2. SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Arbutus BioPharma</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:
ARB-1467 (aka ARB-001467)</td></tr>
<tr><td>Name of Active Ingredient:
UsiHBV-1 contained within lipid nanoparticles</td></tr>
<tr><td colspan="3">Title of Study:
A Phase 2a, Open-Label, Study Evaluating the Safety and Anti-Viral Activity of ARB-001467 in Non-Cirrhotic, HBeAg-Negative Subjects with Chronic HBV Infection (Genotype A or B) in Combination with PEG-IFN α-2a and Tenofovir Disoproxil Fumarate</td></tr>
<tr><td colspan="3">Investigators:
See Appendix 16.1.4 for a list of investigators.</td></tr>
<tr><td colspan="3">Study Centers:
Nine sites in 3 countries were activated for this study: 4 sites in Taiwan, 3 sites in Poland, and 2 sites in Spain. Six of those sites screened subjects for entry into the study; 3 activated sites did not screen any subjects for the study. See Appendix 16.1.4 for a list of study centers.</td></tr>
<tr><td colspan="3">Publication:
None.</td></tr>
<tr><td colspan="2">Study Period (years): ~18.5 months
Date first informed consent form signed: 09 March 2018
Date of last subject last visit: 25 September 2019</td><td>Development Phase: 2a</td></tr>
<tr><td colspan="3">Objectives:
The primary objective of the study was to explore the anti-viral efficacy of combination therapy with ARB-1467 plus tenofovir disoproxil fumarate (TDF) and pegylated interferon alfa-2a (PEG-IFN α-2a) in subjects with chronic hepatitis B infection (CHB) due to hepatitis B virus (HBV) genotype A or B, who were HBV-DNA positive.
Secondary objectives of the study were to:
Evaluate the proportion of subjects who achieved hepatitis B virus surface antigen (HBsAg) <lower limit of quantification (LLOQ) and who achieved HBV-DNA <LLOQ throughout the study.
Evaluate on-treatment safety as measured by the frequency of AEs, discontinuations due to AEs, and selected Grade 3-4 laboratory abnormalities (based on the Common Terminology Criteria for Adverse Events [CTCAE] criteria.)</td></tr>
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Exploratory objectives of the study were to:

- Explore the relationship between safety and/or anti-viral activity and ARB-1467 plasma concentrations. (Note: if analyzed, these results will be presented in a separate report.)
- Describe drug-resistant HBV variants associated with virologic breakthrough if observed.
- Evaluate the role of interferon as an immune modulator when given in combination with ARB-1467.

Methodology:

This was a Phase 2a, open-label, single-arm study that evaluated the safety and anti-viral activity of ARB-1467 in combination with TDF and PEG-IFN α-2a.

All subjects received ARB-1467, pre-medications, and TDF during the course of the study. Based on the outcome of an evaluation on or before Treatment Week (TW)6 (HBsAg results ≤1000 IU/mL and ≥0.7 $\log_{10}$ decline from baseline in HBsAg), qualified subjects also had PEG-IFN α-2a added to their study treatments. The total duration of treatment was up to 30 weeks (24 weeks for PEG-IFN α-2a, which may have been added at TW6).

Number of Subjects (planned and analyzed):

Approximately 20 subjects were planned to be enrolled into the study. Six subjects were enrolled and received study drug. Two subjects qualified for addition of PEG-IFN α-2a to their study treatments.

Diagnosis and Main Criteria for Inclusion:

Eligible subjects were non-cirrhotic, with CHB, with HBV genotype A or B, who 1) had not received treatment for CHB (naive), or 2) who had received treatment (experienced) but discontinued at least 6 months prior to screening.

Test Product: Dose, Mode of Administration, Batch Numbers:

ARB-1467 (aka ARB-001467) Injection; 0.4 mg/kg administered by intravenous (IV) infusion every 2 weeks up to Week 30; batch numbers L00258 (1-FIN-2649) and L00296 (1-FIN-2887).

In addition to the study drug ARB-1467, TDF 245 mg (each film-coated tablet contains 245 mg of tenofovir disoproxil [as fumarate], equivalent to 300 mg of tenofovir disoproxil fumarate) was administered by mouth (PO) daily. TDF was sourced by Arbutus from commercial market(s).

Subjects who attained an HBsAg ≤1000 IU/mL and a ≥0.7 $\log_{10}$ decline from baseline in HBsAg at or before Treatment Week 6 (TW6) received PEG-IFN α-2a 180 μg (1.0 mL vial or 0.5 mL prefilled syringe) subcutaneously (SC) once weekly (QW) for up to 24 weeks.

