SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	STELARA® (ustekinumab)
Name of Active Ingredients	STELARA® (ustekinumab)

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Status: Approved

Date: 18 December 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: CNTO1275PBC2001

Title of Study: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel-group Study Evaluating the Efficacy and Safety of Ustekinumab in Subjects with Primary Biliary Cirrhosis who had an Inadequate Response to Ursodeoxycholic Acid (UDCA)

Study Name: PURIFI

EudraCT Number: 2011-000554-31

NCT No.: NCT01389973

Clinical Registry No.: CR018748

Principal Investigator: Gideon Hirschfield, MD, [redacted], UK

Study Centers: 9 sites initiated (1 in Italy, 4 in Canada, 4 in US)

Publication (Reference): None

Study Period: First subject signed informed consent on 23 August 2011; Last subject completed the last study visit on 28 June 2013

Phase of Development: 2

Objectives: This study was planned to have 2 parts. The objectives of this study were:

PART 1: Open-label

- To evaluate the efficacy of ustekinumab in reducing alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin in subjects with primary biliary cirrhosis (PBC).
- To determine the ustekinumab regimen(s), based on safety and efficacy, for development in Part 2.

PART 2: Double-blind

Primary Objectives

- To evaluate the efficacy of ustekinumab in achieving ALP response (a decrease from baseline of >40% in ALP) in subjects with PBC who had an inadequate response to UDCA.
- To evaluate the safety of ustekinumab in subjects with PBC.

Secondary Objectives

- To evaluate the efficacy of ustekinumab in reducing ALP, ALT, AST, and total bilirubin.
- To evaluate improvement in liver fibrosis as measured by the Enhanced Liver Fibrosis (ELF) test.
- To evaluate improvement in liver histology as measured by the modified Hepatic Activity Index (HAI).
- To evaluate the efficacy of ustekinumab in reducing cholestasis as measured by serum bile acid concentrations.
- To evaluate pharmacokinetics (PK), immune response (IR), and pharmacodynamics (PD) of ustekinumab.
- To evaluate ustekinumab in improving fatigue, pruritus, and quality of life.
- To evaluate the effect of ustekinumab on long-term disease progression (death, transplant, cirrhosis, doubling of bilirubin).

Hypothesis: ALP response to ustekinumab will be superior to placebo at Week 28 in subjects with PBC who had an inadequate response to UDCA.

Methodology:

Part 1: This was an open-label, proof-of-concept study. Twenty subjects were enrolled at 9 global investigational sites. All subjects in Part 1 were assigned to receive open-label ustekinumab 90 mg subcutaneous (SC) injections at Week 0 and Week 4, and every 8 weeks (q8w) through Week 20. Key efficacy assessments in Part 1 included laboratory assessments of ALP, AST, ALT, and total bilirubin. Part 1 subjects were not eligible to participate in Part 2 of the study.

Based on the results from Part 1, a dose selection committee was responsible for making the decisions on whether to proceed to Part 2 and which doses were to be studied in Part 2.

Part 2: This was planned to be a randomized, multicenter, double-blind, placebo-controlled, parallel-group study that would evaluate the efficacy and safety of ustekinumab in subjects with PBC who had an inadequate response to UDCA. Based on the efficacy results of Part 1, the decision was made not to continue to Part 2.

Number of Subjects (planned and analyzed):

Part 1: Up to 20 subjects could be enrolled. Twenty subjects were treated and were included in the safety, and efficacy analyses. Nineteen subjects were included in the PK analysis.

Part 2: One hundred and eight subjects were to be enrolled and included in safety, efficacy, and PK and PD analysis. Based on the efficacy results of Part 1, the decision was made not to continue to Part 2; therefore, no subjects were enrolled for Part 2 of the study.

Diagnosis and Main Criteria for Inclusion: The study population was to consist of men or women 18 years of age or older, with PBC as defined by having at least 2 of the following 3 criteria prior to Week 0: a history of elevated ALP for at least 6 months, a positive antimitochondrial antibody titer or PBC-specific antibodies, and a liver biopsy consistent with PBC. Eligible subjects must have had an inadequate response to UDCA as defined by a screening ALP level >1.67x upper limit of normal (ULN) despite treatment with a stable dose of UDCA for at least 6 months prior to Week 0.

Subjects were excluded if they had hepatic decompensation, screening direct bilirubin value >1.0 mg/dL, previous liver histology with a diagnosis of steatohepatitis, high risk of nonalcoholic steatohepatitis, chronic autoimmune hepatitis, or had a high risk of autoimmune hepatitis overlap syndrome.

