22 February 2024
EMA/153487/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xromi

International non-proprietary name: Hydroxycarbamide

Procedure No. EMEA/H/C/004837/II/0019

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

Abbreviation / Definition

α- : alpha-globin
ACS: Acute Chest Syndrome
ADR: Adverse drug reaction
AE: Adverse Event
AESI: Adverse Events of Special Interest
AHRQ: Agency for Healthcare Research and Quality
ALT: Alanine Transaminase
AML: Acute myeloid leukaemia
ANC: Absolute Neutrophil Count
ANOVA: Analysis of Variance
ARC: Absolute reticulocyte count
AUC: Plasma Concentration Time Curve
$AUC_{0\text{-}inf}$: Plasma Concentration Time Curve Extrapolated to Infinity
$AUC_{0\text{-}t}$: Plasma Concentration Time Curve Calculated to the Last Measured Concentration
$AUC\%_{Extrap}$: Percentage of the area under the curve extrapolated to infinity
$AUC_{(0\text{-}24)ss}$: Exposure variable of hydroxycarbamide: model-predicted area under the plasma concentration-time curve (AUC) from 0 to 24 hours at steady-state.
β-: beta-globin
BABY HUG: A phase III double-blinded, multi-centre, randomised, placebo-controlled infant hydroxyurea study
BBMC: Basic butylated methacrylate copolymer
BE: Bioequivalence
BLQ: Below limit of quantification
BP: Blood Pressure
b.w.: by weight
CEC: Central Ethics Committee
CHMP: Committee for Medicinal Products for Human Use
CI: Confidence Interval
CL/F: Clearance
C_{max}: Concentration Maximum
CSSCD: Cooperative Study of Sickle Cell Disease
CV: Co-efficient of Variation
CVA: Cerebrovascular accident
CWRES: NONMEM notation for conditionally weight residuals
DMT: Disease modifying therapy
DNA: Deoxyribonucleic acid
DSMB: Data and Safety Monitoring Board
ECG: Electrocardiogram
eCRF: Electronic Case Report Form
EDC: Electronic Data Capture
EMA: European Medicines Agency
ENCEPP: European Network Of Centres For Pharmacoepidemiology And Pharmacovigilance
EPO: Erythropoietin
ESRD: End Stage Renal Disease
EU: European Union
FBC: Full blood count
FDA: Food and Drug Administration
FOCE: First order conditional estimation
G: Gram
GD: Gestation Day
Geo: Geometric
GOF: Goodness-of-fit

Hb: Haemoglobin
HbF: Foetal Haemoglobin
HbS: Sickle Haemoglobin
HbSC: Heterozygous haemoglobin SC
HbSS: Homozygous haemoglobin SS
HbSβ: Heterozygous haemoglobin with β (β^0 or β^+) thalassemia
HbSβ^0: Heterozygous haemoglobin with β^0 thalassemia
HbSβ^+: Heterozygous haemoglobin with β^+ thalassemia
HC: Hydroxycarbamide
HIV: Human Immunodeficiency Virus
HPLC: High-performance liquid chromatography
HSCT: Haematopoietic Stem Cell Transplantation
HU: Hydroxyurea (=hydroxycarbamide)
HUSOFT: Hydroxyurea Safety and Organ Toxicity study
HUSTLE: Hydroxyurea Study of Long-Term Effects
ICF: Informed Consent Form
IEC: Independent Ethics Committee
IIV: Inter-individual variability
IMP: Investigational Medicinal Product
IMP: Monte Carlo Importance Sampling
INN: International Non-Proprietary Name
IWRES: NONMEM notation for individual weighted residuals
Kg: Kilogram
L: Litres
LaSHS: Laikon Study of Hydroxycarbamide in Sickle Cell Syndromes
LDH: Lactate Dehydrogenase
LIC: Liver iron concentration
LLOQ: Lower limit of quantification
LS: Least squares
MA: Market authorisation
MAA: Marketing Authorisation Application
MAH: Marketing Authorisation Holder
MCV: Mean corpuscular volume
µg: Microgram
Mg/mg: Milligram
mL/ml: Millilitre
mmHg: Millimetre Of Mercury
MRA: Magnetic Resonance Angiography
MRI: Magnetic Resonance Imaging
MSH: Multicentre Study of Hydroxyurea in Patients with Sickle Cell Anaemia
M&S: Modelling and simulation
MTD: Maximum Tolerated Dose
N: Number
NA: Not applicable
NK-κB: Nuclear factor κB
NHLBI: National Heart, Lung, and Blood Institute
NIH: National Institute of Health
NO: Nitric oxide
NONMEM: Nonlinear mixed-effects modelling
NR: Not reported
OFV: Objective function value
OMAR: Office of Medical Applications of Research
PASS: Post Authorisation Safety Study
pcVPC: Prediction-corrected visual predictive check
PD: Pharmacodynamic(s)

PDCO: Paediatric committee
PK: Pharmacokinetic(s)
Ph. Eur.: European Pharmacopeia
PI: Prediction interval
PI: Product Information
PIP: Paediatric Investigation Plan
PL: Package Leaflet
popPD: Population pharmacodynamics
popPK: Population pharmacokinetics
PRAC: Pharmacovigilance Risk Assessment Committee
PSUR: Periodic safety update report
Q: Inter-compartmental clearance
QD: Regular dosing every 24 hours
QPPV: Qualified Person for Pharmacovigilance
R: Open source programming language and software environment for statistical computing and graphics
RBC: Red blood cell
RCT: Randomised Controlled Trial
RLD: Reference listed drug
RMP: Risk management plan
RR: Ribonucleotide reductase
RSE: Relative standard error
SAE: Serious Adverse Event
SAP: Statistical Analysis Plan
SCA: Sickle Cell Anaemia
SCD: Sickle Cell Disease
SCF: Stem cell factor
SCS: Sickle Cell Syndrome
SD: Standard Deviation
SE: Standard error
SmPC: Summary of Product Characteristics
SOC: System Organ Class
SUSAR: Suspected Unexpected Serious Adverse Reaction
SWiTCH: Stroke With Transfusions Changing to Hydroxyurea
TAMMV: Time averaged maximum mean velocity
TCD: Transcranial Doppler
$t_{1/2}$: Half-Life
T½: Terminal elimination half-life
TAD: Time after dose
TEAE: Treatment Emergent Adverse Event
$t_{max:}$ Amount of Time That a Drug is Present at the Maximum Concentration (Time of C_{max})
TWiTCH: Transfusions Changing to Hydroxyurea
Ml: Microlitre
µM: Micromolar
UK: United Kingdom
USA: United States of America
USAN: United States Adopted Name
V: Volume of distribution
VDJ: Variable, diverse and joining
V_{max}: Maximum rate of metabolism
VOC: Vaso-Occlusive Crises
VPC: Visual predictive check
WBC: White Blood Count
WHO: World Health Organisation

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Nova Laboratories Ireland Limited submitted to the European Medicines Agency on 22 December 2022 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 6 months to 2 years of age for Xromi, based on final results from the paediatric study INV543, listed as a category 3 study in the RMP; this is a single-arm, open-label, multi-center study in children with sickle cell anaemia over 6 months of age.
As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan market exclusivity

Not applicable.

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Anastasia Mountaki Co-Rapporteur: Karin Janssen van Doorn

Timetable	Actual dates
Submission date	22 December 2022
Start of procedure:	27 January 2023
CHMP Rapporteur Assessment Report	28 March 2023

Timetable	Actual dates
PRAC Rapporteur Assessment Report	31 March 2023
PRAC members comments	4 April 2023
CHMP Co-Rapporteur Assessment	4 April 2023
Updated PRAC Rapporteur Assessment Report	5 April 2023
PRAC Outcome	14 April 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 April 2023
Request for supplementary information (RSI)	26 April 2023
CHMP Rapporteur Assessment Report	19 October 2023
PRAC Rapporteur Assessment Report	19 October 2023
Updated PRAC Rapporteur Assessment Report	20 October 2023
PRAC Outcome	26 October 2023
Updated CHMP Rapporteur Assessment Report	2 November 2023
Request for supplementary information (RSI)	9 November 2023
CHMP Rapporteur Assessment Report	23 January 2024
PRAC Rapporteur Assessment Report	30 January 2024
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	08 February 2024
CHMP members comments	12 February 2024
Updated CHMP Rapporteur Assessment Report	15 February 2024
Opinion	22 Februray 2024
The CHMP adopted a report on similarity of Adakveo, Casgevy and Oxbryta (Appendix 1)	22 February 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Xromi is currently indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age. With this application the MAH requests the extension of the currently approved indication to patients below 2 years of age.

Epidemiology risk factors, screening tools

Sickle cell disease (SCD) is an orphan disease in the European Union (EU) which affected 2.6 in 10,000 people in the EU in 2017 (EHA, 2019). SCD is the most prevalent genetic disease in France and the UK, and its frequency is steadily rising in many other countries of Central and Southern Europe (Colombatti, 2016; Thalassaemia International Federation, 2013). Approximately 50% of individuals afflicted with SCD are younger than 18 years of age (based on United States [US] epidemiological data), with clinical manifestations occurring across all paediatric age groups including in children < 1 year of age (Brousseau, 2010; Ansa, 2012).

Importantly, the prevalence of SCD in Europe is rising due to migration to Europe from countries with high SCD prevalence (Angastiniotis, 2013; Colombatti, 2016; EHA, 2019). For example, approximately 4.8% of immigrants in France are from at risk populations (Thalassaemia International Federation, 2013), and the number of migrants and migrant newborns with HbSS (sickle Hb with two sickle Hb genes) in Germany increased by 60% between 2007 and 2015 (Kunz, 2017)

Biologic features Aetiology

Sickle cell disease (SCD) is a group of closely related inherited anaemias characterized by the predominance of sickle haemoglobin (HbS) within circulating erythrocytes, which causes erythrocyte shape changes with subsequent haemolytic anaemia and vascular occlusion. In most cases, the patient inherits the abnormal HbS allele from both parents and has homozygous HbSS but compound heterozygous conditions such as HbS/β-thalassaemia and Haemoglobin SC (HbSC), HbSD, HbSO Arab also contribute to the clinical spectrum of sickle cell disease. HbSS and HbSβ0 thalassaemia are clinically very similar and therefore are commonly referred to as sickle cell anaemia (SCA); these genotypes are associated with the most severe clinical manifestations. Four genotypes - HbSS, HbSC, HbSβ0, HbSβ+ - account for most SCD in Europe.

A neonate with HbSS will have about 90% foetal haemoglobin (HbF), 10% sickle haemoglobin (HbS) and no detectable adult haemoglobin (HbA) (Telfer et al 2015). Foetal haemoglobin (HbF) contains two alpha and two gamma subunits, α2γ2, while the major form of adult haemoglobin, haemoglobin A (HbA), contains two alpha and two beta subunits, α2β2. At birth, foetal haemoglobin (HbF) accounts for 50-95% of the infant's haemoglobin and at around 6 months after birth, adult haemoglobin A (HbA) becomes the predominant type.

