An open-label, dose-escalation, dose-finding, and proof-of-concept trial of SP-420 in subjects with transfusion-dependent β-thalassemia

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Main Information

Primary registry identifying number
LBCTR2023045220

Protocol number
P-SP420-THAL-01

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
13/12/2022

Primary sponsor
Pharmacosmos A/S

Primary sponsor: Country of origin
Denmark

Date of registration in primary registry
07/03/2024

Date of registration in national regulatory agency
13/12/2022

Public title
An open-label, dose-escalation, dose-finding, and proof-of-concept trial of SP-420 in subjects with transfusion-dependent β-thalassemia

Acronym

Scientific title
An open-label, dose-escalation, dose-finding, and proof-of-concept trial of SP-420 in subjects with transfusion-dependent β-thalassemia

Acronym

Brief summary of the study: English

The trial is an open-label, dose-escalation, dose-finding, and proof-of-concept multi-centre trial evaluating the iron clearing efficacy, safety, tolerability, and pharmacokinetic (PK) properties of SP-420 (Pharmacosmos A/S, Holbæk, Denmark) administered 3 times per week to subjects with transfusion-dependent β-thalassemia for 48 weeks. Approximately 90 subjects will be enrolled in 3 dose cohorts of approximately 30 subjects each. Dosing will start with 6 subjects in each cohort (cohort 1a-3a) in a dose-escalating manner, and if no safety issues are identified, inclusion of additional 24 subjects is allowed in each cohort (cohort 1b-3b). Extensive electrocardiography (ECG) measurements and PK assessments will be performed in the 18 subjects in cohort 1a-3a. The trial consists of 2 parts: part 1 with a fixed dosing regimen and part 2 with an adjustable dosing regimen.

Brief summary of the study: Arabic

، التجربة عبارة عن تجربة متعددة المراكز مفتوحة التسمية ، وتصعيد الجرعة ، وإيجاد الجرعة ، وإثبات صحة المفهوم لتقييم فعالية إزالة الحديد مرات في 3 (الدنمارك ، Holbæk ، S / A (Pharmacosmos SP-420 لـ (PK) والسلامة ، والتحمل ، وخصائص الحرائك الدوائية مجموعات3 مريضا في 90 أسبوعًا. سيتم تسجيل ما يقرب من 48الأسبوع للأشخاص الذين يعانون من ثلاسيميا بيتا المعتمد على نقل الدم لمدة أ) بطريقة تصعيد الجرعة ، وإذا لم يتم3 أ -1 مريضا في كل مجموعة (مجموعة 6 مريضا لكل منها. ستبدأ الجرعات بـ 30جرعة من حوالي ب). سيتم إجراء قياسات شاملة لتخطيط3 ب -1مريضاً إضافيًا في كل مجموعة (مجموعة 24تحديد مشكلات تتعلق بالسلامة ، يُسمح بإدراج تتكون التجربة من جزأين: الجزء الأول بنظام الجرعات الثابت والجزء الثاني .1a-3a شخصًا في الفوج 18في PK وتقييمات (ECG) القلب بنظام الجرعات القابل للتعديل.

Health conditions/problem studied: Specify

Transfusion-dependent β-thalassemia

Interventions: Specify

A minimum of 90 subjects with transfusion-dependent β-thalassemia will be recruited, and they will be allocated to 1 the following treatment groups:
• Cohort 1a+b (N=30): SP-420 initially at 28 mg/kg PO 3 times per week
• Cohort 2a+b (N=30): SP-420 initially at 56 mg/kg (or a lower dose as suggested by the DMC) PO 3 times per week
• Cohort 3a+b (N=30): SP-420 initially at 84 mg/kg (or a lower dose as suggested by the DMC) PO 3 times per week

Key inclusion and exclusion criteria: Inclusion criteria

1. Women and men aged ≥18 years
2. Transfusion-dependent β-thalassemia including HbE/β-thalassemia requiring iron chelation therapy (β-thalassemia with mutation and/or multiplication of α-globin is allowed)
3. On a stable dose of iron chelation for at least 4 weeks prior to screening
4. Weight ≥35 kg at screening
5. Willing to discontinue current iron chelation therapy 7 days (± 3 days) prior to the first dose of SP-420 and for the duration of the trial
6. Transfusion iron overload defined as LIC ≥5 and ≤20 mg/g dw on the R2-MRI obtained within 2 weeks prior to baseline
7. Subject has been treated and followed for at least the past 6 months in a specialised centre that maintained detailed medical records, including transfusion and iron chelation histories
8. Willingness to participate and signing the informed consent form

