SYNOPSIS

Name of Sponsor/Company	Aragon Pharmaceuticals, Inc.*
Name of Investigational Product	JNJ-56021927 (apalutamide)

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Status: Approved

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Prepared by: Janssen Pharmaceutical Research and Development, LLC.

Protocol No.: 56021927PCR1018

Title of Study: A Single-Dose, Open-Label Study to Evaluate the Pharmacokinetics of JNJ-56021927 in Subjects With Mild or Moderate Hepatic Impairment Compared With Subjects With Normal Hepatic Function

NCT No.: NCT02524717

Clinical Registry No.: CR107774

Principal Investigators: William Smith, New Orleans Center for Clinical Research, USA and Eric Lawitz, Texas Liver Institute, USA

Study Centers: The study was conducted at 2 centers in the United States of America (USA).

Publication (Reference): None

Study Period: 24 August 2015 to 09 February 2017

Phase of Development: Phase 1

Objectives:

The primary objective was to characterize the pharmacokinetics (PK) of apalutamide in subjects with mild and moderate hepatic impairment.

The secondary objective was to assess the safety of apalutamide.

Methodology: This was an open-label, single-dose, multi-center, non-randomized Phase 1 study of apalutamide in subjects who had either hepatic impairment (mild and moderate) or qualified for the control group (normal hepatic function).

Subjects were screened within 21 days (Day -21 to -2) of providing written informed consent. During the Screening Phase, subjects were evaluated for inclusion and exclusion criteria. Eligible subjects with mild and moderate hepatic impairment and subjects with normal hepatic function received a single oral dose of apalutamide 240 mg on Day 1.

A total of 24 subjects (8 subjects in each group) were enrolled into this study. Subjects with mild (Grade A) and moderate (Grade B) hepatic impairment were classified according to the Child-Pugh Classification of Severity of Liver Disease. Subjects with mild and moderate hepatic impairment were

enrolled concurrently. Subjects with normal hepatic function matched by age and BMI were enrolled after subjects in each of the previous groups completed all assessments.

Serial blood samples were collected predose and over 1,344 hours (Day 57) post dosing, for the determination of apalutamide concentration and its active metabolite JNJ-56142060.

Subjects' safety analysis was based on the incidence, type and severity of treatment-emergent adverse events (TEAEs), and on changes in physical examination findings, vital sign measurements, and clinical laboratory analyte values.

Specific evaluations and their timings can be found in the Time and Events Schedule of the protocol.

Number of Subjects (planned and analyzed): As planned, 24 subjects were enrolled and dosed in this study. All 24 subjects completed the study and were included in the safety and PK analyses.

There was 1 major protocol deviation reported during the study: 1 subject was hospitalized due to PPI on Day 43. This serious adverse event (SAE) was reported late (after 24 Hours reporting period) to the sponsor on Day 105. This deviation was considered to have had no impact on the study results.

Diagnosis and Main Criteria for Inclusion: Healthy men and men with impaired hepatic function between 18 and 80 years of age, inclusive; body mass index (BMI) between 18 and 35 kg/m², inclusive, and a body weight of not less than 50 kg were included in this study. Subjects with normal hepatic function were matched by mean age (±10 years) and mean BMI (±20%) of combined mild and moderate impairment group.

Test Product, Dose and Mode of Administration, Batch No.: Apalutamide was supplied for this study as a 60 mg tablet (G023) which contained 60 mg of apalutamide as a spray dried powder in HPMC-AS polymer, in a 1/3 ratio (API [active pharmaceutical ingredient]/polymer). The apalutamide supply used in the study was Reference Number: 4371273, Bulk Lot Number: 15B19/G023, and expiration date: June 2016/December 2016 (Note: expiry date for lot number 15B19/G023 was extended to December 2016).

Duration of Treatment: The total study duration for an individual subject was approximately 78 days (including 21 days for screening). A screening phase (within 21 days before study drug administration) was followed by an open-label treatment phase where subjects were confined to the study center from Day -1 until completion of the 168-hour PK blood sample collection on Day 8. Subjects returned to the study center on Days 10, 12, and 15 and then returned to the center weekly for subsequent assessments up to Day 57. End-of-study assessments were performed on Day 57.

Criteria for Evaluation:

Pharmacokinetics

Serial blood samples were collected predose and over 1,344 hours (Day 57) after dosing for the determination of apalutamide concentration and the concentration of its active metabolite, JNJ-56142060.

Pharmacokinetic analysis were based on the individual concentration-time data, using actual sampling times, and the following plasma PK parameters of apalutamide and JNJ-56142060 were determined as appropriate: C_{max}, t_{max}, AUC_{last}, CL/F (parent only), AUC_{∞}, $\%AUC_{\infty,ex}$, $t_{1/2,\lambda}$, λ_z, t_{last} and the metabolite to parent drug ratio (MPR) for C_{max}, AUC_{last}, and AUC_{∞}. Plasma protein binding (PPB) was measured using predose plasma sample and PK samples obtained postdose at the time of C_{max}.

