A comparative observational study to evaluate the safety and effectiveness of Xromi® (hydroxycarbamide oral solution 100mg/ml) for the prevention of vaso-occlusive complications of sickle cell disease in children under 2 years of age. [PRECISE PASS]

First published: 16/12/2024

Last updated: 15/05/2025

Study Planned

Administrative details

EU PAS number

EUPAS1000000076

Study ID

1000000076

DARWIN EU® study

No

Study countries

☐ Germany

☐ United Kingdom

Study description

This is a non-randomised, non-interventional, comparative, observational, hybrid prospective and retrospective, post-authorisation cohort study (a matched cohort design) of children with sickle cell disease (SCD) from 9 months to under 2 years of age to assess the safety and effectiveness of Xromi® (100mg/ml hydroxycarbamide) based on primary and secondary data collection.

This study aims to compare the safety and effectiveness of Xromi® (100mg/ml hydroxycarbamide) in children under 2 years old with SCD to a group not receiving the treatment. The study will collect data both prospectively and retrospectively and will be mainly exploratory without testing any previous hypotheses.

The primary goal is to compare the occurrence of specific adverse events (AESIs) between a prospectively recruited Xromi®-treatment group and a retrospective Hydroxyurea naïve (untreated) group. The study will recruit at least 60 children for the Xromi® group (Prospective Exposure Cohort) and at least 120 children for the untreated group (Retrospective Comparator Cohort) from sites in the UK and Germany.

The study will begin on the date of the first site given initiation greenlight and will end up to 4 years (48 months) later. Screening for the Retrospective Comparator Cohort will go back up to 10 years before Xromi® was introduced at each site following initial licensing. Recruitment for the Prospective Exposure Cohort will last 2 years (24 months), and all participants will be followed for 2 years (24 months).

The overall study period spans from 10 years before the study start to 4 years after the study start. The study end date will ensure that all participants in the Exposure and Comparator Cohort have completed 24-month follow-up.

Study status

Planned

Research institutions and networks

Institutions

Nova Laboratories Ltd.

United Kingdom

First published: 22/03/2024

Last updated: 22/03/2024

Institution | Pharmaceutical company

OXON Epidemiology

Spain

United Kingdom

First published: 06/12/2010

Last updated: 15/03/2024

Institution | Laboratory/Research/Testing facility | Non-Pharmaceutical company | ENCePP partner

Contact details

Study institution contact

Hussain Mulla hussain.mulla@novalabs.co.uk

Study contact

hussain.mulla@novalabs.co.uk

Primary lead investigator

Sara Trompeter 0000-0002-7099-8449

Primary lead investigator

ORCID number:

0000-0002-7099-8449

Study timelines

Date when funding contract was signed

Actual: 09/01/2024

Study start date

Planned: 29/04/2025

Data analysis start date

Planned: 28/02/2029

Date of interim report, if expected

Planned: 04/05/2026

Date of final study report

Planned: 03/09/2029

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Nova Laboratories Ltd. will provide funding for the duration of the study.

Study protocol

CONFIDENTIAL_NOVDD-001_ Xromi PRECISE PASS_ Protocol_V2.0_18Oct2024_Unsigned_Redacted_Published.pdf(3.8 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Other study registration identification numbers and links

IRAS Number (UK): 334976

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Study type:

Non-interventional study

Scope of the study:

Safety study (incl. comparative)

Data collection methods:

Combined primary data collection and secondary use of data

Study design:

This is a non-randomised, non-interventional, comparative, observational, hybrid prospective and retrospective, post-authorisation cohort study (a matched cohort design) of children with SCD under 2 years of age to assess the safety and effectiveness of Xromi®.

Main study objective:

To assess the incidence of adverse events of special interest (AESIs) in children who have SCD and are treated with Xromi®, in comparison to a retrospective comparator cohort.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Name of medicine

XROMI 100 MG/ML - ORAL SOLUTION

Study drug International non-proprietary name (INN) or common name

HYDROXYCARBAMIDE

Anatomical Therapeutic Chemical (ATC) code

(L01XX05) hydroxycarbamide

hydroxycarbamide

Medical condition to be studied

Sickle cell disease

Sickle cell anaemia

Haemoglobinopathy

Population studied

Short description of the study population

This is a non-randomised, non-interventional, comparative, observational, hybrid prospective and retrospective, post-authorisation cohort study (a matched cohort design) of children with SCD from 9 months to under 2 years of age to assess the safety and effectiveness of Xromi®.