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

99

Key inclusion and exclusion criteria: Exclusion criteria

1. β-thalassemia with the structural Hb variants HbS and HbC
2. Cardiac MRI-T2* score <10 msec obtained within 2 weeks prior to baseline
3. S-ferritin <500 or >4000 ng/mL*
4. Current malignancy with the exceptions of localised basal cell or squamous cell skin cancer or localised prostate cancer or is receiving immunotherapy, chemotherapy, or radiation therapy for a malignancy
5. Current myelodysplastic syndrome
6. Current biliary disorder
7. ALAT >4 times the upper limit of normal, decompensated cirrhosis, or ascites at screening
8. Past or ongoing history of clinically significant kidney disease
9. Creatinine greater than the upper limit of normal at screening
10. Estimated glomerular filtration rate eGFR <60 mL/min/1.73 m2
11. Urine protein to creatinine ratio >0.5 mg/mg at screening
12. Heart failure grade II, III and IV by NYHA
13. LVEF on MRI <56 % (echocardiography allowed if MRI not available)
14. A QTcF >450 ms, 2nd or 3rd degree atrioventricular block, or incomplete left hemiblock, or the presence of clinically significant abnormalities as determined by the Investigator at screening
15. Hypertransfused defined as more than 6 units/month in average for the last 6 months prior to screening
16. Ongoing symptoms of neuropathy, including peripheral sensory neuropathy, peripheral motor neuropathy, or paresthesia at screening
17. Platelet count <100×109/L at screening
18. History of hypersensitivity to an iron chelator (investigational or marketed) or excipients
19. Documented history of non-compliance to chelation therapy within past 2 years
20. Received another investigational drug within 30 days or investigational antibody within 90 days before screening
21. Treatment with prohibited medication: iron, aluminium containing antacid therapies, systemic corticosteroids (topical and pulmonary corticosteroids are allowed), oral bisphosphonates, chronic use of high dose NSAIDs (as needed and low dose acetylsalicylic acid are allowed), drugs with known renal toxicity, drugs with known QTc prolongation, potent UGT inducers (e.g. rifampicin, phenytoin, phenobarbital, ritonavir) within 7 days prior to baseline
22. Initiation of treatment with luspatercept within 6 months prior to screening (luspatercept is allowed if initiated and dose is stable at least 6 months prior to screening)
23. Subject unable to undergo trial assessments including MRI, e.g. who are claustrophobic to MRI, have a cardiac pacemaker, ferromagnetic metal implants other than those approved as safe for use in MR scanners (e.g. some types of aneurysm clips, and shrapnel), and subjects who are obese (exceeding the equipment limits)
24. Pregnant or nursing women. In order to avoid pregnancy, women of childbearing potential (premenopausal and not surgically sterile) have to use highly efficient contraception (e.g. intrauterine devices, hormonal contraceptives (contraceptive pills, implants, transdermal patches,

hormonal vaginal devices or injections with prolonged release)) during the whole trial period and 4 weeks post-dosing. A sterile sole partner or sexual abstinence is also considered acceptable provided it reflects the usual and preferred lifestyle of the participant
25. Men, even if surgically sterilised, (i.e. status post vasectomy), who do not agree to practice effective barrier contraception during the entire trial period, or agrees to completely abstain from heterosexual intercourse
26. Any other laboratory abnormality, medical condition, or psychiatric disorder which, in the opinion of the Investigator, will put the subject's disease management at risk or may result in the subject being unable to comply with the trial requirements
*If s-ferritin is slightly >4000 ng/mL at the screening, a second blood sample may be taken after at least 7 days for re-assessment of eligibility. This will not be considered a re-screening. If the second sample fulfils enrolment criteria, the subject may be enrolled. The results should be available at the baseline visit at the latest, i.e. max 4 weeks after the screening visit.

Type of study

Interventional

Type of intervention

Pharmaceutical

Type of intervention: Specify type

N/A

Trial scope

Therapy

Trial scope: Specify scope

N/A

Study design: Allocation

Non-randomized controlled trial

Study design: Masking

Open (masking not used)

Study design: Control

Dose comparison

Study phase

2

Study design: Purpose

Treatment

Study design: Specify purpose

N/A

Study design: Assignment

Other

Study design: Specify assignment

Cohort design

IMP has market authorization

No

IMP has market authorization: Specify

Name of IMP

SP-420

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

SP-420((S)-4,5-dihydro-2-[2-hydroxy-4-(3,6-dioxaheptyloxy) phenyl]-4-methyl-4-thiazolecarboxylic acid) is a small molecule, tridentate iron chelator of the desferrithiocin class that chelates iron with a stoichiometry of 2:1 SP-420:Fe(III).