Clinical presentation, diagnosis and prognosis

Sickle cell disease is an inherited disorder so the disease is present from birth.

Newborn screening programs have been implemented in SCD endemic (e.g. Greece) as well as historically non-endemic countries such as United Kingdom, France, and the Netherlands. However, in the majority of EU countries children are still diagnosed after presenting with a crisis, or diagnosed as an incidental finding from family studies or pre-operative testing.

Symptoms of SCD do not develop immediately after birth because the neonate is protected by circulating HbF. Foetal haemoglobin exists during foetal life, and its production switches to adult haemoglobin after birth. Studies have shown that the waning period of HbF within the erythrocytes is between 5 and 6 months and at which point HbS begins to predominate. Hence until this occurs, the circulating HbF provides protection to SCD from vaso-occlusive crises and typically children will not present with any signs and symptoms until after the age of 6 months (Edoh et al 2006).

The spleen is affected earliest, typically in the first 1-2 years of life, but the kidney, brain, and other organs also begin to reflect sickle-related injury in early childhood from chronic and repeated sickling events.

Complications of SCD include vaso-occlusive crisis (VOC), priapism, splenic sequestration crisis, acute chest syndrome (ACS), pulmonary hypertension, CNS effects (stroke and/or vasculopathy), aplastic crises (also known as reticulocytopenias), renal effects, avascular necrosis, functional asplenia (which leads to extreme susceptibility to infection), effects on growth and maturation (growth retardation, delayed sexual

maturation, being underweight), hand-foot syndrome (due to vaso-occclusion), cardiac involvement, cholelithiasis, eye involvement, leg ulcers.

Signs and symptoms might differ between infants, children, and adults (Kanter et al, 2013).

- Infants: pain in chest, abdomen and joints, dactylitis, anaemia mild jaundice, enlarged spleen, fever and frequent upper respiratory tract infections.
- Children acute or chronic pain, acute anaemia, infections, jaundice poor nutritional status and growth academic failure and delayed puberty.
- Adults: Severe joint pain, chronic ulcer legs, retinopathy, thromboembolic complications, neurocognitive impairments opiod dependence/tolerance.

Children with HbSS are managed as outpatients and typically reviewed by a haematologist or specialist every 3 – 6 months. Measurements of height, weight and pubertal development are essential for assessing growth and development. Blood pressure, urinalysis and oxygen saturation may be predictive of long-term complications. Steady state blood parameters (including full blood count, reticulocyte count, renal function, percentage HbF and lactate dehydrogenase) have important prognostic and clinical value and should be assessed annually (Telfer et al 2015).

Management

The goals of treatment are symptom control and management of disease complications. Regular analgesia is given for acute pain. Prophylaxis against infections (pneumococcal vaccine and penicillin administered daily in children until the age of 5 years) are also core to the pharmacological treatment. However, in terms of disease modification, only two treatment modalities are available: blood transfusions and hydroxycarbamide. However, chronic transfusions and exchange transfusions may lead to iron overload and iron deposition in organs (liver, heart, pituitary, and pancreas), with end-organ damage potentially occurring before the onset of symptoms. As a consequence, iron chelation therapy is administered to manage the iron overload.

Whilst disease manifestations are not always clinically evident, the abnormal sickled erythrocytes circulate continuously and cause repeated injury due to hypoxia/reperfusion events related to sickling. For these reasons, disease-modifying treatments are warranted in children with SCD, even in the absence of obvious clinical signs and symptoms. Therapies which increase HbF levels such as hydroxycarbamide are particularly attractive, since they offer direct intracellular protection against in vivo HbS polymerization and sickling. HbF induction can therefore help prevent acute clinical complications of SCD such as pain and stroke, while also ameliorating the long-term complications related to chronic organ injury (McGann et al 2015).

Disease management specific to children: Management programs for paediatric patients with SCD include acute care, routine prevention (e.g. childhood vaccinations and monitoring of growth and development, and the treatment of complications [e.g. cardiac, respiratory, and renal]). Annual

monitoring with transcranial dopplers (TCDs), transfusion therapy with iron-chelation therapy (if indicated), hydroxycarbamide therapy, and aggressive management of asthma (a common comorbidity in SCD) since hypoxaemia and airway inflammation can trigger VOC, have also become standard of care in most comprehensive centres, with evidence-based treatments initiated early to prevent disease progression. Careful attention is paid to the academic achievement of children with SCD in order to screen for possible silent cerebral infarct, which would warrant MRI evaluation. Haematopoietic stem cell transplantation (HSCT) is the only recognised cure for SCD, and has been shown to have an 85–90% success rate in certain paediatric patient groups. The use of HSCT is restricted by the lack of fully matched sibling donors for many potentially eligible patients. Thus, newer studies are examining the use of unrelated donors, including umbilical cord blood donors, for this patient population. Although HSCT is associated with an increased risk of morbidity (e.g. infertility, gonadal failure, and graft-versus-host disease) and mortality, it has been conclusively shown to improve quality of life in high-risk patients with SCD (Kanter et al, 2013).

Medicinal products approved for the treatment of sickle cell disease

Siklos has been authorised in the EU since 29 June 2007, for the *prevention of recurrent painful vaso-occlusive crises including acute chest syndrome* in *adults, adolescents and children older than 2 years suffering from symptomatic* sickle cell syndrome.

Adakveo (active substance crizanlizumab) received a conditional marketing authorisation in EU on 28/12/2020, *for preventing painful crises* in patients with sickle cell disease *aged 16 years and older*, as an add-on treatment with hydroxycarbamide (also known as hydroxyurea) or on its own in patients for whom hydroxycarbamide does not work well enough or causes too many side effects. The MA of Adakveo was revoked on 26/05/2023.

Oxbryta (voxelotor) has been granted a marketing authorisation in EU for the treatment of *haemolytic anaemia* (excessive breakdown of red blood cells) *due to sickle cell disease in patients 12 years of age and older*. Oxbryta is to be used on its own or in combination with hydroxycarbamide (also known as hydroxyurea). Oxbryta was designated an 'orphan medicine' on 18 November 2016.

Casgevy received a positive CHMP opinion on 14 December 2023 for the *treatment of severe sickle cell disease (SCD) in patients 12 years of age and older with recurrent vaso-occlusive crises (VOCs)* for whom haematopoietic stem cell (HSC) transplantation is appropriate and a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Currently there is no medicinal product authorized for children younger than 2 years old.

2.1.2. About the product

Xromi was granted a marketing authorisation in the EU on 01/07/2019, as a "hybrid" medicine (according to Article 10(3) of Directive 2001/83/EC) of the reference product Hydrea 500mg hard capsules, authorised in the UK (BE study conducted with Hydrea), but it was authorised "for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age" according to Siklos (authorised in the EU on 29/06/2007).

Evidence for the efficacy of hydroxycarbamide in reducing the vaso-occlusive complications of Sickle Cell Disease in patients older than 2 years comes from four randomised controlled trials (Charache et al 1995 [MSH Study]; Jain et al 2012, Ferster et al 1996; Ware et al 2015 [TWiTCH]). Furthermore, findings from these pivotal studies are supported by observational studies including some long-term follow up.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

During the development of the product the applicant received Scientific Advice on 01 April 2016 (EMEA/H/SA/3241/1/2016/SME/III) and 23 March 2017 (EMEA/H/SA/3241/1/FU/1/2017/SME/III) for the development programme supporting the indication granted by the CHMP. The Scientific Advice pertained to the following quality, non-clinical, and clinical aspects:

- Suitability of the proposed oral liquid formulation for children. Acceptability of the proposed limit of an identified impurity of NMT 0.5% in the drug product specification during shelf-life.
- Requirement for non-clinical pharmacology or toxicology studies with respect to the excipients proposed for the intended marketed formulation and the drug substance.
- Sufficiency of published efficacy and safety data to support an indication in infants aged 9 months – 2 years, at a dose of 20 mg/kg/day without escalation, regardless of the severity of the disease. Need for additional efficacy and safety data in adults, adolescents and children aged >2 years. Sufficiency of a relative bioavailability study in healthy adult volunteers comparing Nova's hydroxycarbamide 100mg/mL oral solution to the innovator Hydrea 500mg capsule to establish the bridge between the new formulation and Hydrea-based literature. Appropriateness of the proposed clinical study protocol for generating PK data in infants and children, and for providing the reassurance for weight based dosing across the paediatric age range.

Based on this advice, the applicant planned a post-authorisation open label, observational pharmacokinetic (PK) study in children aged 9 months to 18 years. The applicant requested follow-up scientific advice from the EMA on the draft study protocol and on 20 - 23 March 2017 the CHMP adopted the advice (EMA/CHMP/SAWP/172730/2017). The final Clinical study report was submitted to support this EoI application.

2.1.4. General comments on compliance with GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application (other than the required Environmental Risk Assessment), which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

During the initial approval of the product and in the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommended the following points to be addressed: The applicant should conduct an OECD 309 test on biodegradability and submit the results in 18 months. In addition, the applicant should also conduct a full Phase II study including an OECD 308 test with results to be provided in 3 years following approval of Xromi 100 mg/ml oral solution.

Following the initial approval:

- In variation EMEA/H/C/004837/IB/0005 the study Aerobic Mineralisation in Surface Water – Simulation Biodegradation [OECD 309] was submitted and assessed. The PECSURFACEWATER value was estimated to be above the limit of 0.01 µg/l. In the context of the commitment of the applicant to conduct a full Phase II study, as a first step, the applicant was advised to conduct a study of ready biodegradability according to OECD 301. As it is also mentioned in the ERA Q&A (2016), OECD 308 study can be waived if OECD 301 study shows that the compound is readily biodegradable.
- In variation EMEA/H/C/004837/IB/0011 GLP-compliant OECD 301 B study (Biodegradability, CO_2 Evolution Test) was submitted and assessed. No significant degradation of hydroxycarbamide could be measured within the test duration. The test item did not reach the criteria for ready biodegradability (60% of $ThCO_2$ within 28 days and within a 10-d window). The degradation at the end of the test was 2.7% of $ThCO_2$ (28 d considering the inorganic carbon (IC) in the liquid phase, mean of three replicates). The degradation of the toxicity control after 14 days was 42.0%. The test item had no inhibitory effect on the inoculum according to the criterion of the guideline.
- In variation EMEA/H/C/004837/IB/0021 the results of the GLP-compliant OECD 308 study (Aerobic Transformation in Aquatic Sediment Systems) were submitted and assessed. The study showed a high ultimate biodegradation (67-76.6%).