There will be 2 cohorts:

i) a Xromi® exposure cohort, identified prospectively;

and ii) a retrospective comparator cohort with children with SCD unexposed to any formulation of hydroxycarbamide at the index date, identified using data from the last 10 years up to the date Xromi® was first used in children under 2 years of age at the sites. Comparator participants will be matched to exposed participants following a 2:1 ratio (comparator:exposed) based on study site, age

at initiation of Xromi® of the exposed participant, and β-globin genotype. Matching ratio and factors will be reviewed and adjusted (e.g., matching at country level), considering feasibility. Information will be collected from chart review. The index date will be defined as: i) prospective exposure cohort: the date of confirmed initiation of Xromi® or, if unknown, the date of the first prescription of Xromi®; or as ii) retrospective comparator cohort: the date of the recorded visit when their age was closest to the age at index date of the matched exposed participant (i.e., the selected visit for matching).
All participants will be followed up for up to 24 months from their index date, regardless of changes in their treatment regimen. This includes participants in the prospective exposure cohort who discontinue Xromi® or switch to another formulation of hydroxycarbamide, as well as participants in the comparator cohort who initiate any formulation of hydroxycarbamide after their index date.

The inclusion period for the participants within the prospective exposure cohort will be from the date the site is given a site initiation greenlight until 2 years after the study start date. These participants will be identified prospectively, and the follow-up will be prospective.
This period may vary depending on the time needed to achieve the recruitment target. For the retrospective comparator cohort, the inclusion period will begin up to 10 years before the date of first administration of Xromi® to children under 2 years of age at each study site. It will continue until the date of first administration of Xromi® to children under 2 years of age at each study site or 2 years before the study start date, whichever occurs first.
These participants will be identified retrospectively, and the follow-up will be retrospective.

The research question is to evaluate the safety and effectiveness of hydroxycarbamide oral solution 100mg/ml (Xromi®) administered to children

under 2 years of age for the prevention of complications of SCD.

Study Sites

The study will seek the participation of European specialist sites (Haemoglobinopathy Coordinating Centres). The study population will consist of children with SCD who meet all the inclusion criteria and none of the exclusion criteria.

Variables

Information on demographics, anthropometrics, and other medical history will be collected at baseline and during follow-up. Information to describe SCD will be collected at baseline (e.g. age at first SCD symptoms, β-globin genotype, history of SCD manifestations and hospitalisations). Data about SCD management, including previous and concomitant use of treatments, will be collected at baseline and during follow-up.

To assess safety of Xromi®, occurrence of AEs, including AESIs (e.g. myelosuppression), will be collected during follow-up. To assess effectiveness of Xromi®, occurrence of the clinical events of interest (e.g. painful vaso-occlusive events, dactylitis, splenomegaly, acute chest syndrome, hospitalisations, blood transfusions, cerebrovascular accident [stroke]) will be collected during follow-up, and results from laboratory tests and physiological assessments conducted will be collected at baseline and during follow-up.

Data Sources

The data will be collected by the investigational team in participating sites from clinical records. Data obtained as part of participants' routine clinical practice will be collected during clinic visits for prospective data and from chart review for retrospective data.

Sample sizes were estimated assuming that 60 participants will be recruited to the Xromi® cohort, and each exposed participant will be matched to 2 comparators. All calculations were conducted using 80% power and a two-sided type I error rate of 5%. For safety, the minimum detectable hazard ratio (HR) was estimated by assuming the log rank test as the basis of the comparison. As it is possible that not all participants will be followed up for the full 24-month period, the calculations were repeated for average follow-up durations of 18 months and 12 months. For effectiveness, a similar approach was used.

Data analysis This study will be mainly exploratory and there are no a priori hypotheses to test. It will use a comparative matched cohort design. Descriptive analyses will describe the study participants using summary statistics, tabulations, and descriptive figures.

The primary safety analysis will examine the occurrence of safety events of interest. For each AESI the number of events, person-years of exposure and number of participants experiencing an AESI will be reported

Study Population
The study aims to recruit at least 180 participants in total: 60 participants administered Xromi® and 120 comparator participants, during a 4-year study period. Initially, up to 10 sites in the UK and up to 5 sites in Germany are planned to be invited to participate in the study. The inclusion of other potential European countries and sites will be assessed if needed.

Prospective Exposure Cohort
Children with SCD aged 9 months to under 2 years of age who are newly prescribed Xromi®, will be identified prospectively. These participants will be followed up for 24 months from their index date, regardless of whether they

continue treatment with Xromi®, discontinue all hydroxycarbamide treatment, or switch to another formulation of hydroxycarbamide. The decision to prescribe Xromi® will be made solely by the physician independently of the study, as part of standard care.

Retrospective Comparator Cohort
Children with SCD and naïve to any hydroxycarbamide formulation at the index date. These participants will be identified retrospectively using the data from the last 10 years up to the date Xromi® was first used in children from 9 months to under 2 years of age at each individual site. The 24-month follow-up will be retrospective from the date they are matched to the exposed participant, irrespective of whether they start on any formulation of hydroxycarbamide during the follow-up.