Safety

Safety was assessed from the time of informed consent until the end of the study by means of adverse events (AEs), physical examination, vital signs, electrocardiogram (ECG), and laboratory safety (hematology, serum chemistry, coagulation parameters, and urinalysis) (see the protocol for details).

Statistical Methods:

Sample Size Determination

Based on clinical considerations, following the May 2003 FDA Guidance for Industry: *Pharmacokinetics in Patients with Impaired Hepatic Function; Study Design, Data Analysis, and Impact on Dosing and Labeling*, approximately 24 subjects were enrolled (16 subjects with hepatic impairment [8 mild and 8 moderate] at baseline according to Child-Pugh criteria and 8 subjects with normal hepatic function).

Based on a parallel-design study in healthy subjects (Clinical Study Report 56021927PCR1011, March 2015), the inter-subject coefficient of variation (CV) was estimated to be less than 23% for AUCs and C_{max} of apalutamide. With a sample size of 8 subjects per hepatic function group as stated above, the 90% confidence intervals (CI) of geometric mean ratios for AUCs and C_{max} were expected to be within 77% and 130% of the true ratio of means.

Pharmacokinetics

Individual plasma concentrations for apalutamide and its active metabolite JNJ-56142060 were tabulated with descriptive statistics (including arithmetic mean, standard deviation [SD], CV, median, minimum, and maximum) calculated at each sampling time point for each hepatic function group. Individual and mean plasma concentration-time profiles were plotted for each hepatic function group. Individual data were also tabulated with descriptive statistics for PK parameters were calculated. In addition, PPB data (expressed as unbound fraction) were summarized using descriptive statistics.

An analysis of variance (ANOVA) model was applied to the log-transformed total and unbound PK parameters. The geometric mean ratios and the associated 90% confidence intervals (CI) for AUC_{∞}, AUC_{last}, and C_{max} were constructed for the following pairs: (1) mild hepatic impairment versus (vs) normal hepatic function; and (2) moderate hepatic impairment vs normal hepatic function. The results were presented in original scale after back-transformation.

Graphical methods were used to explore the potential relationships between selected PK parameters and measures of hepatic function (bilirubin, albumin, prothrombin time prolongation, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Child-Pugh score, and Child-Pugh classification).

An exploratory analysis was performed to investigate the potential relationship between apalutamide PK parameters and other measures of hepatic impairment or function. Fixed effects models were fitted into the log-transformed PK parameter data with PK parameters as dependent variables and subsets of variables (bilirubin, albumin, prothrombin time, ALT and AST) as fixed effects. Among all covariates (age, body weight, and ethnicity) that were tested, ethnicity was included in the model to reduce the variability in the data.

Safety

The safety population included all subjects. Baseline for all laboratory evaluations, 12-lead ECG measurements and vital signs was defined as the last evaluation done before study drug administration. Safety was evaluated by examining the type and severity of AEs, changes in clinical laboratory test values, physical examination results, 12-lead ECGs, and vital signs measurements from the screening phase through study completion, including the End-of-Treatment visit.

The verbatim terms used in the CRF by investigators to identify AEs were coded using the MedDRA, version 19.1

RESULTS:

STUDY POPULATION:

Overall, 24 men aged 28 to 66 years (median = 54.0 years) inclusive, with a body mass index (BMI) between 18.34 and 34.96 kg/m^2 (median = 27.68 kg/m^2) were enrolled in this study. Eight subjects each with mild (Child Pugh Score = 5 to 6 points) and moderate (Child Pugh Score = 7 to 9 points) hepatic impairment were enrolled concurrently. Eight subjects with normal hepatic function were matched with hepatic impaired subjects based on age (±10 years) and BMI (within 20% of the mean of the mild and moderate groups combined). Demographic data and baseline characteristics were generally similar across the treatment groups.

PHARMACOKINETIC RESULTS: The following tables summarize the statistical analysis of PK parameters of apalutamide and its metabolite JNJ-56142060 after a single oral administration of apalutamide in mild (Table A) and moderate (Table B) hepatic impaired subjects, compared to administration in healthy control subjects with normal hepatic function.

