Millendo Therapeutics US, Inc.

CLINICAL STUDY REPORT

A Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia

Study number/acronym: ATR-101-202

EudraCT Number: 2017-004878-34

Investigational Product Name	Nevanimibe Hydrochloride
Study Phase	2b
Protocol Number	ATR-101-202
	EU/ISR:
	Original Protocol: 22 February 2018 **Global Protocol Amendment 1: 13 March 2018** **Czech Republic Country-Specific Amendment 1: 11 June 2018** **France Country-Specific Amendment 1: 25 June 2018**
	Current: Global Protocol Amendment 2: 31 May 2019
	Brazil:
	Original Protocol: 22 February 2018 **Current: Global Protocol Amendment 1: 13 March 2018**
	Approved, but not implemented: Brazil Country-Specific Amendment 1 to Global Protocol Amendment 2: 26 July 2019
Date First Patient Entered	14 Nov 2018

Date Last Patient Completed	12 July 2020
Sponsor	Millendo Therapeutics US, Inc. 110 Miller Ave Suite 100, Ann Arbor, Michigan 48104 United States
Report prepared by	Svatopluk Svetlik
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1 SIGNATURES

The signatures of the sponsor and coordinating investigator(s), indicating their agreement with the contents of the report, should be provided. If no coordinating investigator is appointed, then the signature of the principal investigators should be obtained. The signature pages may be separate from the clinical investigation report itself.

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2 SYNOPSIS

Name of sponsor:	Millendo Therapeutics US, Inc.
Name of observational product:	Nevanimibe hydrochloride (formerly known as ATR-101)
Name of active ingredients:	Nevanimibe hydrochloride
Title of study:	A Multicenter Dose-Titration Open-Label Study of Nevanimibe Hydrochloride for the Treatment of Classic Congenital Adrenal Hyperplasia
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Publication (reference):	NA
Studied period (years):	2018 – 2020
Objectives:	The objectives were the same for Global Amendment 1 and Global Amendment 2
Primary	To evaluate the efficacy and safety of orally administered nevanimibe hydrochloride for the treatment of classic congenital adrenal hyperplasia
Secondary	• To assess the changes in adrenal cortical steroids and steroid intermediates • To determine the pharmacokinetic (PK) parameters of nevanimibe and its major metabolite(s) • To assess the PK/pharmacodynamic (PD) relationships of nevanimibe and its major metabolite(s)
Number of patients (planned and analyzed):	Global Amendment 1: Approximately 20-24 adults with a documented history of classic CAH will be enrolled Global Amendment 2: Approximately 20-24 evaluable adults with a documented history of classic CAH will be enrolled 20-24 patients planned, 15 patients analyzed
Eligibility criteria for enrollment:	<u>Global Amendment 1 and Global Amendment 2: Inclusion criteria:</u> 1. Provision of signed and dated informed consent prior to any study-specific procedures 2. Men and women 18 to 80 (Czech Republic Country Specific Amendment 11 June 2018: 70 in the Czech Republic) years of age (inclusive) at the time of informed consent 3. Documented historical diagnosis of classic CAH due to 21-hydroxylase deficiency based on either or both of the following criteria: • Documented genetic mutation in the CYP21A2 enzyme consistent with a diagnosis of classic CAH • Historical documentation of elevated 17-OHP (e.g., in infancy or following a cosyntropin/ACTH stimulation test) 4. Serum 17-OHP ≥ 4x ULN during the Baseline Period

- Premenopausal women in the follicular phase of the menstrual cycle must have serum 17-OHP ≥ 4x follicular phase ULN
- Premenopausal women in the luteal phase of the menstrual cycle must have serum 17-OHP ≥ (4x follicular phase ULN + (luteal phase ULN – follicular phase ULN))

5. Chronic glucocorticoid replacement therapy for at least 6 consecutive months prior to Screening
6. Stable glucocorticoid and mineralocorticoid regimen for at least 4 weeks prior to the Screening (S1), Baseline (B1), and Enrollment (T1) Visits
7. For patients who undergo maintenance glucocorticoid dose adjustment between Screening and Enrollment, stable serum 17-OHP levels (adjusted as needed for menstrual cycle phase) prior to Enrollment, defined as the most recent 2 values being within 30% of each other (calculated as 100 × (1 – (smaller value/larger value)))
8. Female patients of childbearing potential must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile male partner (France Country Specific Amendment 1 25 June 2018: (in France: Fertile patients (male and female) must consent to use two medically acceptable methods of contraception, excluding depot progesterone, throughout the study period and for 30 days after the last dose of study treatment during any sexual intercourse with a fertile partner of the opposite sex))

