expanded cohort, this would have been considered as a sign of activity. As the development of olaratumab was put on hold in this indication due to reasons not related to efficacy and/or safety, the study was not completed as planned.	
Number of Patients: Planned: At least eight (8) evaluable patients per cohort during Stage I; additional 24 patients per cohort during Stage II to a minimum total of 32 evaluable patients per cohort. Enrolled: 30 patients; 21 patients assigned to treatment. Treated (at least 1 dose): 7 (Cohort 1), 14 (Cohort 2). Completed: 7 (Cohort 1), 14 (Cohort 2).	

Diagnosis and Main Criteria for Inclusion: Male and female patients ≥ 18 years of age with histologically or cytologically confirmed, unresectable and/or metastatic GIST with objective progression following, or intolerance to, treatment with at least both imatinib and sunitinib were included. Patients had measurable disease (per RECIST version 1.1) and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2.

Olaratumab, Dose, and Mode of Administration: Olaratumab injection for intravenous (IV) use was supplied in single-use 500 mg/50 mL vials containing 10 mg/mL of product in histidine buffer and was administered to patients as an IV infusion at 20 mg/kg every 14 days; supplied from package lots [redacted], and [redacted].

Duration of Treatment: Patients were accrued from August 2011 - November 2012. All patients were treated with olaratumab as described above (20 mg/kg every 2 weeks), until there was radiographic documentation of disease progression, death, or intolerable toxicity, or other withdrawal criteria were met.

Variables:

Efficacy: Imaging studies and tumor measurements/disease response assessments, according to RECIST 1.1, every 6 weeks (±3 days) following the first dose of study therapy until documentation of progressive disease (PD).

Safety: Reported adverse events (AEs), physical examinations, electrocardiograms (ECGs), and clinical/laboratory tests. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA®) and graded using the National Cancer Institute - Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.0. Clinical laboratory toxicity was graded using NCI-CTCAE criteria, Version 4.0.

Pharmacokinetic: Blood samples were obtained from all patients in the first stage for analysis of the PK behavior of olaratumab, with more extensive sampling performed for approximately 10 patients. PK parameters were planned to be estimated using a noncompartmental model; parameters to be reported include, but are not limited to, C_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$, Cl, and V_{ss}. However, as development of olaratumab was put on hold in this indication due to reasons not related to efficacy and/or safety, these analyses were not carried out as planned. Individual patient listings of serum concentrations of olaratumab were generated and are available upon request.

Pharmacodynamic: Samples were collected for nonpharmacogenetic biomarker research. Exploratory biomarker analyses in whole blood included potentially relevant biomarkers of olaratumab pharmacodynamic activity [redacted]. In addition, tissue samples from the primary or metastatic tumor provided at baseline were evaluated for surrogate biomarkers including analysis of PDGFRα expression and analyses of other factors related to PDGFRα.

Immunogenicity: Blood samples for the assessment of antibodies against olaratumab (immunogenicity) were collected for all study patients at specified time points throughout the study. In addition, if a patient should have an infusion reaction to olaratumab, all attempts were made to obtain a blood sample for immunogenicity analysis as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event.

Statistical Evaluation Methods:

Efficacy: The first stage stopping rule for efficacy was based on "Evaluable Population," consisting of all eligible patients (i.e., those patients who met all inclusion/exclusion criteria) who had received at least one dose of study drug and had adequate tumor assessment at 12 weeks. Patients discontinuing early due to progressive disease or death were included in the Evaluable Population. Primary endpoint was also analyzed for all patients included in the modified Intent-to-Treat (mITT) Population, consisting of all patients who received any quantity of study drug. All other efficacy variables were based on the mITT Population.

Statistical analyses were performed for tumor response rate of SD or better at 12 weeks, PFS, OS, ORR, and DCR. The tumor response rate of SD or better at 12 weeks and its two-sided 90% Binomial exact confidence limit was estimated for each cohort. The Kaplan-Meier method was used to estimate the median PFS time and PFS rate at 12 weeks for each cohort, together with their two-sided 90% confidence interval (CI). OS was estimated by the Kaplan-Meier method for each cohort and a two-sided 90% CI was provided for the median OS. The ORR was equal to the proportion of patients achieving a best overall response of partial or complete response (PR + CR), according to RECIST 1.1. For ORR, the number of patients achieving a response (PR + CR) was divided by the total of patients treated to yield the proportion responding. The ORR together with the two-sided 90% CI was also provided for each cohort. The number of patients achieving a response of PR, CR, or SD was divided by the total of patients treated to yield the DCR. The DCR together with the two-sided 90% CI was also

provided for each cohort.