The study population will consist of children with SCD who meet all the inclusion criteria and none of the exclusion criteria. Identification of participants will be conducted as follows:
• Prospective exposure cohort: Potential participants will be identified as they attend the participating sites where eligibility criteria will be assessed.
• Retrospective comparator cohort: Potential participants will be selected from clinical chart review.

Age groups
Paediatric Population (< 18 years)

Estimated number of subjects
180

Study design details

Setting

Study Population The study aims to recruit at least 180 participants in total: 60 participants administered Xromi® and 120 comparator participants, during a 4-year study period. Initially, up to 10 sites in the UK and up to 5 sites in Germany are planned to be invited to participate in the study. The inclusion of other potential European countries and sites will be assessed if needed.

Study Sites

The study will seek the participation of European specialist sites (Haemoglobinopathy Coordinating Centres). The study population will consist of children with SCD who meet all the inclusion criteria and none of the exclusion criteria.

Setting

The study population will consist of children with SCD who meet all the inclusion criteria and none of the exclusion criteria. Identification of participants will be conducted as follows:

• Prospective exposure cohort: Potential participants will be identified as they attend the participating sites where eligibility criteria will be assessed.

• Retrospective comparator cohort: Potential participants will be selected from clinical chart review.

Data Sources

The data will be collected by the investigational team in participating sites from clinical records. Data obtained as part of participants' routine clinical practice will be collected during clinic visits for prospective data and from chart review for retrospective data.

Comparators

Children with SCD and naïve to any hydroxycarbamide formulation at the index date.

These participants will be identified retrospectively using the data from the last 10 years up to the date Xromi® was first used in children from 9 months to under 2 years of age at each individual site.

The 24-month follow-up will be retrospective from the date they are matched to the exposed participant, irrespective of whether they start on any formulation of hydroxycarbamide during the follow-up.

Outcomes

Primary objective:

• To assess the incidence of adverse events of special interest (AESIs) in children who have SCD and are treated with Xromi®, in comparison to a retrospective comparator cohort.

Secondary objective:

• To assess the effectiveness of Xromi® for the clinical events and laboratory tests and physiological assessments of interest, in comparison to a retrospective comparator cohort.

Exploratory objectives:

• To assess the overall safety of Xromi® by describing adverse events (AEs) by severity, seriousness, relatedness, action taken, outcome, and duration.

• To describe occurrence of and reasons for discontinuation of Xromi®.

• To assess the safety of Xromi® at the optimised dose.

• To assess if the effectiveness of Xromi® is associated with the dose.

• To assess the safety and effectiveness of Xromi® by subgroups (age, sex, β-globin genotype, country).

• To assess occurrence of clinical events in comparators exposed to any formulation of hydroxycarbamide during follow-up.
• To assess organ function and potential preservation in children exposed to any formulation of hydroxycarbamide.

Data analysis plan

This study will be mainly exploratory and there are no a priori hypotheses to test. The study will be analysed as a comparative matched cohort design. A descriptive analysis will be performed to describe the study participants using summary statistics, tabulations, and descriptive figures.

The primary safety analysis will examine the occurrence of safety events of interest. For each AESI the number of events, person-years of exposure and number of participants experiencing an AESI will be reported. The incidence rate of the AESI in each study cohort will be calculated and expressed per 100 person years, with 95% confidence intervals (CIs) calculated using the exact Poisson formula. The percentage of participants experiencing each AESI will be reported. Kaplan-Meier curves, stratified by cohort, with risk tables, will be provided. Time-to-AESI will be summarised using Kaplan-Meier estimates of the median time-to-event and 95% CI. A Cox proportional hazards model, including cohort as its only covariate, will be used to derive crude HRs and 95% CIs. A second confounder-adjusted multivariable Cox model will be used to report adjusted HR, 95% CIs and p-value.

A detailed statistical analysis plan (SAP) will be developed and finalised prior to the first interim analysis and will include methods of analysis and presentation and table shells.

Data management

Data sources

Data source(s), other

All data will be collected by the investigational team in participating sites from clinical records obtained as part of participants' routine clinical practice.

Data sources (types)

Electronic healthcare records (EHR)

Laboratory tests and analyses

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Yes

Check completeness

Yes

Check stability

Yes

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after data extraction

Data characterisation details

All data is directly collected and standardized in a single EDC system, no CDM mapping required.
Conformance checks will be performed within the EDC to ensure all data entries follow predefined formats, definitions & coding conventions established at the start of the study.
Completeness checks will be configured within the EDC system to flag any missing or incomplete fields during data entry. The system will enforce completeness checks for critical data elements to ensure no key information is omitted.
Stability checks will involve regular monitoring and validation rules to ensure data consistency & accuracy over time in the participant EDC records.
Logical consistency checks will be implemented in the EDC to identify and flag data entries that do not logically align (e.g., ranges).
Data characterization will be performed to establish baseline metrics on data quality to ID initial quality issues (e.g. completeness, conformance, ID outliers) & inform ongoing data quality assessments.