<u>Global Amendment 1 and Global Amendment 2: Exclusion criteria:</u>

1. Nonclassic CAH
2. Other causes of adrenal insufficiency such as Addison's disease or adrenalectomy; or classic CAH with serum 17-OHP < 4x ULN and daily maintenance glucocorticoid dose in the adrenal insufficiency range (e.g., ≤ 8-10 mg hydrocortisone/m^2 body surface area per day)
3. Surgery within the previous three months prior to screening or planned surgery during study participation. Minor procedures are permitted (e.g., removal of skin tags or other minor dermatological procedures)
4. History of active cancer requiring medical or surgical therapy within the past 6 months (with the exception of successfully treated non-metastatic basal cell or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix)
5. Female patients must not be currently pregnant or breastfeeding or have conceived or given birth within 3 months of Screening
6. Abnormal laboratory tests at Screening:
   - ALT or AST > 2x ULN
   - Bilirubin > 1.5x ULN
   - Serum creatinine > 1.5x ULN
7. Positive screen for HIV, hepatitis B surface antigen or hepatitis C antibody at Screening

	8. An average QTcF value of > 470 (France Country Specific Amendment 1 25 June 2018: 450 in France) msec at Screening 9. Current or ongoing use of any prohibited concomitant medications (Section 5.8) 10. History of substance abuse within the past 1 year prior to informed consent 11. Positive toxicology screening test for substances of abuse, other than marijuana 12. Known allergy to nevanimibe HCl (formerly known as ATR-101) 13. Participation in any study of an investigational drug within 30 days (or 5 half-lives of the investigational drug, whichever is longer) prior to Screening 14. Any other medical or psychiatric condition that, in the opinion of the Investigator, is likely to confound the interpretation of the study results or prevent the patient from understanding the requirements of or successfully completing the study (e.g., myocardial infarction (MI) or cerebrovascular accident/transient ischemic attack (CVA/TIA) within the past 6 months)
Duration of study	Global Amendment 1: Approximately 20-38 weeks (Screening Period of 2-14 weeks, Baseline Period of 2-8 weeks, Treatment Period of 12 weeks, and Follow-up Period of 4 weeks) Global Amendment 2: Approximately 24-42 weeks (Screening Period of 2-14 weeks, Baseline Period of 2-8 weeks, Treatment Period of 16 weeks, and Follow-up Period of 4 weeks)
Duration of treatment:	Global Amendment 1: Treatment Period of 12 weeks and Follow-up Period of 4 weeks Global Amendment 2: Treatment Period of 16 weeks and Follow-up Period of 4 weeks
Parameters:	<u>Primary Efficacy Endpoint:</u> Primary Efficacy Endpoints were the same for Global Amendment 1 and Global Amendment 2 The overall response rate within each cohort, defined as the percentage of patients achieving serum 17-OHP targets as follows: • Men and postmenopausal women: 17-OHP ≤ 2x ULN • Premenopausal women: - Follicular phase: 17-OHP ≤ 2x follicular phase ULN - Luteal phase: 17-OHP ≤ (2x follicular phase ULN + (luteal phase ULN – follicular phase ULN)) <u>Safety Endpoints</u>: The incidence of treatment-emergent adverse events (AEs) and serious adverse events (SAEs), as well as values and changes from baseline in clinical laboratory tests, vital signs, physical examinations, and electrocardiogram (ECG) parameters. <u>Pharmacokinetic Endpoints:</u>