Taking into account the above the applicant considers that hydroxycarbamide use in Xromi 100 mg/ml oral solution does not present an environmental risk, on the basis that:

- Hydroxycarbamide use and environmental exposure from Xromi 100 mg/ml oral solution will not increase in the EU, due to its substitution for other approved hydroxycarbamide medicinal products including Siklos for which a Phase II ERA has not been performed.
- Hydroxycarbamide is ubiquitous in the environment, and was shown to occur in all the organisms examined including invertebrates (molluscs and crustaceans), fishes from several major groups, amphibians and mammals including humans (Fraser et al., 2015).
- As detailed in the Xromi Assessment Report (26 April 2019, EMA/CHMP/170631/2019), hydroxycarbamide does not have Persistent, Bioaccumulative or Toxic (PBT) potential or very Persistent and very Bioaccumulative (vPvB) potential.
- The lack of Persistent, Bioaccumulative or Toxic (PBT) potential or very Persistent and very Bioaccumulative (vPvB) potential can be inferred on the basis of hydroxycarbamide being naturally and ubiquitously found in animals without any evidence of persistence, bioaccumulation or toxicity in the environment. Hydroxycarbamide is very rapidly metabolized/cleared in vivo (as previously discussed in the nonclinical overview (module 2.4), and is rapidly mineralised in aquatic sediment systems as demonstrated in OECD 308 and OECD 309 studies. Hydroxycarbamide has not been recorded in surface waters, despite its use for many years as a drug substance.
- Hydroxycarbamide has shown no evidence of any antimicrobial activity in aquatic sediment systems at concentrations of 50 and 500 µg/L.
- Hydroxycarbamide rapidly and completely degrades with the formation of carbon dioxide, as shown by the results of the OECD 309 study and now the OECD 308 study.

- Hydroxycarbamide clearly is not persistent in water and sediments, as clearly demonstrated in both aquatic sediment systems in the OECD 308 study where total system normalized DT50 values (12ºC) were extremely short at 7.0 and 2.9 days for Sediments A and B, respectively.

Based on the above, the MAH argued that there was no need to conduct a full phase II study.Upon request, the applicant submitted a Calculation of Predicted Environmental Concentration (PEC) at Phase I as follows;

In Phase I, the PEC calculation is restricted to the aquatic compartment. The calculation of the PEC in surface water further assumes that the predicted amount used per year is evenly distributed over the year and throughout the geographic area, the sewage system is the main route of entry, there is no biodegradation or retention of the drug substance in the sewage treatment plant (STP) and metabolism in the patient is not taken into account. Thus, a PEC has been calculated for the active moiety, hydroxycarbamide, which is rapidly degraded/mineralised.

A market penetration (F_{pen}) default value of 0.01 (1%) is proposed in the guideline. However, reasonably justified market penetration data, e.g., based on published epidemiological data, can be used to estimate a more accurate refined F_{pen}.

The refined F_{pen} value is calculated to be 21,668 in 67,750,000 = 0.0003, based on the highest prevalence data in France (Brousse et al 2023).

The $\underline{DOSE_{ai}}$ (maximum daily dose) is 35 mg/kg/day. Assuming a body weight of 60 kg, this is equivalent to 2100 mg per day.

$PEC_{SURFACEWATER}$ is calculated as:

$$PEC_{SURFACEWATER} = \frac{\underline{DOSE_{ai}} \text{ x Refined } F_{pen}}{WASTEW_{inhab} \text{ x DILUTION}}$$

$$PEC_{SURFACEWATER} = \frac{\underline{2100 \text{ x } 0.0003}}{200 \text{ x } 10}$$

$PEC_{SURFACEWATER}$ = 0.315 µg/L
In which:
$\underline{DOSE_{ai}}$ = maximum daily dose (mg/inh/day)
Refined F_{pen} = market penetration factor (refined based on prevalence data)
$WASTEW_{inhab}$ = amount of wastewater per inhabitant per day = default 200 L/inh/day
DILUTION = dilution from STP = default 10”

2.2.2. Discussion on non-clinical aspects

New non-clinical data have been submitted in this variation application concerning the Environmental Risk Assessment (ERA). No other non-clinical data have been submitted, which is considered acceptable.

Regarding the ERA, the claim to waive full phase II studies was not accepted by the CHMP. Hydroxycarbamide does not meet the criteria for ready biodegradability in the submitted test for ready biodegradability [(OECD 301, Report 1662, F. Flach, 2021, provided within the variation procedure EMEA/H/C/004837/IB/0011, result: 2.7% degradation (28d)]. Even though the OECD 308 confirms a high ultimate biodegradation (67-76.6%), it does not replace the result of the OECD 301 (ready biodegradability). Thus, regardless of the outcome of the 308 study, a phase II should have already

been initiated. The result of the OECD 308 study shows 11% active ingredient is still in the sediment (parent+NER) which also triggers the submission of a Sediment-Water Chironomid Toxicity Test. Furthermore, an update of the PEC calculation was requested, in order to include the application also for adults as outlined in the SmPC.

The Applicant provided a recalculation for $PEC_{SURFACEWATER}$ value, taking into account the maximum daily dose of 35 mg/kg/day assuming a body weight of 60 kg, and the highest prevalence data in France (refined F_{pen} value). $PEC_{SURFACEWATER}$ value is estimated to be above the limit of 0.01 µg/l. Consequently, the applicant agreed to perform the complete Phase II assessment regarding the ERA and provide results by Q4 2026.

2.2.3. Conclusion on the non-clinical aspects

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points are recommended for further investigation:

The applicant is requested to fulfil the post-authorisation commitment to perform the complete phase II assessment regarding the ERA (REC).

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Timings	Study Objective	Study Design	Treatments	Number of Subjects	Key Endpoints
Paediatric Pharmacokinetic Study (INV543)					
Completed, Last Patent Last Visit Dec 2021, report finalised Jul 2022	*Primary objective* to determine the pharmacokinetics of oral hydroxycarbamide solution. *Secondary objectives* will be to evaluate the efficacy/safety of oral hydroxycarbamide solution and the acceptability and palatability	An open label, observational, pharmacokinetic study of oral hydroxycarbamide solution administered daily to children who are hydroxycarbamide naïve and aged 9 months – 17.99 years over a 12 – 15 month period.	Hydroxycarbamide 100 mg/mL oral solution, daily dose 15 – 35 mg/kg/day, individualised.	Up to 25	Primary Endpoints: *Pharmacokinetic parameters* (CL/F, V/F, T_{max}, C_{max}, AUC, $t_{1/2}$) Secondary Endpoints: *Safety:* Absolute neutrophil count, White cell count, Platelets, Liver function tests, Haemoglobin/Anaemia, Bacterial infections, Viral infections, Fungal infections, Leg ulcers *Efficacy:* Foetal Haemoglobin, Incidence of acute pain crises, Number and frequency of blood transfusions, Incidence of acute chest syndrome *Palatability and Acceptability*

Trial	Trial Type	Design	Sample Size; Age Range (yrs)	Dose (mg/kg/day)	Primary End Points	Formulation[1]
Wang et al 2011 (BABY HUG)	Randomised Controlled Trial	Placebo controlled, RCT (efficacy and safety)	193; 9 – 18 months	20 (fixed)	Splenic function, renal function	Oral liquid 100mg/ml

2.3.2. Pharmacokinetics

The PK of hydroxycarbamide is fairly well defined in both adults and children > 2 years with SCD and reflected in the approved SmPC.

For the purpose of this procedure, the MAH conducted an open label, single arm, multicenter, PK, safety, and efficacy study, involving sites in Jamaica and the U.K. (Paediatric Study INV543). The primary objective was to determine the PK of oral hydroxycarbamide solution in patients with SCA. The secondary objectives were to determine the safety and tolerability and also to assess the effects of hydroxycarbamide on various laboratory and clinical parameters, along with its palatability and acceptability.

The design and conduct of the study are being described in detail in section 2.4.

The main inclusion criteria were male or female children aged from 6 months to 17.99 years of age (i.e., to the day before 18th birthday) with a diagnosis of SCA (HbSS and HbSβ^0 genotype). The main exclusion criteria were hydroxycarbamide use within 6 months of enrollment, renal insufficiency (known creatinine more than twice the upper limit of normal (ULN) for age and >1.0 mg/dL [88.4

μmol/L]), hepatic compromise (alanine aminotransferase [ALT] > 3 times the ULN), severe active infections, active chronic leg ulcers and positive pregnancy test.

All study participants started on an oral dose of 15 mg/kg hydroxycarbamide once daily. When feasible, the dose was escalated by 5 mg/kg/day every 8-12 weeks until the MTD was achieved (defined by mild myelosuppression determined by the ANC and the ARC, or a maximum dose of 35 mg/kg/day was reached).

The study treatment duration was for 6 months at the MTD, which was usually reached by 6 months after initiation of treatment. For participants in whom time to MTD was longer than 6 months or not achieved at all, the maximum duration of study treatment was 15 months. Doses were calculated based on the most current bodyweight (measured at each in-clinic visit) and rounded where necessary to the nearest 10 mg.

Since the study involved infants and young children, a population PK design (with sparse PK sampling) was implemented. Hence, PK samples (3 to 5 samples post-dose) were collected on 2 occasions, at Day 1 and approximately 6 months later with additional single PK samples taken at interim clinic visits where feasible. The full description of this analysis is summarized in section 2.3.4.

The plasma concentrations of hydroxycarbamide were analysed by validated analytical methods. The lower limit of quantification (LLOQ) value for hydroxycarbamide plasma concentrations was 0.5 μg/mL. Concentrations reported as below LLOQ were included in the PK model development process.