Test Product, Dose and Mode of Administration, Batch No.: Ustekinumab was supplied in a prefilled syringe, as a single-use, sterile solution in a BD Hypak™ 1 mL, type 1 glass syringe with 27 gauge, ½ inch-fixed needle. There were 2 dose strengths (ie, 90 mg in 1 mL nominal volume or 45 mg in 0.5 mL nominal volume) for ustekinumab for SC administration. Each 1 mL of ustekinumab solution contained 90 mg ustekinumab, L-histidine, L-histidine hydrochloride monohydrate, sucrose, and polysorbate 80 at pH 6.0. No preservatives were present in ustekinumab.

Batch numbers for ustekinumab were 364800 and 365278.

Duration of Treatment:

Part 1: Ustekinumab 90 mg SC injections at Week 0 and Week 4, and q8w through Week 20. Subjects could enter a study extension and continue q8w dosing if they satisfied certain criteria.

Criteria for Evaluation:

Efficacy: The efficacy evaluations across Part 1 included biochemical measurements (ALP, AST, ALT, and total bilirubin), ELF, serum bile acids, Mayo Risk Score, fatigue impact scale (FIS), 5-D itch scale, PBC-40, patient perceived change in PBC-related fatigue, and patient perceived change in PBC-related pruritus.

Pharmacokinetics and immunogenicity: The PK assessments included measurement of serum ustekinumab concentrations over time including trough concentration of drug (C_{trough}) at steady state. Immunogenicity assessments included detection of antibodies to ustekinumab in serum samples, and the titer of confirmed positive samples.

Pharmacodynamic Biomarkers: Serum- and urine-based biomarkers of inflammation, autoantibodies and liver damage including but not limited to, IL-6, soluble IL-2 receptor, and 8-isoprostane were evaluated. RNA was used for differential gene expression analysis. These results will be summarized in a separate technical report.

Pharmacogenomic: DNA analyses were performed on samples from all consenting subjects. These results will be summarized in a separate technical report.

Medical resource utilization and health economics data: The medical resource utilization and health economics data were collected in the CRF by the investigator and staff for all subjects throughout the study. Utilization was based on PBC-related hospitalizations, surgeries and procedures, and the duration of the hospitalizations.

Safety: Safety assessments included monitoring adverse events (AE), clinical laboratory parameters (hematology and chemistry), electrocardiogram (ECG), vital signs, physical examination, and concomitant medication review at each visit, injection-site reactions, allergic reactions, and evaluation for tuberculosis.

Statistical Methods:

Sample Size Determination:

Part 1: The sample size calculation was based on a 1-sided exact binomial test for 1 population. Twelve subjects were estimated to provide >90% power to detect an ustekinumab treatment effect.

Analysis sets:

- Efficacy analysis set: Efficacy analyses for Part 1 were based on the modified intent-to-treat principle. All subjects who received at least 1 administration of ustekinumab (full or partial) were included in the efficacy analysis set.
- Safety analysis set: All subjects who received at least 1 administration of ustekinumab were included in the safety analysis set.
- Pharmacokinetics and immunogenicity analysis sets: All subjects who received at least 1 administration of ustekinumab and had at least 1 measurable serum ustekinumab concentration obtained after administration of a scheduled treatment were included in the PK and immunogenicity analysis sets, excluding 1 subject who after screening was found not to have PBC.
- Health economics analysis set: All subjects for Part 1 who received at least 1 administration of ustekinumab were included in the health economics analysis set.

Efficacy Analyses:

Part 1: The assessment of efficacy for Part 1 was primarily based on ALP response at Week 12.

Part 2: The study was terminated at the end of Part 1; therefore Part 2 of the study was not initiated.

RESULTS:

STUDY POPULATION:

Twenty subjects were enrolled in part 1 of the study. The majority of subjects were white (19 [95.0%]), and female (19 [95.0%]). The median age was 45.5 years and ranged from 32 to 69 years, which is consistent with a population of subjects with PBC in the earlier stages of the disease. The median duration of PBC at baseline was 3.20 years, ranging from 0.9 to 13.2 years. The ALP concentration at baseline was >3x ULN for 65% of the subjects, and the median Mayo Risk Score at baseline was 3.71 with a range of 2.9 to 4.6, which reflected a population with compensated liver disease. All subjects were on appropriate doses of UDCA at baseline. Two (10.0%) subjects had major protocol deviations due to entering the study without meeting all the entry criteria.