	The PK and PD endpoints include the following, additional PK and PD endpoints may be described in the SAP. • The C_{max}, T_{max}, AUC_{0-4}, and other PK parameters of nevanimibe and its major metabolite(s) (as appropriate and as the data allow) • The relationship between the C_{max} and AUC_{0-4} of nevanimibe and its major metabolite(s) in relation to the change in 17-OHP levels (as appropriate and as the data allow)
Statistical methods:	Sample Size: Global Amendment 1: Based on results of the previous Phase 2a study of nevanimibe HCl in classic CAH (ATR-101-201), the sample size of approximately 20-24 patients was considered to be sufficient for evaluating whether nevanimibe HCl at doses of 1000-2000 mg BID has clinically meaningful efficacy in the treatment of classic CAH. Global Amendment 2: Based on results of the previous Phase 2 study of nevanimibe HCl in classic CAH (ATR-101-201), the sample size of approximately 20-24 evaluable patients was considered to be sufficient for assessing whether nevanimibe HCl at doses of 500-2000 mg BID has clinically meaningful efficacy in the treatment of classic CAH. An evaluable patient is defined as a patient who has efficacy data following at least 8 weeks of continuous dosing with nevanimibe HCl. Efficacy Analyses: Only observed case data were used for the efficacy summaries. The levels of adrenal steroids, steroid intermediates, and other measured hormones were summarized using descriptive statistics, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), maximum (max) and 90% confidence intervals, if applicable. The analysis was performed by value and by change from baseline in the value, where appropriate, for each time point, overall, by nevanimibe HCl dose, and by cohort. The percentage of patients achieving serum 17-OHP targets, the primary endpoint, was summarized overall and was to be summarized for each cohort. However, as there is only 1 patient in Cohort 2, the by-cohort analysis was not performed. The study was to be considered positive if 40% or more of enrolled patients in either cohort achieved the primary endpoint. Safety Analyses: Only observed case data were used for safety summaries. The summarization of AEs included treatment-emergent AEs (TEAEs; defined as AEs that begin or worsen after the first dose of study drug). TEAEs and treatment-emergent SAEs were summarized by MedDRA system organ class and preferred term, severity, and relationship to study drug, overall, by nevanimibe HCl dose. Summaries by cohort were also planned but were not performed as there is only 1 patient in Cohort 2 and this comparison was not deemed meaningful. Deaths and discontinuations due to AEs were to be summarized, overall, by nevanimibe HCl dose, and by cohort; however, summaries by cohort were not performed for the above reasons. PE findings, vital signs, and ECG readings were summarized by value and by change from baseline

	in the value, where appropriate. This was done for each time point, overall and by nevanimibe HCl dose using summary statistics for continuous parameters, including number of non-missing observations (n), mean and/or median, standard deviation (SD) and/or percentiles, minimum (min), and maximum (max). Summaries by cohort were also planned but are not presented for above reasons. Frequencies and percentages as well as shift tables were prepared for categorical parameters. Clinical safety laboratory results were assessed during the study and are available in the corresponding SAS dataset. Pharmacokinetic Analyses: Individual patient PK data were to be analyzed along with pooling of patients' data at each dose level. Individual PK parameters were to be computed to the extent allowed by the PK data collection times. Tabular summaries were to be provided using descriptive summary statistics. PK/PD analyses were to be detailed in the Statistical Analysis Plan. As no PK data were in the end available, PK analysis were not done.
Summary of results	The study was prematurely terminated due to insufficient efficacy after analysis of data from 10 evaluable patients. Only one patient (10%) clearly achieved a serum 17-OHP ≤ 2x ULN while on nevanimibe. Hence, the predefined criterion for considering the study a success (40% of evaluable patients achieving serum 17-OHP ≤ 2x ULN, adjusted for menstrual cycle phase as needed) was not met.
Efficacy results:	Three of the 14 patients of the mITT population (21.4%) achieved the serum 17-OHP target at some point during the study. Of note however, two of these patients achieved the predefined criterion after they had already discontinued the study and hence were no longer receiving the study medication. Consequently, there is only one "true" responder, and the predefined criterion was not met for the primary endpoint.
Safety results:	At the initial starting dose of 1000 mg BID, a larger than expected proportion of patients discontinued the study due to adverse events. After the protocol was amended to lower the starting dose to 500 mg BID, the discontinuation rate decreased, and the study drug was much better tolerated. No study drug-related serious adverse events nor deaths were recorded. Twelve patients (80% of the 15 patients dosed) experienced study drug-related treatment emergent adverse events.
Conclusions:	Nevanimibe hydrochloride administered orally at doses of 500-2000 mg BID for up to 16 weeks in the first 10 evaluable patients did not result in sufficient efficacy to justify continued development of nevanimibe for the treatment of classic CAH. No serious safety issues were identified.
Date of the report:	28-OCT-2020