Therapeutic indication

Treatment of patients with Transfusion-dependent β-thalassemia

Therapeutic benefit

An ideal iron chelator would have high iron chelating efficiency with oral dosing, high penetration into all organs adversely affected by iron overload (e.g. liver, heart, pancreas, and kidney), and minimal toxicity, particularly to the renal, hepatic, and gastrointestinal systems, and an easy to use, palatable formulation. The ambition with SP-420 is to develop an efficacious iron chelator with a favourable safety profile and dosing regimen.

Study model

N/A

Study model: Explain model

Study model: Specify model

N/A

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
NA

Target sample size
90

Actual enrollment target size

Date of first enrollment: Type
Anticipated

Date of first enrollment: Date
24/04/2023

Date of study closure: Type
Anticipated

Date of study closure: Date
20/12/2024

Recruitment status
Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan
Yes

IPD sharing statement description

The trial will be registered in public registries (e.g. EudraCT, clinicaltrials.gov, or other national registries, if applicable).
When part 1 of the trial is final it will be reported as a statistical report. When part 2 of the trial is final, all endpoints will be reported in a CSR. The CSR will be prepared by Pharmacosmos or its designee and reviewed and approved by Pharmacosmos. The CSR or a summary of the CSR should be sent to the IRB/IEC and Competent Authorities according to local legislation. The results of the trial, positive as well as negative, will be published by the end of the trial. Any publication or disclosure must comply with all applicable regulations and must be limited to scientific findings and must not constitute promotion under the applicable regulations.
No data from the clinical trial may be published, presented, or communicated, except to Competent Authorities, prior to the release of the CSR, unless approved by Pharmacosmos in writing. The data and results from all sites participating in the trial shall be aggregated and analysed for publication in a primary publication. When and where the full results will be published will be decided on by Pharmacosmos. The Investigator and the site agree that they shall not publish any results (own data or aggregated data) until the primary publication has been published.

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

No Sources

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

Contact type	Contact full name	Address	Country	Telephone	Email	Affiliation
Public	Aziz Zoghbi	MCT-CRO,Berytech Technology and Health,5th Floor Damascus Road,Beirut,Lebanon	Lebanon	009611612500	aziz.zoghbi@mct-cro.com	Regional Manager
Scientific	Ali Taher	Chronic Care Center, Hazmieh, Lebanon	Lebanon	009613755669	ataher@aub.edu.lb	Principal Investigator

Centers/Hospitals Involved in the Study

Center/Hospital name	Name of principles investigator	Principles investigator speciality	Ethical approval
Chronic Care Center	Dr. Ali Taher	MD Hematology	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Chronic Care Center	30/01/2023	Michelle Abi Saad	cccmas@chroniccare.org.lb	9615455101
American University of Beirut Medical Center	27/02/2023	Abeer Dakik	irb@aub.edu.lb	961350000 ext 5445

Countries of Recruitment

Name
Denmark
United Arab Emirates
Canada

Health Conditions or Problems Studied

Condition	Code	Keyword
Transfusion dependent beta-thalassemia	Thalassaemia (D56)	TDT

Interventions

Intervention	Description	Keyword
SP-420 – 28 mg/kg	28 mg/kg, oral dosing 3 times per week, Monday, Wednesday, and Friday	SP-420
SP-420 – 56 mg/kg	56 mg/kg, oral dosing 3 times per week, Monday, Wednesday, and Friday	SP-420
SP-420 – 84 mg/kg	84 mg/kg, oral dosing 3 times per week, Monday, Wednesday, and Friday	SP-420

Primary Outcomes

Name	Time Points	Measure
dose-response relationship of SP-420 for 24 weeks	from baseline to week 24	Total body iron removed by SP-420

Key Secondary Outcomes

Name	Time Points	Measure
clearing iron from the liver	from baseline to week 24	liver iron concentration (LIC)measured by R2-MRI
clearing iron from the liver after 12 and 48 weeks	from baseline to week 12 and week 48	LIC measured by R2-MRI
total body iron removal after 12 and 48 weeks	from baseline to week 12 and week 48, and from week 24 to week 48	Total body iron removed by SP-420
serum (s-) ferritin	from baseline to weeks 1, 2, 3, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48	s-ferritin
safety and tolerability	NA	adverse events (AEs)/physical examination (including auditory and ophthalmologic examinations), height, vital signs, ECG, and safety laboratory parameters (including urinalysis)/extensive ECG measurement will be performed in the 18 subjects in cohort 1a-3a

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