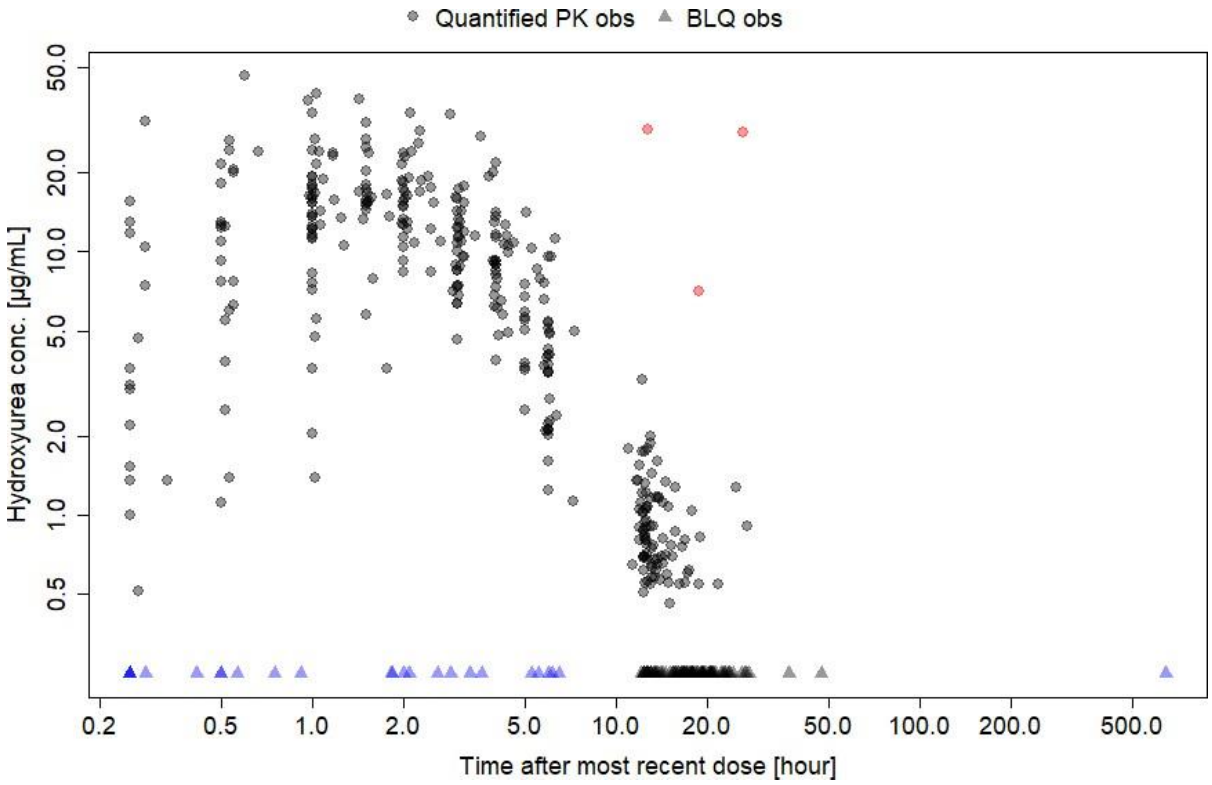
The interim PK data file contained 401 PK measurements from 32 participants after the start of the first administration of hydroxycarbamide. Of which, 106 PK measurements (26%) were below the LLOQ. The model was later updated once final data became available and the final population PK model was established. The final PK data file contained 464 PK measurements from 32 participants after the start of the first administration of hydroxycarbamide. Of which, 94 PK measurements (20%) were below the LLOQ. A total of 29 PK measurements were omitted, including 3 quantified, kinetically implausible PK measurements with high plasma hydroxycarbamide concentrations more than 10 hours after the most recently administered dose of study drug, and 26 measurements below the LLOQ of which 25 were sampled within 10 hours of receiving a dose of study drug and one that was sampled 100 hours after receiving a dose of study drug (see table below).

Table 1: Paediatric Study INV543 Overview of Final hydroxycarbamide Plasma Concentration Measurements Used in the Final Population PK Model

Age	Participants	Quantified observations	Observations < LLOQ	Implausible observations excluded in the final model
6 months to 1.99 years	6	48	15	2
2 to 5.99 years	16	186	46	20
6 to 17.99 years	10	107	33	7
All	32	341	94	29

LLOQ = lower limit of quantification; PK = pharmacokinetic

The figure below summarizes the results.



BLQ = below the limit of quantitation; LLOQ = lower limit of quantitation; PK = pharmacokinetic; popPK = population PK
Circles represent quantified observations and triangles represent below the limit of quantification (BLQ) observations positioned at the LLOQ/2. Black shapes depict observations included in the final popPK model development, whereas blue shapes depict BLQ observations that were excluded while red shapes depict other observations that were excluded.

Figure 1: Paediatric Study INV543 Scatter Plot of Observed hydroxycarbamide Plasma Concentrations Versus Time After Most Recent Dose in the Final Data – log y axes

2.3.3. Pharmacodynamics

An exploratory model-free analysis of several efficacy and safety markers were conducted. Key efficacy biomarkers explored included HbF and Hb; key safety biomarkers explored included absolute neutrophil count (ANC), platelets, absolute reticulocyte count (ARC), and liver function tests.

Exploratory plots of HbF demonstrated the consistent response to taking the new liquid formulation of hydroxycarbamide across the full age range from 6 months to 18 years. Furthermore, exploratory evaluations indicated that increasing hydroxycarbamide exposure (through up-titrations of dose) is expected to lead to a greater increase in HbF. Additional exploratory plots of efficacy markers Hb, MCV, MCH, bilirubin and LDH broadly mirrored what has previously been reported in literature. Plots of safety markers WCC, ANC, platelets, ARC, ALP, GGT, AST and ALT revealed behaviour in alignment with what has been reported in literature and did not identify new safety concerns (Wang et al. 2011, Dong et al. 2016, McGann et al. 2019).

A comparison of the laboratory efficacy and safety biomarkers, clinical benefits and toxicity of hydroxycarbamide in children and adults with SCD reported in the literature and study INV543 are appropriately summarized in sections 2.3.4, 2.4 and 2.5 of this report.

2.3.4. PK/PD modelling

PK Modelling and Simulation Methods

The population PK model was developed with the nonlinear mixed effects modelling program NONMEM (ICON Development Solutions, version 7.4). All other data file preparation, model evaluation, graphical and statistical analyses were executed using R version 3.6.1 (https://www.r- project.org/). Exploratory evaluations of PD over time during treatment of hydroxycarbamide were also done in R.

An 'interim popPK model' was developed using an interim dataset (included all participants of study INV543 with at least one measurable PK sample from data received on the 26th of May 2021) and was later updated using a final dataset following primary completion of study INV543 (all participants of study INV543 with at least one measurable PK sample from data received after declaration of "clean database").

An initial popPK base model (primary PK parameters with associated inter-individual variability [IIV] and model residual variability) for hydroxycarbamide was developed. The influence of intrinsic and extrinsic factors (covariates) was first tested for significance on structural parameters of the population PK model developed using interim data.

The primary tool for model qualification was the prediction-corrected visual predictive check (pcVPC).

Table 2: Paediatric Study INV543 Baseline Covariates Included in Population PK Analysis

Variable	Unit	Type	Description
AGE	years	Continuous	A subject's age at start of treatment
AGEC	-	Categorical	A subject's age at start of treatment, above / below or equal to 2 years old
SEX	-	Categorical	Phenotypically defined gender
RACE	-	Categorical	Black/African American or other
REGION	-	Categorical	Geographic region
STUD	-	Categorical	Study site
WGHT	kg	Continuous	A subject's body weight at start of treatment.
WGHTC	-	Categorical	A subject's body weight at start of treatment, above / below or equal to median.
HGHT	cm	Continuous	A subject's height at start of treatment.
BILI	µmol/L	Continuous	Total Bilirubin at baseline, if available, else at screening or earliest record after first dose.
ALP	µkat/L	Continuous	Total Alkaline Phosphatase at baseline, if available, else at screening or earliest record after first dose.
AST	µkat/L	Continuous	Total Aspartate Aminotransferase at baseline, if available, else at screening or earliest record after first dose.
ALT	µkat/L	Continuous	Total Alanine Aminotransferase at baseline, if available, else at screening or earliest record after first dose.
LDH	µkat/L	Continuous	Lactate Dehydrogenase at baseline, if available, else at screening or earliest record after first dose.
UREA	mmol/L	Continuous	Urea at baseline, if available, else at screening or earliest record after first dose.
CREAT	µmol/L	Continuous	Serum Creatinine at baseline, if available, else at screening or earliest record after first dose.
CYST	nmol/L	Continuous	Cystatin–C at baseline, if available, else at screening or earliest record after first dose.

Source: Study INV543 M&S Report Table 10-1
ALP = alkaline phosphatase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase

Once final data for study INV543 were received, the interim popPK model was re-inferred. Parameter values of the two models were compared and an assessment was made whether the final data of study INV543 contained additional information to justify further model adjustment.

Covariate relationships were then confirmed once the final data were available, and the final population PK model was established. The distribution of individual ETA values obtained from the interim popPK model re-inferred onto final data were analysed and plotted against covariates. If any relationships between individual ETA values and covariates were subsequently observed, the corresponding relationships were tested in a new covariate search via a forward inclusion and backward elimination process. The covariate model following the additional covariate search was called the 'final popPK model'.

Simulations of various age groups were then conducted using the final popPK model (individual post-hoc PK parameters) to determine the influence of age on hydroxycarbamide exposures. These simulations were facilitated by sampling age-appropriate body weights for children from the National Health and Nutrition Examination Survey (NHANES) III database.

Descriptive analyses of secondary PK parameters were performed on the following age-defined subgroups as well as the overall analysis population(s): 6 months to 1.99 years, 2 years to 5.99 years and 6 years to 17.99 years (where .99 represents the day before the study participant's birthday).

Comparisons of hydroxycarbamide exposure in study INV543 were made to previous studies reported in literature.

As a further activity, which was not part of the original objectives, various PD biomarker data from the final dataset was evaluated in a model-free exploratory analysis.

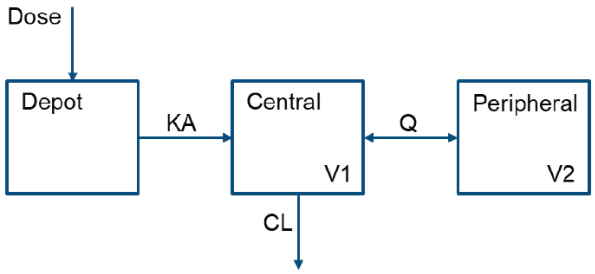
Following assessment of the final model an adjustment was made after deriving and applying a maturation function.

A schematic of the adjusted popPK model with maturation function is given in Figure 2. Parameter estimates of the adjusted popPK model with maturation function are given in Table 3.

PK Model Development

Model building began by considering a single compartment model for oral drug administration utilizing a proportional residual error model. Observations below LLOQ were set to LLOQ/2 if they immediately followed a quantified observation or were excluded from model fitting, as per the M6 method. Parameters were re-estimated utilizing the M3 method for BLQ observations. An additional 7 BLQ PK observations immediately following an in-clinic dose of hydroxycarbamide were included. V2 was then set to the same value as V1 during model fitting (run341) which passed all model selection criteria and only resulted in a 0.078 unit increase in OFV. Run341 was therefore declared as the 'interim base popPK model'.

Using the interim base popPK model, covariates listed in Table 2 were tested on model parameters with IIV (KA and CL).



$$KA = KA_{pop} \cdot exp(\eta_1)$$

$$CL = FMAT \cdot \left(\frac{WGHT}{15.05}\right)^{0.75} \cdot CL_{pop} \cdot exp(\eta_2)$$

$$V1 = \left(\frac{WGHT}{15.05}\right) \cdot V1_{pop}$$

$$Q = \left(\frac{WGHT}{15.05}\right)^{0.75} \cdot Q_{pop}$$

$$V2 = V1$$

CL, clearance; V1, volume of central compartment; Q, intercompartmental clearance; V2, volume of peripheral compartment; KA, absorption rate constant; WGHT, bodyweight. CLpop, estimated CL for a patient with median bodyweight; KApop, estimated KA for a patient with median bodyweight; V1pop, estimated V1 for a patient with median bodyweight; FMAT, maturation function.

Figure 2: Diagram of the adjusted popPK model with maturation function

Using the final data, all model parameters were re-estimated from the interim popPK model. For completeness, the entire covariate search was repeated in order to verify that the final data did not contain evidence of new relationships compared to the interim data. Again, no covariate was significant after a full forwards inclusion / backwards deletion procedure. As a final step, the exponents of the allometric scaling (currently set to 0.75 for CL, Q and 1 for V1, V2) were re- estimated. This did not result in an improved model fit, indicating that the exponent values of 0.75 for CL, Q and 1 for V1, V2 are sufficient.