Treatment Duration:

Subjects were treated with ARB-1467 and TDF for up to 30 weeks. Subjects who qualified to receive PEG-IFN α-2a at TW6 were treated for up to 24 additional weeks.

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Reference Therapy: Dose, Mode of Administration, Batch Numbers:

There was no reference therapy.

CRITERIA FOR EVALUATION:

Anti-viral Activity Criteria:

The primary endpoint was the proportion of treated subjects with HBsAg decline ≥2 $\log_{10}$ from baseline at Week 30.

The secondary endpoint was the proportion of subjects who achieved HBsAg <LLOQ and HBV-DNA <LLOQ at each of the following Weeks: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, and 30; and Post-treatment Weeks 4, 8, 12, and 24.

Safety Criteria:

The safety endpoint was on-treatment safety, as measured by the frequency of adverse events (AEs), discontinuations due to AEs, and selected Grade 3-4 laboratory abnormalities (including hematologic and liver function, based on CTCAE.

Statistical Analyses:

All analyses were performed using the Safety Population, which was comprised of the 6 subjects who received study drug.

Anti-viral Activity

Measures of virologic response included quantitative HBsAg and HBV-DNA assessments. HBsAg actual, change from baseline, and percentage change from baseline were summarized. The $\log_{10}$ HBsAg actual, change from baseline, and proportion of treated subjects with HBsAg change from baseline ≥2 $\log_{10}$ was also summarized. A summary of proportion of treated subjects with HBV-DNA <LLOQ is provided by visit. Individual plots of HBsAg and HBV-DNA are provided.

Subjects who met the on-treatment virologic breakthrough criteria were listed. Virologic breakthrough criteria were:

- Confirmed HBV-DNA ≥LLOQ after 2 consecutive HBV-DNA <LLOQ; OR
- Confirmed >1 $\log_{10}$ IU/mL HBV-DNA increase compared to the HBV-DNA nadir.

Safety

Safety data, including AEs, clinical laboratory data, vital signs, and electrocardiograms (ECGs), were summarized using descriptive statistics and listed individually for each subject.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0. Each verbatim term was coded to a low-level term, which was mapped to a preferred term (PT), high level term (HLT), and a system organ class (SOC).

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AE summaries included only treatment-emergent AEs (TEAEs), which were defined as AEs occurring or worsening with an onset at the time of or following the start of treatment with study medication (i.e., the first dose of protocol-specified study pre-medication on Day -1) and up to 28 days after the last dose of study treatment.

Individual data listings of laboratory results (hematology, clinical chemistry, coagulation, and urinalysis) are presented by treatment, subject, and visit. Values outside of the laboratory's reference range (i.e., those with high or low values) were flagged in the laboratory listings. Continuous laboratory results and changes from baseline are summarized descriptively. Laboratory abnormalities were graded according to the CTCAE. Any graded abnormality that occurred following the initiation of study drug dosing and represented at least a 1 grade increase from the baseline assessment was defined as treatment emergent. A summary of treatment-emergent Grade 3 and Grade 4 laboratory abnormalities by treatment is provided. Laboratory abnormality shifts from baseline to worst post-baseline assessments are also summarized.

SUMMARY and CONCLUSIONS

STUDY POPULATION:

The mean (standard deviation [SD]) age of the 6 subjects was 45.8 (14.19) years and the median age was 49.0 years (range: 28 to 62 years). Four subjects (66.7%) were male. Three subjects (50.0%) were genotype A and 3 subjects (50.0%) were genotype B. The mean (SD) BMI for 5 of the 6 subjects (height was not reported for 1 subject) was 24.8 kg/m^2 (1.95 kg/m^2) and the median BMI was 25.4 kg/m^2 (range: 21.8 to 26.7 kg/m^2).

The mean (SD) duration of HBV infection was 25.8 (15.9) years and the median duration was 30 years (range: 3 to 40 years). All 6 subjects (100%) were HBeAg negative as required by the study protocol.

ANTI-VIRAL ACTIVITY:

HBsAg

The mean (SD) HBsAg $\log_{10}$ maximum reduction from baseline was -1.47 (1.055) and the median HBsAg $\log_{10}$ maximum reduction from baseline was -1.00 (range: -3.2 to -0.5). All 6 subjects (100%) had a $\geq$0.5 $\log_{10}$ reduction from baseline in HBsAg during the treatment period or the follow-up period. Three subjects (50.0%) had a $\geq$1.0 $\log_{10}$ reduction and 2 subjects (33.3%) had a $\geq$2.0 $\log_{10}$ reduction. Three subjects (50.0%) had a $\geq$1.0 $\log_{10}$ reduction in HBsAg and a post-baseline HBsAg level <1000 IU/mL.

