ACENT 1

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Main Information

Primary registry identifying number
LBCTR2024015480

Protocol number
NN7533-4470

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
15/01/2024

Primary sponsor
Novo Nordisk

Primary sponsor: Country of origin
Denmark

Date of registration in primary registry
26/03/2024

Date of registration in national regulatory agency
15/01/2024

Public title
ACENT 1

Acronym

Scientific title
A multicentre trial evaluating the efficacy and safety of oral decitabine-tetrahydrouridine (NDec) in patients with sickle cell disease

Acronym

Brief summary of the study: English

Sickle cell disease (SCD) pathophysiology is driven by the polymerisation of mutated sickle cell haemoglobin (HbS) in red blood cells. Foetal haemoglobin (HbF) decreases polymerisation of HbS but is epigenetically silenced in early infancy and onward by DNA methyltransferase 1 (DNMT1). A mechanism to re-induce HbF expression is via epigenetic therapy by inhibiting DNMT1 activity. NDec is an oral formulation of a combination of decitabine and tetrahydrouridine. Decitabine depletes DNMT1 while tetrahydrouridine inhibits cytidine deaminase, the enzyme that otherwise rapidly deaminates/inactivates decitabine.

The primary purpose of this trial is to investigate two dosing regimens of oral decitabinetetrahydrouridine (NDec) in terms of treatment-related effects on total haemoglobin and HbF as well as clinical efficacy and safety parameters compared with placebo in patients with SCD who are not receiving hydroxyurea (HU) treatment at screening (HU-non-eligible patients). An active comparator HU treatment arm is included to allow exploratory comparisons between NDec and HU in patients receiving HU treatment at screening (HU-active patients).

Brief summary of the study: Arabic

في خلايا الدم الحمراء. يقلل (HbS) مدفوعة ببلمرة الهيموغلوبين المنجلي المتحور (SCD) الفيزيولوجيا المرضية لمرض فقر الدم المنجلي ولكن يتم إسكاته وراثيا في مرحلة الطفولة المبكرة وما بعدها بواسطة HbS من بلمرة (HbF) الهيموغلوبين الجنيني DNA methyltransferase 1 (DNMT1). هي عن طريق العلاج اللاجيني عن طريق تثبيط نشاط HbF آلية إعادة تحفيز تعبير DNMT1. بينما يثبط رباعي هيدروووريدين DNMT1عبارة عن تركيبة فموية لمزيج من ديسيتابين وتتراهيدرويوريدين. يستنفد ديسيتابين ال NDec الديأميناز السيتيدين، وهو الإنزيم الذي يزيل / يعطل ديسيتابين بسرعة.

من حيث التأثيرات (NDec) الغرض الأساسي من هذه التجربة هو التحقيق في نظامين لجرعات ديسيتابينيتتراهيدروريدين عن طريق الفم بالإضافة إلى الفعالية السريرية ومعايير السلامة مقارنة بالدواء الوهمي في المرضى الذين HbF المرتبطة بالعلاج على إجمالي الهيموغلوبين و HU). يتم تضمين ذراع علاج HU المرضى غير المؤهلين ل) عند الفحص (HU) الذين لا يتلقون علاج هيدروكسي يوريا SCD يعانون من عند الفحص (المرضى النشطين في HU في المرضى الذين يتلقون علاج HU و NDec للمقارنة النشطة للسماح بإجراء مقارنات استكشافية بين HU).

Health conditions/problem studied: Specify

Patients with Sickle Cell Disease.

Interventions: Specify

Patients will be receiving a new medication oral decitabinetetrahydrouridine (NDec).

Key inclusion and exclusion criteria: Inclusion criteria

Key inclusion criteria:
- Age above or equal to 18 years at the time of signing informed consent
- Confirmed diagnosis of SCD (including HbSS, HbSC, HbSβ0 thalassaemia and HbSβ+ thalassaemia or other Sickle Cell disease variants)
- 2–10 episodes of documented VOCs within the last 12 months prior to the screening visit
- Haemoglobin ≥5.0 g/dL and ≤10.5 g/dL at visit 1
- Absolute reticulocyte (absolute) count above ULN at visit 1
- Body weight 40 to 125 kg (inclusive)