A: Effect of Mild Hepatic Impairment

Analyte	Pharmacokinetic Parameters	n	Geometric Mean		Geometric Mean Ratio, (%)	90% CI, (%)
			Normal Hepatic Function (reference)	Mild Hepatic Impairment (test)		
Apalutamide	C_{max} (µg/mL)	8	1.91	1.94	101.66	77.07 – 134.09
	AUC_{last} (µg h/mL)	8	190	178	93.52	74.82 – 116.90
	AUC_{∞} (µg h/mL)	8	200	189	94.59	76.06 – 117.64
JNJ-56142060	C_{max} (µg/mL)	8	0.271	0.267	98.85	72.90 – 134.03
	AUC_{last} (µg h/mL)	8	165	156	94.74	80.74 – 111.18
	AUC_{∞} (µg h/mL)	8	177	171	96.28	83.79 – 110.62

B: Effect of Moderate Hepatic Impairment

Analyte	Pharmacokinetic Parameters	n	Geometric Mean		Geometric Mean Ratio, (%)	90% CI, (%)
			Normal Hepatic Function (reference)	Moderate Hepatic Impairment (test)		
Apalutamide	C_{max} (µg/mL)	8	1.91	1.99	104.21	74.01 – 146.71
	AUC_{last} (µg h/mL)	8	190	206	108.72	78.87 – 149.89
	AUC_{∞} (µg h/mL)	8	200	226	113.35	81.70 – 157.26
JNJ-56142060	C_{max} (µg/mL)	8	0.271	0.199	73.48	50.43 – 107.06
	AUC_{last} (µg h/mL)	8	165	124	75.32	60.21 – 94.21
	AUC_{∞} (µg h/mL)	7	177	144	81.15	65.00 – 101.32

SAFETY RESULTS: An overall summary of TEAEs is provided in the table below. Across all treatment groups, 7 (29.2%) subjects reported at least 1 TEAE, including 3 (37.5%) subjects with mild hepatic impairment and 4 (50.0%) subjects with moderate hepatic impairment. None of the subjects with normal hepatic function experienced any TEAEs. None of the reported TEAEs were considered as treatment related, except for 1 subject with moderate hepatic impairment who had a Grade 1 decrease in testosterone levels, considered as possibly related to the study drug by the investigator.

Overall Summary of Treatment Emergent Adverse Events; Safety Analysis Set
(Study JNJ-56021927PCR1018)

	Hepatic Function Group			
	Normal	Mild	Moderate	Total
Number of Subjects in Safety analysis set	8	8	8	24
Treatment-Emergent Adverse Events	0	3 (37.5%)	4 (50.0%)	7 (29.2%)
Drug-related[a]	0	0	1 (12.5%)	1 (4.2%)
Toxicity Grade 1	0	2 (25.0%)	3 (37.5%)	5 (20.8%)
Toxicity Grade 2	0	2 (25.0%)	1 (12.5%)	3 (12.5%)
Toxicity Grade 3	0	0	2 (25.0%)	2 (8.3%)
Serious Treatment Emergent Adverse Events	0	0	2 (25.0%)	2 (8.3%)
Drug-related[a]	0	0	0	0
Toxicity Grade 1	0	0	0	0
Toxicity Grade 2	0	0	0	0
Toxicity Grade 3	0	0	2 (25.0%)	2 (8.3%)

[a]Drug related adverse events are adverse events causality reported as possible, probable and very likely. Percentage is based on the number of subjects in safety analysis set as denominator

In mild hepatic impairment group, 2 (25.0%) subjects reported 3 TEAEs of Grade 2 severity, which included back pain and diarrhea (1 subject; doubtfully related), and skin ulcer (1 subject; not related).

In the moderate hepatic impairment group, of 4 (50.0%) subjects with TEAEs: 1 subject experienced two Grade 2 TEAEs: spinal compression fracture (not related) and dyspnea (doubtfully related), and a Grade 3 event of hypoxia (doubtfully related). The Grade 3 TEAE of hypoxia was reported as a SAE. Another subject experienced a Grade 3 SAE of PPI , which was considered as not related to the study drug by the investigator.

There were no study discontinuations due to TEAEs reported during the study. All TEAEs had resolved by the end-of-study.

There were no clinically significant, ECG or vital signs observations which were reported during the study. No clinically significant laboratory findings were observed, except in 1 subject with moderate hepatic impairment who had a Grade 1 decrease in testosterone levels on Day 57 and at 6 subsequent assessments. This event was reported as a TEAE and was considered as possibly related to the study drug by the investigator.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

CONCLUSIONS:

- The PK of apalutamide following a single 240 mg dose were similar in subjects with mild or moderate baseline hepatic impairment compared to subjects with normal hepatic function.
- JNJ-56142060 C_{max} and AUC were similar for subjects with mild hepatic impairment compared to subjects with normal function, while in subjects with moderate hepatic impairment, JNJ-56142060 C_{max}, AUC_{last} and AUC_{∞} were 26.52%, 24.68% and 18.85% lower, respectively.
- A single, oral dose of apalutamide 240 mg was well tolerated and the observed AE profile was as expected, based on the known side effects observed to date with single dose of apalutamide. No new safety signals were noted in any of the groups.

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