The parameter estimates of the final popPK model (run500) together with their RSE and CI, are presented in Table below.

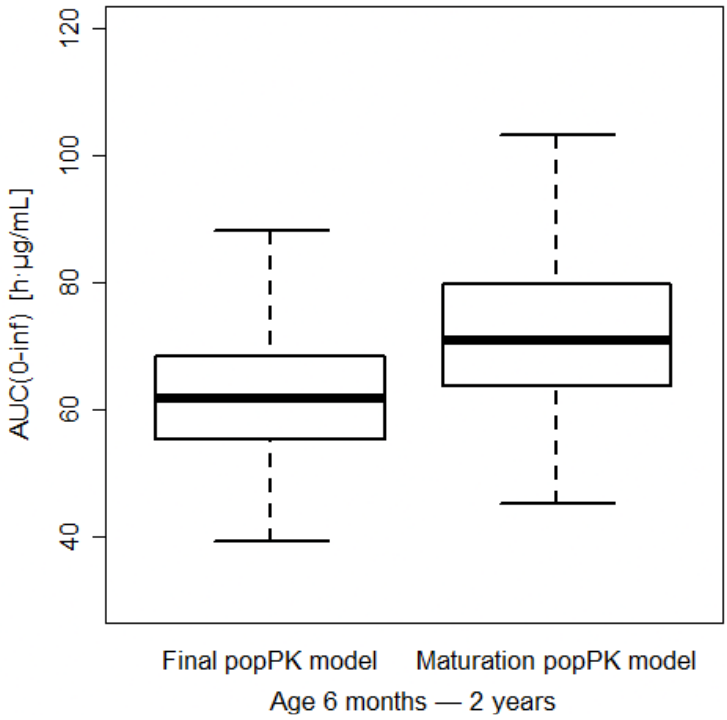
Table 3: Parameter estimates for the maturation adjusted popPK model (run601)

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
KA	1/h	1.95	20.8	1.15	2.74	Absorption rate constant
CL	L/h	3.86	4.18	3.55	4.18	Clearance value for patient of 15.05 kg
V1 and V2	L	11.4	8.10	9.59	13.2	Volume of distribution for central and peripheral compartments for patient of 15.05 kg
Q	L/h	0.337	19.8	0.206	0.468	Intercompartmental clearance value
Random effects: Inter-individual variability (OMEGA)						
KA (ω^2)	-	0.519	47.2	0.0391	0.999	IIV on absorption rate constant
KA (CV[d])	%	82.5		20.0	131	
KA (Shrinkage)	%	27.2				
CL (ω^2)	-	0.0175	27.4	0.00811	0.0269	IIV on clearance
CL (CV[d])	%	13.3		9.02	16.5	
CL (Shrinkage)	%	12.3				

Residual error (SIGMA)						
σ^2 (TAD ≤ 1 h)	-	0.359	14.9	0.255	0.464	Variance of proportional residual error during absorption
CV[e]	%	59.9		50.5	68.1	
σ^2 (TAD ≤ 1 h)	-	0.102	26.3	0.0493	0.155	Variance of proportional residual error after absorption
CV[e]	%	31.9		22.2	39.3	

[a] RSE = relative standard error (100·SE/estimate)
[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[c] ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
[d] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[e] Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.

The results of simulations for the calculation of exposure parameters are presented in **section 2.4**. For comparison purposes between the models boxplots comparing the predictions of AUC(0-inf) and Cmax from the final popPK model and adjusted popPK model with maturation function, following 8 days of QD dosing with 15 mg/kg of hydroxycarbamide, are given in figure below.



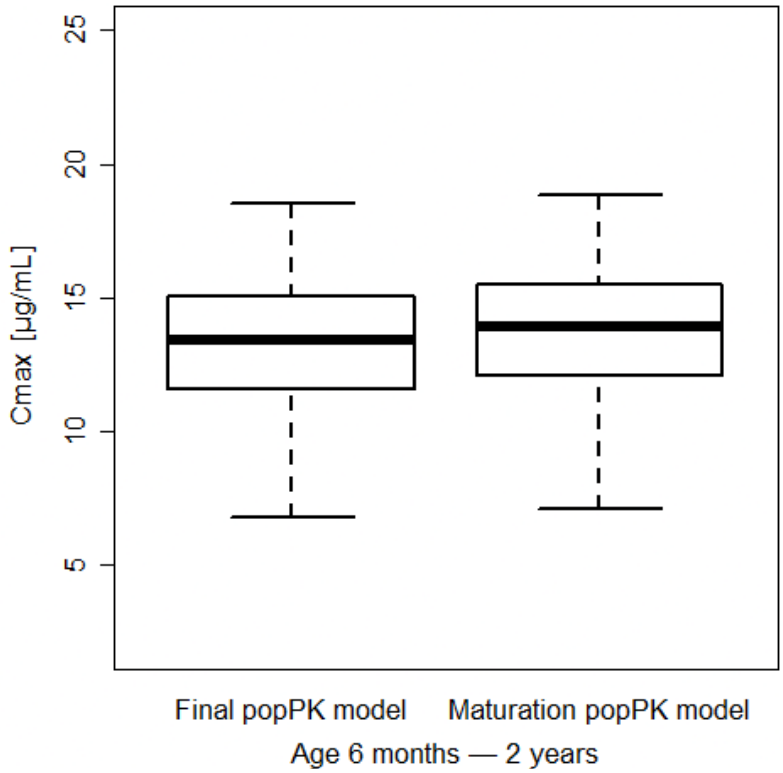


Figure 3: Comparison of predicted AUC and Cmax in patients aged 6 months to 2 years using the final popPK model and adjusted popPK model with maturation function

Additional PK-PD models

Upon request by the CHMP a semi-mechanistic population PK-PD model that describes the indirect relationship between hydroxycarbamide concentration and foetal haemoglobin (HbF) in patients of study INV543 was built. The goal was to produce an informative model that can produce predictions that align with observed data. Existing popPK-PD models from literature [Pandey, A et al. 2022] were used as a guide for model development. The data file used for this analysis was created using the previously extracted hydroxycarbamide PK and HbF data from the initial M&S report, with the inclusion of all recorded doses.

$$\frac{dC_i}{dt} = KE_0(C_p - C_i)$$

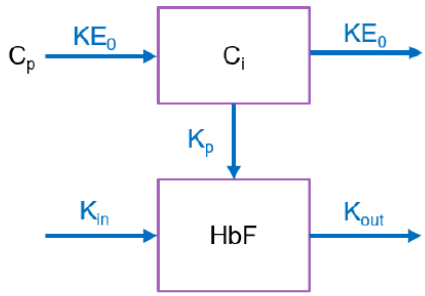
$$\frac{dHbF}{dt} = K_{in} + K_p \cdot C_i - K_{out} \cdot HbF$$

$$C_i(0) = 0$$

$$HbF(0) = K_{in}/K_{out}$$

$$K_{in} = K_{in,TV} \cdot \left(\frac{AGE}{5\ years}\right)^{COV1} \cdot (LTTWO \cdot e^{\eta_1} + (1 - LTTWO) \cdot e^{\eta_2})$$

$$K_p = K_{p,TV} \cdot e^{\eta_3}$$



C_p, hydroxycarbamide concentration; C_i, hydroxycarbamide intermediate; HbF, fetal hemoglobin; KE_0, intermediate production/removal rate; K_p, Additional HbF production rate; $K_{p,TV}$, Additional HbF production rate for a typical patient; K_{in}, basal production rate of HbF; $K_{in,TV}$, basal production rate of HbF for a typical patient; K_{out}, basal removal rate of HbF; LTTWO, flag for patients less than 2 years old (set to 1 if patient is less than 2 years old, set to 0 otherwise); AGE, baseline age of patient; COV1, covariate influence of age on K_{in}.

Figure 4: Structure of the selected popPK-PD model for HbF (run731)

Table 4: Parameter estimates for model run731

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
$K_{in,TV}$	%/h	0.0193	13.6	0.0142	0.0244	Basal production rate of HbF for a typical patient
K_{out}	1/h	0.00290	Fixed	Fixed	Fixed	Basal removal rate of HbF
$K_{p,TV}$	%·ml/µg/h	0.00725	13.0	0.00540	0.00909	Additional production rate of HbF for a typical patient
1000·KE_0	1/h	0.553	24.5	0.287	0.819	Intermediate production/removal rate
COV1	-	-0.612	17.6	-0.823	-0.401	Covariate influence of age on Kin
Random effects: Inter-individual variability (OMEGA)						
ETA(1,1) (ω^2)	-	0.435	20.5	0.260	0.610	IIV on K_{in} for patients ≥2 years old
ETA(1,1) (CV[d])	%	73.8		54.4	91.6	
ETA(1,1) (Shrinkage)	%	1.36				
ETA(2,2) (ω^2)	-	0.103	45.2	0.0118	0.193	IIV on K_{in} for patients <2 years old
ETA(2,2) (CV[d])	%	32.9		10.9	46.2	
ETA(2,2) (Shrinkage)	%	-4.62				
ETA(3,3) (ω^2)	-	0.223	25.9	0.110	0.337	IIV on K_p
ETA(3,3) (CV[d])	%	50.0		34.1	63.3	
ETA(3,3) (Shrinkage)	%	16.73				
Residual error (SIGMA)						
EPS(1,1) (σ^2)	-	0.0220	37.5	0.00582	0.0382	Proportional error model
CV[e]	%	14.8		7.63	19.6	

[a] RSE = relative standard error (100·SE/estimate)
[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)
[c] ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)
[d] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.
[e] Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.

Results of simulations are given in section 2.4.

In addition to building a population PK-PD model for the primary efficacy marker (HbF), an attempt was made to build a semi-mechanistic population PK-PD model absolute neutrophil count (ANC) in patients of study INV543. Existing popPK-PD models from literature [16] were used as a guide for model development.

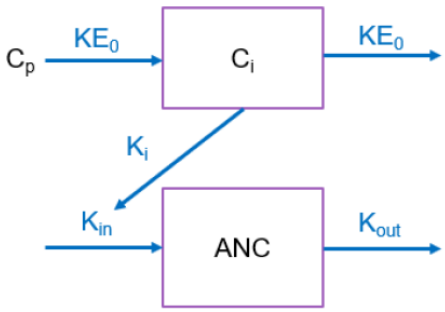
The data file used for this analysis was created using the previously extracted hydroxycarbamide PK, foetal haemoglobin data and absolute neutrophil count data from the M&S report [1], with the inclusion of all recorded doses (even after the last PK observation). Time varying infection (viral, bacterial, or fungal) data in patients under 6 years of age was also included.

$$\frac{dC_i}{dt} = KE_0(C_p - C_i)$$

$$\frac{dANC}{dt} = K_{in} \cdot (1 - K_i \cdot C_i) - K_{out} \cdot ANC$$

$$C_i(0) = 0$$

$$ANC(0) = K_{in}/K_{out}$$



$$K_{in} = \left(\frac{AGE}{5\ years}\right)^{COV1} \cdot (1 + INFECT \cdot COV2) \cdot K_{in,TV} \cdot e^{\eta_1}$$

C_p, hydroxycarbamide concentration; C_i, hydroxycarbamide intermediate; ANC, absolute neutrophil count; KE_0, intermediate production/removal rate; K_i, inhibition of production rate; K_{in}, basal production rate of ANC; $K_{in,TV}$, basal production rate of ANC for a typical patient; K_{out}, basal removal rate of ANC; AGE, baseline age of patient; COV1, covariate influence of age on K_{in}; INFECT, time-varying infection flag for patients under 6 years of age; COV2, covariate influence of INFECT on K_{in}.

