2. SYNOPSIS

Name of Sponsor/Company: Liminal R&D BioSciences Inc. **Name of Finished Product:** PBI-4050 **Name of Active Ingredient:** 3-pentylbenzeneacetic acid sodium salt	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Title of Study: An open-label, rollover study of PBI-4050 in subjects with Alström Syndrome (PBI-4050-CT-9-10)		
Principal Investigator: Tarekegn Hiwot MD		
Study centres: Queen Elizabeth Hospital, Birmingham, UK.		
Publications (reference): None		
Studied period (years): Date first subject enrolled: 04 Oct 2017 Date last subject completed: 07 Apr 2020		**Phase of development:** 2

Objectives:

Primary:

- To evaluate the long-term safety and tolerability of PBI-4050, administered orally once daily, in subjects with Alström Syndrome (ALMS) who had completed treatment in a preceding Liminal-sponsored ALMS study with PBI-4050

Secondary:

- To evaluate the effect of PBI-4050 on metabolic syndrome parameters
- To assess the effect of PBI-4050 on liver stiffness using transient elastography (FibroScan)
- To assess the effect of PBI-4050 on the fat content and fibrosis burden in the liver using magnetic resonance imaging (MRI)
- To assess the effect of PBI-4050 on cardiac fibrosis using MRI

Methodology:

This was a Phase 2, open-label, single-arm, rollover study evaluating the long-term safety and tolerability of PBI-4050 in subjects with ALMS who had completed the end-of-treatment (EoT) visit in a preceding Liminal-sponsored ALMS study with PBI-4050. This study was to also evaluate the efficacy and pharmacological effects of PBI-4050 in this multi-faceted disorder. Approximately 20 to 30 subjects were to be enrolled to receive 800 mg PBI-4050 orally once daily for up to 5 years or until product licensing or study termination by the Sponsor, whichever occurred first. In addition, subjects with type 2 diabetes mellitus could adjust their antidiabetic medications according to local standard practice during the study.

Subjects who completed the EoT visit in preceding Liminal-sponsored ALMS studies with PBI-4050 and signed informed consent for the present study were enrolled; this visit was designated as the Week 1, Day 1 (baseline) visit of the present study. Subjects were to return to the study site every 24 weeks from Week 1 to Week 96 and then every 26 weeks thereafter until the end-of-study visit (30 days after the last dose of PBI-4050).

A Data and Safety Monitoring Board (DSMB) reviewed individual subject safety data in an ongoing manner.

Number of subjects (planned and analysed):

Approximately 20 to 30 subjects were to be enrolled from preceding Liminal-sponsored ALMS studies with PBI-4050. A total of 9 patients from Study PBI-4050-ATX-9-05 met the eligibility criteria and were enrolled at 1 site in the UK. All 9 subjects received at least 1 dose of 800 mg PBI-4050.

Diagnosis and main criteria for inclusion:

Subjects had to have a documented diagnosis of ALMS and have completed the EoT visit of the preceding Liminal-sponsored ALMS study with PBI-4050.

Test product, dose and mode of administration, batch number:

PBI-4050 800 mg was administered orally once daily as 4 × 200 mg gel capsules at least 1 hour before or 2 hours after a meal.

Batch/lot numbers: Lot 3373, Lot 3450, Lot 3628, Lot 3729

Duration of treatment:

The planned duration of treatment was 5 years; however, study treatment was terminated after 131 weeks.

Reference therapy, dose and mode of administration, batch number:

None.

Criteria for evaluation:

Safety:

Safety was assessed from the time the subject gave informed consent until the final follow-up visit. Safety endpoints included treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs), clinical laboratory tests, vital signs, physical examination, and electrocardiograms (ECGs).

Efficacy:

Changes from baseline at each visit for the following metabolic syndrome parameters: fasting plasma glucose, glycated haemoglobin (HbA1c), fasting insulin, C-peptide, homeostasis model assessment for steady state beta-cell function, and homeostasis model assessment for insulin sensitivity.

Change from baseline in the liver stiffness (measured in kPa correlated to fibrosis) by using a transient elastography (FibroScan).

Change from baseline in the fat content and fibrosis burden in liver MRI.

Change from baseline in cardiac fibrosis on cardiac MRI.