No subject had a $\geq$2.0 $\log_{10}$ decrease from baseline at Week 2 or 4, and 1 subject (16.7%) had a $\geq$2.0 $\log_{10}$ decrease at Week 6.

Only 2 of the 6 enrolled subjects met the Week 6 HBsAg criteria and continued to receive ARB-1467 and TDF with the addition of PEG-IFN α-2a. Of the 2 subjects who continued in the study past Week 6 and had PEG-IFN α-2a added, 1 subject had a $\geq$2.0 $\log_{10}$ decrease in HBsAg at Weeks 8, 10, 12, 14, and 16, and both subjects had a $\geq$2.0 $\log_{10}$ decrease at Weeks 18, 20, 22, 24, and 26.

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Hepatitis B Virus DNA

A rapid decrease in HBV-DNA was observed in all 6 subjects at the Week 2 time point. In 2 subjects the decrease in HBV-DNA was <LLOQ at Week 2, and in the other 4 subjects the HBV-DNA level continued to decrease at Weeks 4 and 6.

Two subjects (33.3%) had an HBV-DNA level <LLOQ at Weeks 2 and 4, and 1 subject (16.7%) had an HBV-DNA level <LLOQ at Week 6. Of the 2 subjects who continued in the study past Week 6, 1 subject had an HBV-DNA level <LLOQ at Week 8, and both subjects had an HBV-DNA level <LLOQ at Weeks 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28.

SAFETY RESULTS:

ARB-1467 administered at a dose of 0.4 mg/kg by IV infusion every 2 weeks was well tolerated in this Phase 2a study.

No subject had an AE that led to discontinuation of treatment or to discontinuation from the study. There were no Grade 4 or 5 (fatal) AEs. There were no serious adverse events (SAEs).

All 6 subjects (100%) had at least 1 AE that was, in the opinion of the investigator, related to treatment with ARB-1467. All of the ARB-1467 treatment-related AEs were Grade 1 (mild); the AEs were hypoesthesia, somnolence, flushing, phlebitis, dry mouth, dyspepsia, and pruritus (all occurring in 1 subject each [16.7%]).

Two subjects (33.3%) reported 12 AEs that were related to treatment with PEG-IFN α-2a: fatigue, injection site erythema, malaise, pyrexia, diarrhea, angular cheilitis, neutrophil count decreased, bone pain, myalgia, somnolence, nervousness, and pruritus. The event of neutrophil count decreased was the only Grade 3 AE reported in the study.

Two subjects (33.3%) had 1 AE each that was related to treatment with TDF: nocturia and pruritus. Both events were Grade 1 (mild).

There were no clinically significant findings in the change from baseline results for any hematology, serum chemistry, coagulation, or urinalysis laboratory parameter. After Week 6, neutrophil and lymphocyte counts were decreased from baseline values in the 2 subjects who continued on study treatment with PEG IFN α 2a added.

One abnormal laboratory test in 1 subject (16.7%) was reported as an AE. The event was neutrophil count decreased on Day 115 (Grade 3) that resolved on Day 141. The event was related to treatment with PEG-IFN α-2a and resulted in a dose reduction.

There were no clinically significant mean values or mean change from baseline values in any vital sign parameter.

There were no clinically significant mean values or mean change from baseline values in any ECG parameter. No subject had a change from baseline in QT interval corrected by Fridericia formula (QTcF) interval of >60 msec at any time point.

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CONCLUSION:

The small number of subjects enrolled in this study combined with the fact that only 2 out of 6 subjects met the predefined Week 6 criteria to add-on PEG-IFN α-2a did not allow any definitive conclusions to be made about the combined anti-viral activity of ARB-1467, TDF, and PEG-IFN α-2a in reducing HBsAg and HBV-DNA levels. In the 2 subjects who met the Week 6 criteria to add PEG-IFN α-2a, HBsAg levels continued to decline beyond Week 6, reaching 9.20 IU/mL and 8.64 IU/mL by the end of treatment (Week 30). However, neither subject achieved a functional cure, as HBsAg levels rebounded to near baseline levels during the follow-up period.

ARB-1467 administered at a dose of 0.4 mg/kg by IV infusion every 2 weeks was well tolerated in this Phase 2a study.

Date of the report: 07 January 2020

This study was discontinued early due to futility in enrollment and the program has since been closed for lack of efficacy in favor of next generation siRNA inhibitors.