Figure 5: Structure of the selected popPK-PD model for ANC (run833)

Table 5: Parameter estimates for model run 833

Parameter	Unit	Estimate	RSE [%][a]	LLCI[b]	ULCI[c]	Description
Fixed effects (THETA)						
$K_{in,TV}$	%/h	43.7	5.96	38.6	48.8	Basal production rate of ANC for a typical patient
K_{out}	1/h	10	Fixed	Fixed	Fixed	Basal removal rate of ANC
Ki	ml/µg	0.0620	6.34	0.0543	0.0697	Inhibitory influence of intermediate concentration on ANC production
$1000 \cdot KE_0$	1/h	0.477	49.2	0.0169	0.937	Intermediate production/removal rate
COV1	-	0.215	28.1	0.0966	0.333	Covariate influence of age on Kin
COV2	-	0.358	17.1	0.238	0.478	Covariate influence of infections on Kin
Random effects: Inter-individual variability (OMEGA)						
ETA(1,1) (ω^2)	-	0.0593	37.8	0.0153	0.103	IIV on K_{in}
ETA(1,1) (CV[d])	%	24.7		12.4	33.0	
ETA(1,1) (Shrinkage)	%	5.72				
Residual error (SIGMA)						
EPS(1,1) (σ^2)	-	0.160	7.47	0.137	0.183	Proportional error model
CV[e]	%	40.0		37.0	42.8	

[a] RSE = relative standard error (100·SE/estimate)

[b] LLCI = lower limit of 95% confidence interval (estimate - 1.96·SE)

[c] ULCI = upper limit of 95% confidence interval (estimate + 1.96·SE)

[d] Coefficient of variation (CV) calculated as 100·SQRT(EXP(ω^2)-1). The confidence intervals of CV are derived through transformation of confidence intervals of ω^2.

[e] Coefficient of variation (CV) calculated as 100·SQRT(σ^2). The confidence intervals of CV are derived through transformation of confidence intervals of σ^2.

Results of simulations fort this models are presented in section 2.4.

2.3.5. Discussion on clinical pharmacology

Following the initial approval of XROMI it was accepted by the CHMP that uncertainty remained regarding the PK, safety and efficacy in young children under 2 years of age considering that hepatic and renal function may be still immature at that age. In addition, metabolism/excretion of hydroxyurea is not fully characterized and differences in PK in this age group cannot be excluded. Furthermore, according to the Scientific Advice EMA/CHMP/SAWP/187964/201 the lack of PK data in infants between 9 months and 2 years does represent an uncertainty, particularly in the case of dose escalation. These uncertainties precluded the extrapolation of the indication to children under 2 years of age. Thus, CHMP has asked the applicant for results from a clinical study involving patients above 9 months until 2 years and to expand the number of participants of this age by using a PK model.

The applicant submitted the results of M&S analysis of study INV543 to support extension of indication to children aged 6 months to 2 years old. Following the assessment of the submitted data it was concluded that the number of patients which participated in the submitted PK study below 2 years of age (n=6) was not considered adequate to establish safety and efficacy of hydroxyurea in this age group and that the PK model submitted by the applicant was not considered adequate for the requested extension of indication to children from 6 months to 2 years of age.

The applicant was requested to update the PK/PD model appropriately in order both to support the proposed posology (escalation of dose until MTD) in children of the age group from 6 months to 2 years of age, and to predict adequately all the observed data (adequate predictive performance of the PK/PD model should be demonstrated). Several concerns were raised and additional data were requested.

In response the applicant submitted an adjusted pop PK model with the inclusion of a maturation function (see section 2.3.4) to describe the time course of hydroxycarbamide in plasma in children under 2 years of age. The applicant used the adjusted popPK model with maturation function to simulate exposure for patients <2 years of age in comparison to literature results from McGann et al. (2019) from 50 children from 10 months of age and above, after a single 20 mg/kg hydroxycarbamide dose.

In addition, the applicant used individual predictions of hydroxycarbamide exposure to develop popPK-PD models for foetal haemoglobin (HbF) taking into account the higher baseline HbF in children less than 2 years], and the safety marker absolute neutrophil count (ANC) [an ANC exposure-response model was provided], to support the efficacy and safety of a dose-titration approach starting with a low dose of 15 mg/kg/day up to a maximum of 35 mg/kg/day. The applicant used the M6 method in early model development while the widely acceptable M3 method was used for model refinements before starting the covariate search. Furthermore, the applicant also provided predicted concentrations for the BLQ samples and pcVPCs stratified for observations below and above LLOQ, which are considered acceptable.

The use of volume of central and peripheral compartments as equal (V1=V2) was statistically acceptable while the use of a saturable model was not supported by the data. Even though the maturation function was based on the assumption that "50% of the dose of hydroxycarbamide is metabolized by the liver through the monoxygenated system and the maturation of this system can be approximated through the established maturation of P450 CYP3A4", according to Bouillon-Pichault et al. (2010), without any data that confirm that this is applicable to HU, it is considered acceptable due to the fact that the exact CYP enzymes involved in the metabolism of HU are not known and the applicant used what was available in the literature. The updated popPK/PD models were considered adequate.

The fact that the applicant had not included maturation function in the initial PK model, led to insufficiencies and inadequacies of the model, including the absence of identification of age by the PK model as a covariate. The inclusion by the applicant of a maturation function on clearance, with parameter estimates taken from literature, has subsequently provided a visually improved fit to the data. It should also be noted that the model did not identify age as a covariate, due to the limited number of subjects less than 2 years of age (n=6) in study INV543.

Additionally, the applicant provided the actual ages of the patients between 6 months and 2 years who participated in study INV543 and discussed the effect of the scarcity of data of this group of patients on parameter estimation. Parameter estimation is acceptable according to the amended report and the pcVPCs for the adjusted popPK model with maturation function, but no patients from 6-9 months were enrolled in study INV543. Thus, the fact that both in the study INV543 and the study of McGann et al. (2019), only patients from 10 months of age and above were enrolled, should be noted. PK and PD data for the age group of 6-9 months of age are only based on simulation and the extrapolation of data from older children and not on clinical data in this age group.

Accordingly, results from a) the adjusted popPK model with maturation function, b) popPK-PD modelling for HbF and c) popPK-PD modelling for ANC, do not support the proposal to extend current posology (dose escalation until MTD in the range 15 mg/kg/day to 35 mg/kg/day) to children aged 6-9 months. The lack of observed data in the age group "6-9 months" hampers the possibility to validate the reliability of prediction in this age range, making difficult any extrapolation of data from older children to children below 9 months of age.

The small number of patients included in the pivotal study could have been overcome provided clear conclusions could be drawn from PK/PD data and clinical extrapolation in children below 9 months of age, however, this is not the case as per assessment of the responses provided by the MAH, failing to demonstrate clinical relevance, PK/PD extrapolation and adequate posology definition.

In particular, PK/PD extrapolation to the younger subjects <9 months, including posology, does not seem possible due to a) the lack of PK/PD data, b) unknown ontogeny of metabolizing enzymes, c) change in renal clearance of HU and d) potential impact of the high HbF levels on the needed dose in these young subjects. Considering the absence of observed PK and PD data in the age group of 6-9 months to support extrapolation of efficacy and safety, the B/R in the age group of 6-9 months of age is considered negative and the MAH has accepted to restrict the indication accordingly (See also discussion in efficacy and safety).

2.3.6. Conclusions on clinical pharmacology

The clinical pharmacology of the product is considered well described.

2.4. Clinical efficacy

Evidence for the efficacy of hydroxycarbamide in reducing the vaso-occlusive complications of Sickle Cell Disease in children older than 9 months comes from five randomised controlled trials (Charache *et al* 1995 [MSH Study]; Jain *et al* 2012, Ferster *et al* 1996; Ware *et al* 2015 [TWiTCH], Wang et al 2011 [BABY HUG]). Furthermore, findings from these pivotal studies are supported by observational studies including some long-term follow up

Clinical efficacy in the treatment of children above 9 months was shown in the 2011 BABY-HUG trial which randomly assigned 193 infants 9 to 18 months with HbSS or sickle beta0 thalassemia irrespective of clinical severity to receive placebo or hydroxyurea (20 mg/kg daily without dose escalation) for two years. The median age at entry was 13.6 months. Primary endpoints included splenic function and glomerular filtration rate (GFR), both of which were chosen because they become abnormal in SCD early in life. Compared with controls, hydroxyurea-treated infants had a trend towards improved splenic function (assessed by cell morphology after qualitative radionucleotide scans were discontinued) and no difference in GFR. However, there were reductions in clinical endpoints including pain episodes (hazard ratio [HR] 0.59; 95% CI 0.42-0.83), acute chest syndrome (HR 0.36; 95% CI 0.15-0.87), dactylitis (HR 0.27; 95% CI 0.15-0.50), and gastroenteritis (HR 0.35; 95% CI 0.20-0.60), as well as in need for transfusions (HR 0.55). The difference in the endpoints between groups was not statistically significant. Therapy was well tolerated with no severe adverse events. Observational studies have demonstrated similar benefits. Other potential benefits of hydroxyurea include improved general quality of life and daily functioning. The data from the 2011 BABY-HUG trial supports the rationale that early use of hydroxycarbamide early in asymptomatic infants with SCD would be beneficial.

During the development of the product the MAH asked for scientific advice regarding the extension of indication to children from 9 months of age. *'Taking into account the rarity of the disease, the unmet medical need, and the totality of data available, the CHMP is of the opinion that the use of hydroxycarbamide in infants between the ages of 9 months and 2 years, at a dose of 20 mg/kg/day without escalation, could be supportable subject to assessment in a MAA. Furthermore, careful dose escalation to achieve mild myelosuppression up to a maximum of 35 mg/kg/day, in infants between the ages of 9 months and 2 years could also be proposed for assessment, considering that these patients are treated at specialist centres under close monitoring. To this end, long-term follow-up data*

from BABY HUG are considered supportive, and should preferably be provided as part of a MAA. In lieu of bridging data, arguments that the data generated with the formulation used in BABY HUG and its extension are relevant to the formulation proposed should be available.
The lack of PK data in infants between 9 months and 2 years does represent an uncertainty, particularly in the case of dose escalation. In the event that an application for marketing authorisation is made without such data, a plan to generate these data post-approval should be considered. Furthermore, consideration should be given to the prospective collection of "real world" data in infants 9 months and 2 years in a post-approval registry.
In conclusion the CHMP is of the opinion that the BABY HUG data, the accumulating literature, and a BE study in HVs, maybe be sufficient to support a MA in infants between the ages of 9 months and 2 years pending full assessment of data and possible post-approval conditions. The precise wording of an indication, including disease severity and effects on different components of SCD, is a matter of assessment (CHMP EMA/CHMP/SAWP/187964/2016).

