A Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics and Safety and Tolerability of a Single Oral Dose of Risdiplam Compared to Matched Healthy Participants With Normal Hepatic Function

CLINICALTRIALS.GOV IDENTIFIER	RECRUITMENT STATUS	FIRST POSTED	LAST UPDATE POSTED
NCT03920865	COMPLETED	APRIL 19, 2019	FEBRUARY 21, 2021

STUDY DESCRIPTION

Brief Summary

This is a multi-center, open-label, non-randomized, parallel-group, 2-part study to evaluate the effect of hepatic impairment on the PK and safety and tolerability of a single oral dose of risdiplam compared to matched healthy participants with normal hepatic function.

Condition or Disease: Muscular Atrophy, Spinal

Intervention/treatment: Drug: Risdiplam

Phase: Phase 1

DETAILED DESCRIPTION

N/A

STUDY DESIGN

Study Type: Interventional

Estimated Enrollment : 26 participants

Intervention Model : Parallel Assignment

Masking: None (Open Label) ()

Primary Purpose: Treatment

Official Title: An Open-Label, Single-Dose, Parallel-Group, Two-Part Study to Evaluate the Pharmacokinetics and Safety of Risdiplam in Subjects With Mild or Moderate Hepatic Impairment Compared to Subjects With Normal Hepatic Function

Actual Study Start Date: May 2019

Actual Primary Completion Date: January 2020

Actual Study Completion Date: January 2020

ARMS AND INTERVENTIONS

Arm	Intervention/treatment
Experimental: Part 1 Participants with mild hepatic impairment and demographically matched healthy participants with normal hepatic function will be enrolled. Participants will receive a single oral dose of 5 mg risdiplam.	Drug: Risdiplam 5 milligram (mg) oral dose administered in fasted state
Experimental: Part 2 Participants with moderate hepatic impairment and demographically matched healthy participants with normal hepatic function will be enrolled. Participants will receive a single oral dose of 5 mg risdiplam.	Drug: Risdiplam 5 milligram (mg) oral dose administered in fasted state

OUTCOME MEASURES

Primary Outcome Measures:
1. Part 1: Area Under the Plasma Concentration-Time Curve From Time Zero to Infinity (AUCinf) of Risdiplam and Its Metabolite (M1) [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
2. Area Under the Plasma Concentration-Time Curve From Time Zero to the Last Measurable Concentration (AUClast) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
3. Part 1: Maximum Observed Plasma Concentration (Cmax) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
4. Part 2: AUCinf of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
5. Part 2: AUClast of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
6. Part 2: Cmax of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]

Secondary Outcome Measures:
1. Part 1: Time of the Maximum Observed Plasma Concentration (Tmax) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
2. Part 1: Apparent Plasma Terminal Elimination Half-Life (t1/2) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]

3. Part 1: Percentage of Area Under the Plasma Concentration-Time Curve Due to Extrapolation (%AUCextrap) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
4. Part 1: Terminal Elimination Rate Constant (λz=Lambda-Z) of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
5. Part 1: Apparent Total Clearance (CL/F) of Risdiplam [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
6. Part 1: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for AUCinf of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
7. Part 1: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for Cmax of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
8. Part 1: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for AUClast of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
9. Part 2: Tmax of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
10. Part 2: t1/2 of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
11. Part 2: %AUCextrap of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
12. Part 2: λz of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
13. Part 2: CL/F of Risdiplam and M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
14. Part 2: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for AUCinf of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
15. Part 2: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for Cmax of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
16. Part 2: Molecular Weight-Adjusted Metabolite-to-Parent Ratio for AUClast of Risdiplam M1 [Time Frame: Predose, 1, 2, 4, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216, 240, 264, 312, 336, 360, 408, 456, 504, and 552 hours Postdose]
17. Part 1 and Part 2: Percentage of Participants With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs) [Time Frame: Up to 31 Days]
An adverse event is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events.

ELIGIBILITY CRITERIA

Ages Eligible for Study: 18 to 70 Years (Adult, Older Adult)

Sexes Eligible for Study: All

Accepts Healthy Volunteers: Yes

Criteria

Inclusion Criteria:
All Participants:
- BMI between 18.0 and 36.0 kilograms per square metre (kg/m2), inclusive, and body weight > / = 50 kg
- Females must not be pregnant or lactating and must be of non-childbearing potential
- Male participants (whether surgically sterilized or not) with female partners of childbearing potential must use methods of contraception from Screening until 4 months after their dose of the study drug as detailed in the protocol
- Male participants must not donate sperm from Check-in (Day -1) until 4 months after their dose of the study drug
Participants with Normal Hepatic Function Only:
- Matched to participants with mild or moderate hepatic function in sex, age, BMI, and smoking status
- In good health, as determined by no clinically significant findings from medical history, physical examination, 12-lead ECG, vital sign measurements, and clinical laboratory evaluations
Participants with Hepatic Impairment Only:
- Documented chronic stable liver disease
- Currently on a stable medication regimen, defined as not starting new drug(s) or changing drug dose(s) within 3 months of administration of study drug
- Anemia secondary to hepatic disease will be acceptable, if hemoglobin >/= 9 gram per decilitre (g/dL). Participants must have a platelet count </= 35 000 platelets Exclusion Criteria: All Participants - Significant history or clinical manifestation of any metabolic, allergic, dermatological, renal, hematological, pulmonary, cardiovascular, gastrointestinal, neurological, respiratory, endocrine, or psychiatric disorder - History of significant hypersensitivity, intolerance, or allergy to any drug compound, constituents or excipients of the study drug, food, or other substance - History of stomach or intestinal surgery or resection that would potentially alter absorption and/or excretion of orally administered - Ventricular dysfunction or history of risk factors for Torsades de Pointes - Evidence of hepatorenal syndrome and estimated creatinine clearance range 150 millimetre of mercury (mmHg) or 159 mmHg or < 90 mmHg - Values outside the normal range for liver function tests that are not consistent with their hepatic condition - Use of a new medication, or a change in dose, for the treatment, or worsening of, hepatic encephalopathy - Use of prescription drugs within 14 days of study drug administration - Recent history of, or the treatment of, esophageal bleeding - Presence of a portosystemic shunt - Recent history of paracentesis - Current functioning organ transplant or are waiting for an organ transplant - Evidence of severe ascites - History or current symptoms of hepatic encephalopathy Grade 2 or above

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CONTACTS AND LOCATIONS

Contacts

Locations

United States, Florida	Clinical Pharmacology of Miami, Inc.	Miami
United States, Florida	Orlando Clinical Research Center	Orlando
United States, Texas	American Research Corporation Inc.	San Antonio

Sponsors and Collaborators

Hoffmann-La Roche

Investigator

Study Director :	Clinical Trials	Hoffmann-La Roche

MORE INFORMATION

Responsible Party :	Hoffmann-La Roche
ClinicalTrials.gov Identifier :	NCT03920865
Other Study ID Numbers :	BP40995
First Posted :	April 19, 2019
Last Update Posted :	February 21, 2021
Last Verified :	January 2021
Individual Participant Data (IPD) Sharing Statement:	
Plan to Share IPD:	No
Plan Description:	Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).
Studies a U.S. FDA-regulated Drug Product:	Yes
Studies a U.S. FDA-regulated Device Product:	No
Additional relevant MeSH terms :	*Atrophy* *Muscular Atrophy* *Muscular Atrophy, Spinal*