Pharmacokinetics and Pharmacodynamics of Rifaximin Novel Formulations in Patients With Sickle Cell Disease

20/08/2025 05:56:17

Main Information

Primary registry identifying number
LBCTR2022095104

Protocol number
RBSC2161

MOH registration number

Study registered at the country of origin
Yes

Study registered at the country of origin: Specify

Type of registration
Prospective

Type of registration: Justify
N/A

Date of registration in national regulatory agency
29/09/2022

Primary sponsor
Bausch Health LLC

Primary sponsor: Country of origin
United States of America

Date of registration in primary registry
17/05/2024

Date of registration in national regulatory agency
29/09/2022

Public title
Pharmacokinetics and Pharmacodynamics of Rifaximin Novel Formulations in Patients With Sickle Cell Disease

Acronym

Scientific title
A Phase 2a Randomized, Double-Blind, Placebo-Controlled Study to Characterize the Pharmacokinetics and Pharmacodynamics of Rifaximin Novel Formulations in Patients With Sickle Cell Disease

Acronym

Brief summary of the study: English
This is a randomized, double-blind, placebo-controlled study in sickle cell disease participants with a history of Vaso-occlusive Crises (VOCs). Approximately 60 participants with sickle cell disease will be enrolled and randomized: 12 participants in each of four active novel formulation rifaximin groups and 6 participants in each of 2 placebo groups.

Brief summary of the study: Arabic
هذه دراسة عشوائية مزدوجة التعمية يتم التحكم فيها بالعلاج الوهمي في المشاركين في مرض الخلايا المنجلية الذين لديهم تاريخ من أزمات انسداد الأوعية الدموية (VOCs). سيتم تسجيل ما يقرب من 60 مصابًا بمرض الخلايا المنجلية وتوزيعهم عشوائيًا: 12 مشاركًا في كل من أربع مجموعات ريفاكسيمين ذات تركيبة جديدة نشطة و6 مشاركين في كل مجموعة من مجموعتي العلاج الوهمي.

Health conditions/problem studied: Specify
Sickle Cell Disease patients with history of VOCs

Interventions: Specify
Subjects will be enrolled and randomized 2:2:1:2:2:1 to one of 6 parallel arms to receive oral treatment twice daily (BID) for approximately 29 days:
- Group 1: 40 mg rifaximin ER, BID
- Group 2: 40 mg rifaximin DER, BID
- Group 3: Placebo for 40 mg rifaximin, BID
- Group 4: 80 mg rifaximin ER, BID

• Group 5: 80 mg rifaximin DER, BID
• Group 6: Placebo for 80 mg rifaximin, BID

Key inclusion and exclusion criteria: Inclusion criteria

A subject will be eligible for inclusion in this study if he/she meets all the following criteria:
1. Subject must have the ability and willingness to sign a written informed consent form.
2. Subject is between the ages of 18 to 70 years old (inclusive) at the time of consent.
3. Subject has SCD of any genotype (HbSS, HbSC, HbS β-thalassemia). If the subject's genotype has not been previously documented, genotyping will be performed during Screening using high-performance liquid chromatography (HPLC)/electrophoresis.
4. Subject must have experienced at least 2 VOCs within the 12 months prior to Screening. A VOC is defined as:
a. The occurrence of appropriate symptoms consistent with a painful crisis, acute chest syndrome (ACS), or priapism (Section 2.2.3) , and
b. Requires a visit to a medical facility and/or healthcare professional, and
c. Receipt of either a parenteral or oral opioid or NSAID analgesia.
5. If subject is receiving hydroxyurea (HU)/hydroxycarbamide (HC), subject must have been receiving the treatment for at least 6 months prior to Screening and must agree to maintain the same dose and schedule for the duration of the study.
6. Subjects must have laboratory values at Screening as follows:
a. Absolute Neutrophil Count (ANC) ≥1.0 x 109/L
b. Platelets ≥ 75 x 109/L
c. Hemoglobin (Hgb) ≥ 6.0 g/dL
d. Glomerular filtration rate (GFR) ≥ 45 mL/min/1.73 m2 using the CKD-EPI formula
e. Total bilirubin ≤ 15 mg/dL
f. Alanine transaminase (ALT) ≤ 3.0 x ULN
g. International Normalized Ratio (INR) ≤ 2.0
7. Eastern Cooperate Oncology Group (ECOG) performance status ≤ 2
8. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, must have a negative serum pregnancy Test at Screening and agree to use standard prevention methods for the duration of the study.