Statistical methods:

All collected data were presented for each subject in individual line listings and were summarised using descriptive statistics. For qualitative parameters, the population size and the percentage of available data for each parameter were presented. For quantitative parameters, the population size, the mean, standard deviation (SD), median, interval interquartile (Q1-Q3), minimum, and maximum values were presented. All collected numerical data were presented at each time points unless otherwise stated.

The statistical analysis was performed prior to the DSMB analysis and after the database lock. Since the analysis was exploratory and informative in nature, and because the DSMB recommendations did not depend on the efficacy endpoints, no adjustment was needed to protect the Type I error for either the DSMB analysis or the final analysis. No adjustment was made for multiplicity and no subgroup analyses were performed. All summaries were made on all available data, and no imputation was made. All summaries and statistical analyses were generated using SAS version 9.4.

Safety Analyses

Adverse events (AEs) were characterised as treatment-emergent or non-treatment emergent (those that occurred after informed consent was obtained but before IMP administration). The focus of all AE tables was on TEAEs and TESAEs. Study drug-related TEAEs/TESAEs included all TEAEs/TESAEs that were definitely, probably, or possibly related to PBI-4050.

An overview of TEAEs/TESAEs was summarised with the number and percentages of subjects experiencing at least 1 of the following: TEAE/TESAE, study drug related TEAE/TESAE, TEAEs/TESAEs leading to treatment permanent discontinuation, TEAEs leading to discontinuation and TEAEs leading to death.

TEAEs/TESAEs were summarised by the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) system organ class (SOC) and preferred term (PT), showing the number and percentage of subjects experiencing a given event. A subject experiencing the same AE multiple times was counted only once for the corresponding PT. Similarly, if a subject experienced multiple AEs within the same SOC, that subject was counted only once for that SOC. The AEs were presented in alphabetical order by SOC. Similar tables were presented for SAEs.

Laboratory parameters (haematology, biochemistry, and urinalysis), vital signs, and other safety variables were summarised using descriptive statistics at each visit.

Efficacy Analyses

No efficacy parameters were analysed because of early termination of the study.

SUMMARY – CONCLUSIONS:

A total of 9 patients from Study PBI-4050-ATX-9-05 met the eligibility criteria and were enrolled at 1 site in the UK. All 9 subjects received at least 1 dose of 800 mg PBI-4050 and completed the first 48 weeks of the study. Seven (77.8%) subjects completed Week 72 and 6 (66.7%) completed Week 96. Of these 9 subjects, 1 was withdrawn from the study due to non-compliance with the study drug and 2 subjects withdrew consent.

Six subjects were ongoing in the study by the time the coronavirus disease 2019 pandemic occurred in early 2020. The pandemic affected subjects' ability to travel to the site and the availability of site staff. On 01 April 2020, in consideration of the subsequent redeployment of study team staff and the potential impact on the subjects, who were considered a high-risk group, the Sponsor decided, after careful evaluation of possible alternatives, that it would be difficult for the specialised site team to provide adequate clinical trial safety oversight and terminated the study. Subjects had received treatment for more than 3 years, allowing the Sponsor to draw a conclusion from the analysis of data collected to date. The efficacy evaluation was not performed. This study therefore presents all available safety data only.

SAFETY RESULTS:

A total daily oral dose of 800 mg PBI-4050 appeared to be safe and well tolerated in subjects with ALMS. There were no deaths, and no subjects had an AE that resulted in permanent discontinuation of study drug. The severe TESAE of cardiac ventricular thrombosis (ongoing from Study PBI-4050-ATX-9-05), 1 mild TESAE of gastroenteritis and 3 moderate TESAEs of acute kidney injury, groin abscess and groin infection were all judged by the Investigator as not related to study drug. The most frequent TEAEs (> 2 subjects) were headache, haemoglobin decreased and hepatic lesion. All but 1 TEAE were mild or moderate, and most (90.0%) were judged by the Investigator as not related to study drug. All 4 study drug related AEs were mild/moderate in severity. Routine haematology, biochemistry, and urinalysis results were unremarkable, and there were no clinically significant vital sign or ECG findings.

CONCLUSION:

A daily oral dose of 800 mg PBI-4050 appeared to be well tolerated for over 3 years in subjects with ALMS aged 18 to 53 years.

Date of the report: 23 November 2021