Assuming that the improvement in proportion of patients with a response of SD or better at 12 weeks from 35% to 59% is applied to a Simon's two-stage optimal design, the study planned to enroll eight (8) evaluable patients during Stage I and an additional 24 patients in Stage II to a minimum total of 32 evaluable patients for each cohort. The design assumes a type I error=0.1 and power at 90%. Thus, for two independent cohorts, the total maximal sample size is 64 (32*2). Assuming a dropout rate of 10%, approximately 72 patients were planned to be accrued in total if both cohorts continued to the second enrollment stage.

Safety: Safety analyses were performed based on the "Safety Population," consisting of all patients who received any quantity of study drug; it is the same as the mITT Population. AEs were summarized by MedDRA® System Organ Class and preferred term, classified from verbatim terms. The incidence and percentage of patients with at least one occurrence of a preferred term was included, according to the most severe NCI-CTCAE, Version 4.0 grade. The number of AEs reported per MedDRA® preferred term was also summarized. Causality (relationship to study drug) was summarized separately. Duration of AE was determined and included in listings along with action taken and outcome. Safety data were monitored and reviewed by a Safety Review Committee (SRC) after the first eight patients in each cohort had received three cycles of treatment. Incidence of laboratory abnormalities was summarized; laboratory results not corresponding to an NCI-CTCAE, Version 4.0 term were not graded. Laboratory toxicity shifts from baseline to worst grade were also provided. The results from physical examination, vital sign measurement, and ECG assessment were tabulated. Descriptive statistics were provided as appropriate.

Pharmacokinetic/Pharmacodynamic: As development of olaratumab was put on hold in this indication due to reasons not related to efficacy and/or safety, these analyses were not carried out as planned. Individual patient listings of serum concentrations of olaratumab following olaratumab infusion at 20 mg/kg every 14 days can be provided upon request and pharmacodynamic data were summarized using descriptive statistics. The association between the pharmacodynamic data (biomarkers), including but not limited to PDGFRα, and efficacy endpoints was explored.

Summary: The study was conducted to determine efficacy of single agent olaratumab in two molecularly distinct subsets of previously treated patients with refractory unresectable and/or metastatic GIST. Cohort 1 included 7 patients with GIST harboring PDGFRα mutations (D842V and any others), while Cohort 2 included 21 patients with GIST not harboring PDGFRα mutations (PDGFRα wild-type). As primary outcome measure, tumor response to treatment with olaratumab was evaluated at 12 weeks (according to RECIST 1.1 criteria). In PDGFRα mutant patients at 12 and 24 weeks, a PFS rate of 51.4% was observed, while PFS at 12 weeks in non-PDGFRα mutant patients was recorded at 14.3%. All patients in Cohort 2 had come off study at 24 weeks, mostly because of disease progression, and therefore could not be evaluated. Median PFS was 32.1 weeks for the Cohort 1 and 6.1 weeks for Cohort 2. Median OS for Cohort 1 is not evaluable yet and was recorded to be 24.9 weeks for Cohort 2.

There were some minor discrepancies in the distribution of treatment emergent adverse events between both cohorts, which is felt to be related to the small study size. One patient in Cohort 1 had a SAE (syncope) which was judged by the investigator to be related to olaratumab. All patients in Cohort 1 had various AEs, which were labeled by the investigators to be study drug-related. Nine (9) (out of 14) patients in Cohort 2 had study drug-related AEs. No distinct AE or SAE could be identified which would specifically indicate an olaratumab-related emerging trend. Comparison to other randomized olaratumab trials could not verify particular emerging AEs in olaratumab-treated patients. This was because these appear to be rather balanced between control and treatment cohorts. Because this trial was a single-arm study, we assume the AEs and SAEs more likely were caused by the underlying disease or progression thereof.

Clearly, the results are strikingly different between the mutated and non-mutated cohort. Despite the small sample numbers, it is highly unlikely to observe such a difference just by chance. Although no objective disease responses were recorded, disease stabilization over the reported time frame of 24 weeks in a highly refractory patient population who have no other reasonable or standard therapeutic option left is remarkable (Cohort 1). The results observed in GIST allow to expand the hypothesis that olaratumab might have in general activity in not only PDGFRα mutated sarcomas (of which GIST is a subtype), but possibly in all PDGFRα mutated cancers where this

pathway is felt to be a driver. To this end, Study JGDH is the only one of the entire olaratumab program which has enriched patients for PDGFRα mutation, which allowed studying PDGFRα mutated patients in one dedicated trial arm.

Conclusions: In conclusion, single agent olaratumab represents a highly promising single agent therapy for PDGFRα mutated GIST patients with a predictable and well tolerated safety profile. These results represent a platform for design of future strategies in PDGFRα mutated cancers.