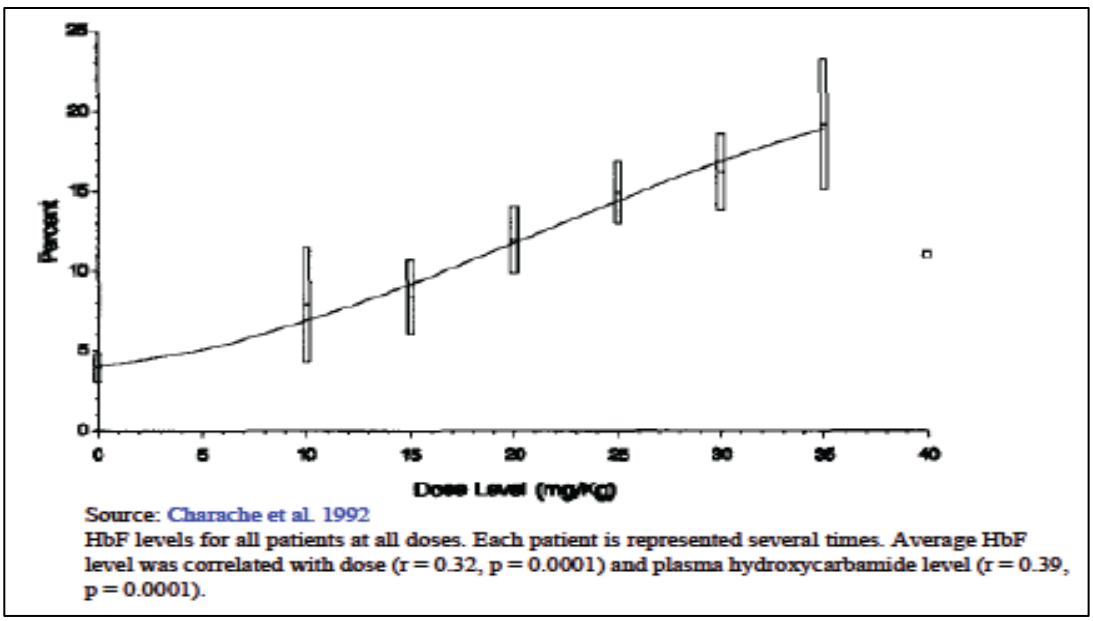
According to this and the follow up advice EMA/CHMP/SAWP/172730/2017 the applicant planned a post-authorisation open label, observational pharmacokinetic (PK) study in children aged 9 months to 18 years (Study INV543).

This section of the report describes the design, conduct and results of study INV543

2.4.1. Dose response study

A dose-response relationship of hydroxycarbamide with improvement in clinical markers of SCD in children has been demonstrated by clinical studies and is also evident in study INV543.

Charache et al, (1992) showed that the effects of hydroxycarbamide are dose dependent. They studied the hydroxycarbamide dose-response curve in 49 patients and reported an increase in %HbF and %F cells with increasing doses, approaching an asymptote at around 35 mg/kg/day. Subsequently many clinical trials have demonstrated that the laboratory and clinical benefits of hydroxycarbamide are optimized when escalated to MTD.

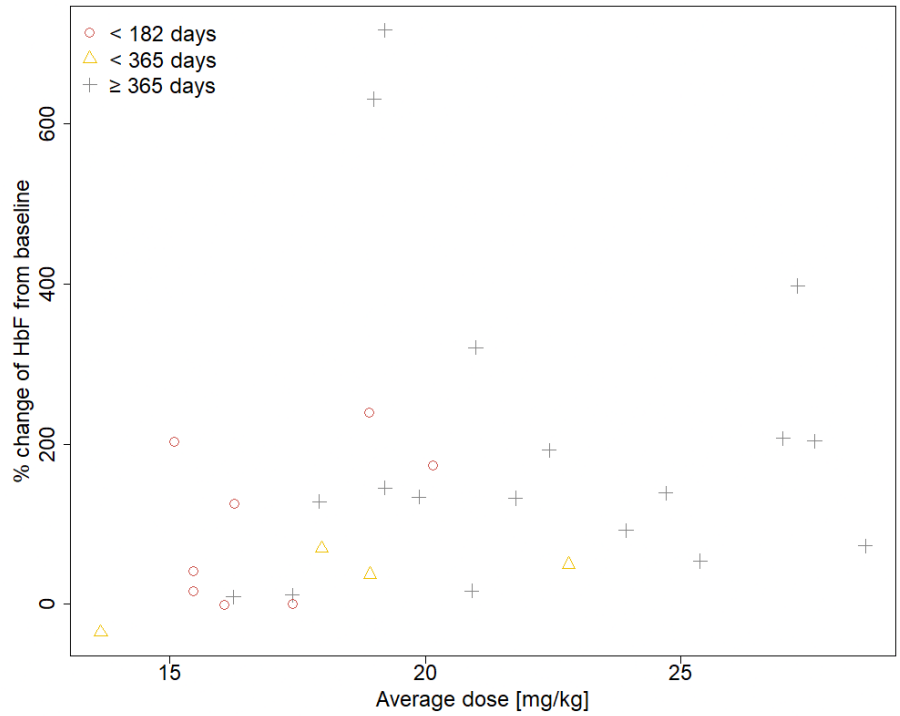


Source: Charache et al. 1992
HbF levels for all patients at all doses. Each patient is represented several times. Average HbF level was correlated with dose (r = 0.32, p = 0.0001) and plasma hydroxycarbamide level (r = 0.39, p = 0.0001).

Figure 6: Hydroxyurea dose versus Foetal Haemoglobin (%) response

This positive relationship between dose and HbF response also appeared to manifest in paediatric study INV543. Figure 7 shows percentage of change of the last observed HbF from baseline against

average dose in mg/kg up to the last HbF observation. The plot suggests that higher doses are associated with larger % increase in HbF.



HbF = foetal haemoglobin

The x-axis shows average dose (in mg/kg), a patient received up to their last foetal haemoglobin observation. The y-axis % change of last observed foetal haemoglobin from baseline. Red, gold and grey colours represent time window of last foetal observation to be less than 182 days, 182 days up to 365 days, and greater than 365 days, respectively.

Figure 7: Paediatric Study INV543 Percent Change in HbF Versus Average Dose

2.4.2. Main study

Title of Study

A Prospective Open Label, Pharmacokinetic Study of an Oral Hydroxyurea Solution in Children with Sickle Cell Anaemia

Methods

Study INV543 was an open label, observational, safety and PK study of Xromi oral hydroxycarbamide solution administered to children from 6 months to 17.99 years (i.e. to the day before 18th birthday), with a 12- to 15-month treatment period for each participant. The study treatment duration was for 6 months at the MTD, which was usually reached by 6 months after initiation of treatment. For patients in whom time to MTD was longer than 6 months or not achieved at all, the maximum duration of study treatment was 15 months. The study was conducted at one clinical site in Jamaica and 5 clinical sites in the U.K.

Study participants

- Main Inclusion Criteria
  1. Male or female aged from 6 months – 17.99 years of age (i.e., to the day before 18th birthday).
  2. Diagnosis of SCA (HbSS and HbSβ0).
  3. Parent(s)/legal guardian able and willing to provide written informed consent for the child to take part in the study.
  4. Where applicable, the child should assent to undergo blood sampling for PK and biochemistry purposes and to allow physiological measurements to be made.
- Main Exclusion Criteria
  1. Any clinically significant medical condition or abnormality, which, in the opinion of the investigator, might have compromised the safety of the patient or which might have interfered with the study.
  2. Hydroxycarbamide use within 6 months before enrolment.
  3. Renal insufficiency (known creatinine more than twice the upper limit of normal (ULN) for age and >1.0 mg/dL [88.4 µmol/L]).
  4. Clinical evidence of hepatic compromise with alanine aminotransferase (ALT) >3 times the ULN (a temporary swing in ALT will not result in exclusion).
  5. Other significant organ system dysfunction based on the site investigators discretion.
  6. Severe active infections: fungal, viral or bacterial (as confirmed by culture), examples included tuberculosis, malaria, active hepatitis, osteomyelitis or any other illness that would have precluded the use of hydroxycarbamide in normal clinical practice.
  7. Active chronic leg ulcers.
  8. Known allergy to oral hydroxycarbamide solution or any of the excipients.
  9. Positive pregnancy test for females of child-bearing potential (in post-menarcheal females) before initiation of treatment, unless participant was sexually abstinent. Note: True abstinence is considered as being in line with the preferred and usual lifestyle of the subject. Periodic abstinence (such as calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
  10. Inadequate contraception measures in sexually active females (post-menarcheal females) and males of child-bearing age.
  11. Breastfeeding at study initiation
  12. Participation in another clinical trial of an investigational medicinal product
  13. Known infection with HIV.

Treatments

Patients meeting entry criteria and providing informed consent were started on an oral dose of 15 mg/kg Xromi once daily. The dose was escalated by 5 mg/kg/day every 8-12 weeks until the MTD was achieved (defined as occurrence of haematological toxicity, an ANC of 1-3 ×109/L occurred, or a maximum dose of 35 mg/kg/day;). Once the MTD was established, treatment was maintained for a maximum of 12-15-months. Doses were calculated based on most current body weight (measured at each in-clinic visit). Doses were rounded where necessary to the nearest 10 mg. Calculations were made using a dosing calculator or by formula.

Objectives

Primary:

- To determine the pharmacokinetics (PK) of oral hydroxyurea (HU) solution (a population PK [popPK] approach was adopted to characterize the PK in this population)

Secondary:

- To further evaluate the safety of oral HU solution
- To assess effects on foetal haemoglobin (HbF), haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count and differentials, absolute neutrophil count (ANC), absolute reticulocyte count (ARC), platelets, bilirubin, cystatin C and lactate dehydrogenase (LDH)
- To assess effects on pain, transfusions, hospitalizations, and acute chest syndrome (ACS)
- To assess the acceptability and palatability of oral HU solution
- To investigate the effects of HU dose escalation on laboratory and clinical parameters
- Safety endpoints included the incidence of adverse events (AEs).

Outcomes/endpoints

Primary:

- Pharmacokinetic parameters: Clearance (CL/F), volume of distribution (V/F), time to maximum concentration (Tmax), maximum plasma concentration (Cmax), area under the plasma concentration time curve (AUC(0-inf)), half-life (t½).