Key inclusion and exclusion criteria: Gender

Both

Key inclusion and exclusion criteria: Specify gender

Key inclusion and exclusion criteria: Age minimum

18

Key inclusion and exclusion criteria: Age maximum

70

Key inclusion and exclusion criteria: Exclusion criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:
1. Subject is receiving concomitant treatment with voxelotor, crizanlizumab, or L-glutamine.
2. Subject has any history of stem cell transplant, is planning to begin or has received in past 30 days.
3. Subject experiences an acute VOC, requiring a visit to a medical facility and/or healthcare professional, ending within 7 days prior to Day 1 dosing.
4. Subject has received any blood products within 30 days prior to Day 1 dosing.
5. Subject has uncontrolled liver disease or renal impairment, ulcerative colitis, Crohn's disease, or other chronic GI disorder.
6. Subject has received active treatment in another investigational trial within 30 days or 5 half-lives of the last dose of the investigational agent, Whichever is greater, prior to Screening.
7. Subject has received penicillin prophylaxis or antibiotics for treatment of infection within 30 days or 5 half-lives of the treatment, whichever is greater, prior to Screening.
8. Subject has a significant medical condition that required hospitalization (other than for a VOC) within 2 months prior to Screening.
9. Subject is planning on undergoing an exchange transfusion during the duration of the study or has completed one within 4 weeks prior to Day 1 dosing.
10. Subject has a hypersensitivity to rifaximin, rifampin, rifamycin antimicrobial agents, or any components of rifaximin ER and DER.
11. Subject is pregnant or a nursing woman.
12. Subject has a history of illicit drug use or abuse, either documented or in the opinion of the Investigator.
13. Subject is using any medication that is known to inhibit or induce CYP3A4, P-gp and OATP1B1/B3 within 30 days or 5 half-lives, whichever is longer, prior to Day 1 dosing, or in the opinion of the Investigator, may affect the evaluation of the study product or place the subject at undue risk.
14. Subject has had any prior gastrointestinal surgery which has altered the anatomy of the esophagus, stomach, or small/large intestine (with the exception of appendectomy, cholecystectomy, and fundoplication).
15. Subject has had a colonoscopy or sigmoidoscopy within 30 days prior to Day 1 or plans to undergo such a procedure during the duration of the study.
16. Subject has used bowel prep, laxative, or enema within 30 days prior to Day 1.
17. Subject has a bleeding disorder including, but not limited to, acquired or congenital platelet function defects, disseminated intravascular coagulation (DIC), bleeding factor deficiencies, hemophilia, idiopathic thrombocytopenia purpura (ITP), or von Willebrand's disease.
18. Subject is planning to undergo a major surgical procedure during the duration of the study.
19. Subject has a positive test for human immunodeficiency virus (HIV)1 or HIV2.
20. Subject has an active Hepatitis B infection (HBsAg positive). Prior infection that is not active (i.e., HBsAg negative, HBcAb positive, and HBsAb positive) is permitted.
21. Subject has a positive test for Hepatitis C (HCV RNA). Prior infection with spontaneous resolution or sustained resolution for ≥ 24 weeks after cessation of antivirals is permitted.
22. Subject has an active COVID-19 infection or complication(s) related to COVID-19 infection that are unresolved or, in the opinion of the Investigator, may affect evaluation of the study drug or place the subject at undue risk.
23. Subjects has received a vaccine (including COVID-19 vaccine) within 2 weeks prior to Screening. If subject has received their first of two COVID-19 vaccination doses, as applicable, they must wait for at least 2 weeks after receiving the second dose, and be symptom-free, prior to

beginning
Screening. Subject must not be planning for COVID-19 or other vaccinations while on study.
24. Subject has a malignant disease. Exceptions include malignancies that were treated curatively and have not recurred within 2 years prior to study treatment, completely resected basal cell and squamous cell skin cancers, and any completely resected carcinoma in situ.
25. Subjects has prolonged QT interval as assessed by ECG history within the past 3 months. For subjects with no historical ECG information, subject has a resting QTcF ≥ 460 msec for males and ≥ 470 msec for females at Screening.
26. Subject has any unstable cardiac condition that, in the opinion of the Investigator, may worsen during the study or interfere with successful evaluation of the study treatment.
27. Subject has a serious mental or physical illness which, in the opinion of the Investigator, would compromise participation in the study.
28. Subject has any condition which, in the opinion of the Investigator, is likely to interfere with the successful collection of the measurements required for the study.
29. Subject is unable to understand or comply with study instructions and requirements.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Other