Based upon the efficacy results of Part 1, the decision was made not to continue to Part 2. Five subjects (25%) discontinued study agent prior to or at Week 28, and the other 15 subjects (75%) discontinued study agent while participating in the study extension. Nine (45%) subjects discontinued study agent due to lack of efficacy, 9 (45%) subjects because the Sponsor stopped the study, 1 (5.0%) subject because of loss to follow-up, and 1 (5.0%) subject for an "Other" reason.

EFFICACY RESULTS:

No subjects achieved ALP response (>40% decrease in ALP concentration from baseline) at Week 12 or Week 28. No subjects achieved ALP remission (normalization of ALP for subjects with baseline ALP between 1.67x and 2.8x ULN, or an ALP <1.67x ULN for subjects with baseline ALP >2.8x ULN) at Week 12 or Week 28. The median percent reduction from baseline in ALP concentration was 12.07% at Week 28.

The median percent reduction from baseline in ALT and AST concentrations at Week 28 were 15.42% and 13.35%, respectively.

There was a small decrease in median ELF score from baseline to Week 28.

Total serum bile acid concentrations at baseline were highly elevated with a small median decrease in concentration from baseline to Week 28.

Little improvement was observed for the PBC-40 domain scores, FIS, FIS domain scores, 5-D itch scale and patient perceived change in PBC-related fatigue from baseline through Week 28. However, some improvement was observed in patient perceived change in PBC-related pruritus.

PHARMACOKINETIC AND IMMUNOGENICITY RESULTS:

The mean serum ustekinumab concentrations at Week 4 (4.26 µg/ml) and Week 8 (5.70 µg/mL) following administration of ustekinumab at Weeks 0 and 4 (ie, 4-week dosing interval) were higher than the mean trough serum ustekinumab concentrations at Weeks 12, 20, and 28 (2.54 to 2.71 µg/mL) during maintenance therapy with 8-week dosing interval. The mean trough serum ustekinumab concentrations at Weeks 12, 20, and 28 (2.63, 2.54, and 2.71 µg/mL, respectively) were similar, suggesting that serum ustekinumab concentrations achieved steady-state by Week 12.

Of the 19 ustekinumab-treated subjects with appropriate samples, 1 subject (5.3%) tested positive for antibodies to ustekinumab (which were neutralizing) through Week 28.

HEALTH ECONOMICS RESULTS:

All health economics analyses were conducted using the 20 treated subjects in Part 1. One subject required hospitalization for PBC-related issues on Study Day 280. Two subjects had PBC-related surgeries/procedures through Week 28. One subject had 2 column varices banded and an upper endoscopy on Study Day 280, and 1 subject had a liver ultrasound on Study Day 213 and a liver biopsy on Study Day 226.

SAFETY RESULTS:

Ustekinumab 90 mg SC injections at Weeks 0, 4, and q8w through the final safety visit, with an average exposure of 6.5 administrations per subject, were generally well-tolerated with no new safety events identified.

The most commonly reported AE was fatigue, reported in 8 subjects (40.0%). Other than fatigue, the AEs reported in more than 2 subjects were headache (5 subjects; 25.0%), urinary tract infection (4 subjects; 20.0%), nausea (3 subjects; 15.0%), and back pain (3 subjects; 15.0%).

One subject (5.0%) had a serious adverse event (SAE) of an upper gastrointestinal haemorrhage that was not considered related to study drug. There were no serious infections or discontinuations due to an AE through the final safety visit.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The subject population studied in the CNTO1275PBC2001 study represented a refractory PBC population with advanced baseline disease.

Overall changes in ALP were modest although serum ustekinumab concentrations achieved steady-state by Week12 and, proof-of-concept was not established:

- No subjects achieved ALP response (>40% decrease from baseline) at Week 12 or Week 28.
- No subjects achieved ALP remission at Week 12 or Week 28.
- Although larger changes in ALP were observed in the week 36 and week 52 data, the interpretation of these data is limited by the small number of subjects and discontinuation of subjects who had less than a 20% ALP response.

In addition, no improvement was seen in most other endpoints. Based upon the efficacy results of Part 1, the decision was made not to continue to Part 2.

Overall, ustekinumab was well tolerated in subjects with PBC. There were no new safety signals observed for ustekinumab.

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