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

75

Key inclusion and exclusion criteria: Exclusion criteria

Key exclusion criteria:
- Patient is on chronic transfusion therapy as defined by receiving scheduled (pre-planned) series of blood transfusion (simple or exchange) for prophylactic purposes, or the patient is likely to begin chronic transfusion therapy during the course of the trial, or has received RBC or whole blood transfusion for any reason within 28 days of visit 1
- Receipt of erythropoietin or other haematopoietic growth factor treatment within 28 days of signing ICF, or planned treatment with these agents during the trial
- Receipt of voxelotor, crizanlizumab or L-glutamine treatment within 12 weeks of signing the informed consent form, or planned treatment with such agents during the trial
- Platelet count >800 x 109/L at visit 1
- Absolute neutrophil count ≤1.5 x 109/L at visit 1
- Any condition/concurrent chronic disease involving the stomach or small intestine which may affect drug absorption, as per investigator's judgement
- Female who is:
    - pregnant, breast-feeding or intends to become pregnant within 6 months after the final trial product administration or
    - child-bearing potential and not using highly effective methods of contraception and whose male partner is not using effective contraception, at screening and until 6 months after the last dose of trial product
- Male with female partner of childbearing potential who does not agree to use condom and whose female partner of childbearing potential is not using a highly effective contraceptive measure from trial start to:
    - Six (6) months after the last dose of trial product for patients on NDec/Placebo
    - Six (6) months after the last dose of trial product for patients outside US and CA randomised to HU
    - Twelve (12) months after the last dose of trial product for patients randomised to HU in US and CA

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

Study design: Masking

Randomized controlled trial

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

No

IMP has market authorization: Specify

Name of IMP

Oral decitabine-tetrahydrouridine

Year of authorization

Month of authorization

Type of IMP

Others

Pharmaceutical class

Haemoglobin F inducer

Therapeutic indication

Patients with sickle cell disease

Therapeutic benefit

NDec is being investigated for efficacy and safety for use as a disease-modifying treatment to prevent complications associated with SCD. NDec specifically targets the root cause of the disease (polymerization of haemoglobin S (HbS)), and treatment might therefore provide therapeutic benefits and improve outcomes. Among clinical benefits, patients may have fewer and/or less severe VOCs and a reduced need for blood transfusion when treated with NDec. They may also experience fewer hospital visits/admissions into hospital, and fewer days spent in hospital. Patients treated with NDec might also experience improvements in laboratory parameters predicting clinical benefits in laboratory parameters, including, but not limited to, an increase in total Hb and HbF levels and decreases in measures of haemolysis. HbF decreases erythrocyte sickling and subsequent haemolysis. Clinical observations and standard clinical practice indicate that an increase in total haemoglobin by decreasing haemolytic anaemia is clinically meaningful (improvement in an established surrogate for clinical benefit).

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

Samples with DNA**

Biospecimen description

Genetic variation may impact a patient's response to trial treatment, susceptibility to, and severity and progression of disease. Variable response to trial treatment may be due to genetic determinants that impact drug absorption, distribution, metabolism and excretion, mechanism of action of the drug, disease aetiology, and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, samples will be collected for DNA analysis from consenting patients. DNA samples will be used for research related to NDec and SCD and other heamatological diseases. Genetic research may consist of the analysis of one or more candidate genes, or the analysis of genetic markers throughout the genome or analysis of the entire genome as appropriate.

Target sample size

87

Actual enrollment target size

Date of first enrollment: Type

Anticipated

Date of first enrollment: Date

26/02/2024

Date of study closure: Type

Anticipated

Date of study closure: Date

31/08/2025

Recruitment status

Pending

Recruitment status: Specify

Date of completion

IPD sharing statement plan

No

IPD sharing statement description

Not applicable

Additional data URL

Admin comments

Trial status

Approved

Secondary Identifying Numbers

No Numbers

Sources of Monetary or Material Support

Name
Novo Nordisk A/S

Secondary Sponsors

No Sponsors

Contact for Public/Scientific Queries

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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	Paediatric Haematologist Oncologist	Approved

Ethics Review

Ethics approval obtained	Approval date	Contact name	Contact email	Contact phone
Nini Hospital	11/12/2023	Elias Bitar	NA	00961 6 431 400 Ext: 3164

Countries of Recruitment

Name
Lebanon
Turkey
United States of America
France
Spain
Italy
South Africa
Canada
Greece
India
United Kingdom

Health Conditions or Problems Studied

Condition	Code	Keyword
Sickel Cell	Sickle-cell disorders (D57)	Sickle cell disease (SCD) Foetal haemoglobin (HbF) mutated sickle cell haemoglobin (HbS)

Interventions

Intervention	Description	Keyword
HU-non-eligible block	NDec once weekly: 1 dose of active treatment and 1 dose of placebo on 2 consecutive days NDec twice weekly: 1 dose of active treatment on each of 2 consecutive days Placebo: 1 dose of placebo on each of 2 consecutive days	decitabine-tetrahydrouridine (NDec) Placebo
HU-active block	HU	hydroxyurea HU

Primary Outcomes

Name	Time Points	Measure
Change in total haemoglobin	From baseline (week 0) to week 24	g/dL

Key Secondary Outcomes

Name	Time Points	Measure
Cmax for decitabine from pharmacokinetic assessment	At week 24	ng/mL
Cmax for tetrahydrouridine from pharmacokinetic assessment	At week 24	ng/mL
Change in DNMT1 activity	From baseline (week 0) to week 24	MFI
Change in CDA activity	From baseline (week 0) to week 24	µmol/L/min
Change in foetal haemoglobin (g/dL)	From baseline (week 0) to week 24	g/dL
Number of adverse events of grade 3b or higher	From baseline (week 0) to week 52	Number of events

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