Trial scope: Specify scope

Study design: Allocation

Randomized controlled trial

Study design: Masking

Blinded (masking used)

Study design: Control

Placebo

Study phase

2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Parallel

Study design: Specify assignment

N/A

IMP has market authorization

Yes, Lebanon and Worldwide

IMP has market authorization: Specify

USA

Name of IMP

Rifaximin

Year of authorization

2004

Month of authorization

5

Type of IMP

Others

Pharmaceutical class

Non-aminoglycoside, semi-synthetic antibiotic derived from rifamycin that has antimicrobial activity of varying levels against Gram-positive, Gram-negative, aerobic, and anaerobic enteric bacteria.

Therapeutic indication

Sickle Cell Disease

Therapeutic benefit

Reduction of circulating aged neutrophils (CANs), significantly elevated during a VOC, in Sickle Cell Disease patients with history of VOCs

Study model

N/A

Study model: Explain model

N/A

Study model: Specify model

N/A

Time perspective
N/A

Time perspective: Explain time perspective
N/A

Time perspective: Specify perspective
N/A

Target follow-up duration

Target follow-up duration: Unit

Number of groups/cohorts

Biospecimen retention
None retained

Biospecimen description
N/A

Target sample size
9

Actual enrollment target size

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
01/12/2022

Date of study closure: Type
Anticipated

Date of study closure: Date
25/04/2024

Recruitment status
Complete

Recruitment status: Specify

Date of completion

IPD sharing statement plan
No

IPD sharing statement description
N/A

Additional data URL

Admin comments

Trial status
Approved

Secondary Identifying Numbers

Full name of issuing authority	Secondary identifying number
ClinicalTrials.gov	NCT05098028

Sources of Monetary or Material Support

Name
Bausch Health Americas, Inc.

Secondary Sponsors

Name
N/A

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Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Nini Hospital	Dr. Adlette Inati	Hematology	Approved
American University of Beirut Medical Center	Dr. Miguel Abboud	Hematology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	07/07/2022	Dr. Elias Bitar	-	+9616431400
American University of Beirut Medical Center	07/12/2022	Dr. Nathalie K. Zgheib	irb@aub.edu.lb	+9611350000 – Ext 5445

Countries of Recruitment

Name
Lebanon
United States of America
Canada

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickle Cell Disease	Sickle-cell disorders (D57)	Anemia, Hemolytic, Congenital, Hematologic Diseases,

Interventions

Intervention	Description	Keyword
Drug	Low Dose Rifaximin Extended Release Twice Daily	Rifaximin
Drug	Low Dose Rifaximin Delayed Extended Release Twice Daily	Rifaximin
Drug	High Dose Rifaximin Extended Release Twice Daily	Rifaximin
Drug	High Dose Rifaximin Delayed Extended Release Twice Daily	Rifaximin
Drug	Placebo Twice Daily	Placebo

Primary Outcomes

Name	Time Points	Measure
Plasma concentration of rifaximin and 25-desacetyl rifaximin for PK profiles	Day 1 and Day 29	Blood samples for PK analysis
Cmax and Ctrough	Days 8, 15, and 29	Blood samples for PK analysis
PD biomarkers	Day 1, 8, 15, 29, 31, 43 and during medical facility visit for VOC, when possible	Collection of PD biomarkers (ANC, CANs, serum CD62L, hsCRP, the gut permeability biomarkers serum iFABP and LPS, and the gut bacteria biomarker urine 3-indoxyl sulfate)

Key Secondary Outcomes

Name	Time Points	Measure
Safety	throughout the duration of the study	Incidence of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
Safety	throughout the duration of the study	Clinically significant changes from Baseline in clinical laboratory results (chemistry, coagulation, hematology, urinalysis, and high sensitivity C-reactive protein (hsCRP), physical examinations, and electrocardiograms (ECGs))
Safety	throughout the duration of the study	Changes from Baseline in vital signs (systolic and diastolic blood pressure, heart rate, oral body temperature, and oxygen saturation)
Safety	throughout the duration of the study	Information on any potential VOCs occurence

Trial Results

Summary results

Study results globally

Date of posting of results summaries

Date of first journal publication of results

Results URL link

Baseline characteristics

Participant flow

Adverse events

Outcome measures

URL to protocol files