Secondary:

- Safety: incidence of AEs, ANC, WBC count and differential, platelets, MCH, haematocrit, LDH, bilirubin, elevation in liver function tests, Hb/anaemia.
- Additional safety laboratory parameters (haematology/biochemistry): bacterial infections, viral infections, fungal infections, leg ulcers.
- Biomarkers: HbF, MCV, Cystatin C.
- Clinical Status: incidence of acute pain crises (defined as an acute episode of pain with no known cause for pain other than a vaso-occlusive event; requiring a visit to a medical facility; and requiring treatment with a narcotic (including opiates) and/or non-steroidal anti-inflammatory drugs; but is NOT classified as an ACS, hepatic sequestration, splenic sequestration, or priapism), number and frequency of blood transfusions, incidence of ACS, hospitalizations, dose escalation (i.e. time to MTD), clinical parameters (symptoms), parent/caregiver acceptability/usability by questionnaire, palatability and acceptability of the taste of the new oral liquid formulation of HU

Exploratory:

- Transcranial doppler velocity
- Urine parameters (albumin and creatinine for albumin-to-creatinine ratio)

Sample size

Up to 35 patients, both male and female, aged 6 months – 17.99 years of age were to be recruited. This 'up to' recruitment figure allowed additional patients to be recruited to account for those patients from whom it was not possible to obtain sufficient valid PK samples for the age groups set out in the protocol. There was a minimum requirement for the age group categories, with a minimum of 6

patients in the 6 months to < 1.99 years age group and a minimum of 6 patients in the ≥ 2 to < 5.99 years age group (where .99 represents the day before the patient's birthday).

Randomisation and Blinding (masking)

Not applicable.

Statistical methods

There were no power calculations carried out for this study. The primary objective of this study was to estimate the population PK of Xromi following administration. From a statistical point of view, the collected plasma concentration data were expected to relate to a non-linear, mixed effects model involving repeated measures. The developed PK model estimated the parameters of the model and their associated within- and between-patient variability.

The primary efficacy endpoint in paediatric study INV543 was standard PK parameters derived from the population time-concentration hydroxycarbamide profile obtained at proscribed timepoints throughout the study.

PK analyses

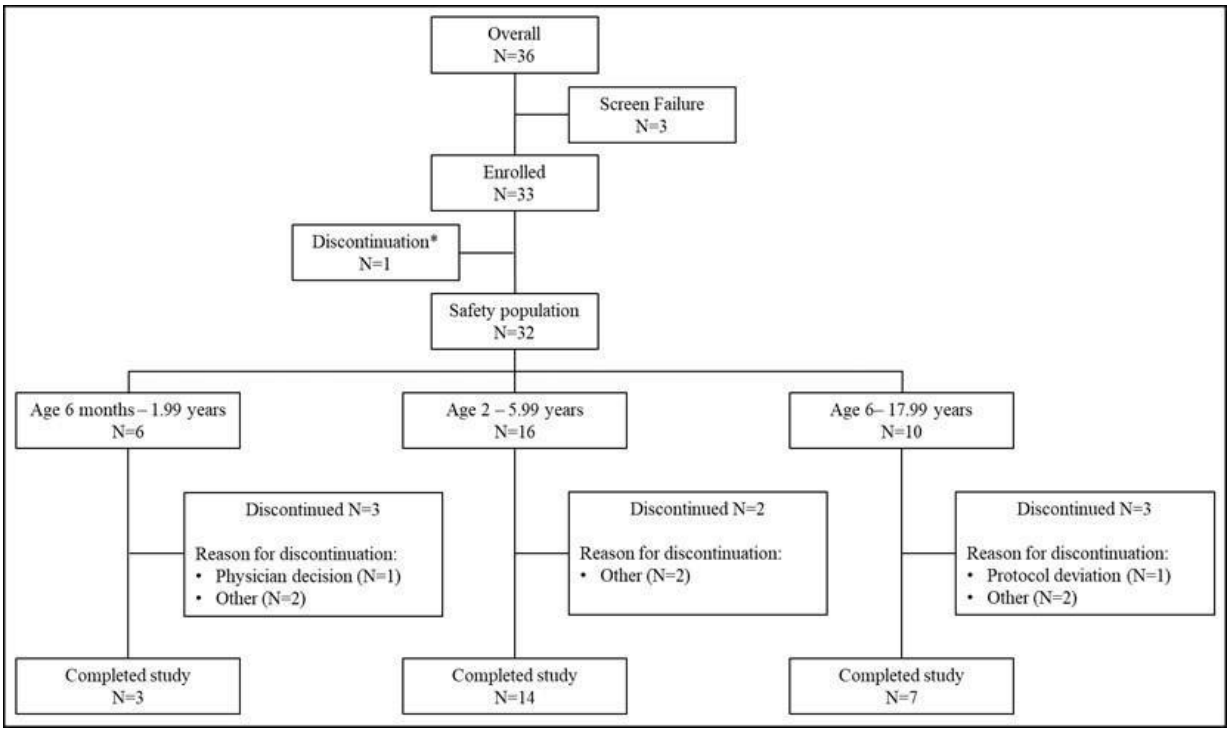
One interim analysis was planned when all study participants completed approximately 9 months of the study (i.e., when the last study participant reached their week 40 visit).

A popPK model was to be used to estimate individual post-hoc PK parameters which in turn were used to calculate (or determine through simulation) the following secondary PK parameters for each child in the PK study population.

Reporting of secondary efficacy endpoint data was descriptive and presented using appropriate summary statistics (e.g., n, mean, standard deviation [SD], coefficient of variation [%CV], median, minimum, maximum, quartiles [if appropriate]) or frequency distributions (n and %) by age group (age 6 months to 1.99 years, 2 years to 5.99 years, and 6 years to 17.99 years). Where shift tables were presented, definitions of categories (e.g., lower and upper limit of normal values) were taken from the literature or clinical experience.

Results

Participant flow



A total of 36 children were screened for the study of whom 33 were enrolled as study participants and 32 received at least one dose of the investigational medicinal product. One participant underwent pre-dose blood sampling but was discontinued prior to receiving treatment by the Investigator as unwilling to commit to the study. The participant was classified as 'enrolled' but subsequently withdrawn and hence excluded from the safety population.

Recruitment

Participants were enrolled at 6 centers, 1 in Jamaica and 5 in the UK.

Conduct of the study

The original protocol was dated 28 Mar 2018 in v3.0. The final version of the protocol was v.9.0 dated 03 Jun 2021. Study was conducted from 03 Jan 2019 to 12 Apr 2022.

A total of 219 protocol deviations were recorded, all of which were deemed to be minor in implication, and 60 explicitly mentioned the COVID-19 pandemic in the description. At least one protocol deviation was recorded for all 32 study participants who were enrolled and received at least one dose of Xromi. The most common deviations were study drug dosing (24 study participants), laboratory assessments/ procedures (22 participants), study procedures (20 participants) and visit schedule/interval (19 participants).

Impact of COVID-19 Pandemic on Treatment Compliance: Following COVID-19 responsiveness guidelines from the U.K. National Haemoglobinopathy meeting held on March 19, 2020, during an

active pandemic period of COVID-19, dose escalations were to be avoided. If necessary, these should only have been carried out per protocol or at investigator discretion where sufficient infrastructure was in place within the hospital/clinic or central laboratories to ensure study participant safety. These would have been carried out only after an on-site study participant visit in which safety laboratory parameters had been obtained, but advice on dose changes could be given to participants by telephone. Due to the possible extended period between clinic visits of up to 12 weeks, any indication of a trend towards toxicity identified by the Investigator was treated at the discretion of the investigator to ensure study participant safety. During this period, it was permissible to treat trends towards toxicity proactively, as though they had reached a threshold of toxicity prior to confirmation with dose reductions (at 2.5-5.0 mg/kg/day) or temporary halts, as applicable. Such actions were reported to Nova Laboratories and documented in the participants medical notes and case report form (CRF) but were not considered deviations during the COVID-19 pandemic active period between 2020-2021. Home delivery of Xromi study drug was offered after obtaining consent from participants to facilitate the continued use of the medication during extended periods of time between clinic visits.

Baseline data

Overall, mean (SD) age was 5.0 (4.25) years ranging from 0.8–16.0 years. All except for two study participants were Black or African American, and 31 safety population participants were of the HbSS genotype and one was of the HbSβ^0 genotype (Table 6).

Table 6: Paediatric Study INV543 Patient Demographics and Key Baseline Characteristics (All Screened Subjects)

	6 Months–1.99 Years (N=6)	**2–5.99 Years (N=16)**	**6–17.99 Years (N=11)**	**Overall (N=33)**
Age (years; mean [SD])	0.97 (0.068)	3.06 (0.929)	10.09 (3.506)	5.03 (4.251)
Female Sex (n [%])	5 (83.3)	5 (31.3)	7 (63.6)	17 (51.5)
Race (n [%])				
American Indian or Alaska Native	0	0	0	0
Asian	0	0	0	0
Black or African American	5 (83.3)	15 (93.8)	11 (100)	31 (93.9)
Native Hawaiian/Other Pacific Islander	0	0	0	0
White	0	0	0	0
Other	1 (16.7)	1 (6.3)	0	2 (6.1)
Ethnicity (n [%])				
Hispanic or Latino	*0*	*0*	*0*	*0*
Not Hispanic or Latino	*6 (100)*	*16 (100)*	*11 (100)*	*33 (100)*
SCA type (n [%])				
HbSS	*6 (100)*	*15 (93.8)*	*11 (100)*	*32 (97.0)*
HbSβ^0	*0*	*1 (6.3)*	*0*	*1 (3.0)*
Height (cm; mean [SD])	79.40 (5.237)	98.08 (6.947)	142.09 (15.872)	109.26 (26.038)
Weight (kg; mean [SD])	11.18 (1.017)	14.74 (2.092)	32.52 (11.441)	19.63 (10.955)
BMI (kg/m²; mean [SD])	17.78 (2.326)	15.31 (1.164)	15.66 (2.228)	15.82 (1.917)
Temperature (°C; mean [SD])	36.74 (0.270)	36.73 (0.443)	36.88 (0.447)	36.78 (0.414)
RR (breaths/min; mean [SD])	33.20 (6.058)	25.07 (2.895)	22.67 (2.179)	25.75 (4.956)
Heart Rate (beats/min; mean [SD])	119.00 (13.115)	111.56 (9.158)	92.30 (7.072)	106.55 (13.667)
SBP (mmHg; mean [SD])	103.40 (5.941)	102.13 (9.273)	105.60 (7.849)	103.50 (8.245)
DBP (mmHg; mean [SD])	56.40 (11.415)	57.07 (7.324)	64.20 (4.492)	59.33 (7.902)

For age, .99 denotes the day before the study participant's birthday.
BMI = body mass index; DBP = diastolic blood pressure; RR = respiratory rate; SBP = systolic blood pressure; SCA = sickle cell anaemia; SD = standard deviation.

Acute complications and hospitalizations occurring in the 12 months prior to each study participant's screening visit were recorded. The proportion of study participants who experienced an acute complication or were hospitalized in the 12 months prior to screening (verified by medical record review) increased with age group. Febrile episodes (9 participants, 28.1%), hepatic sequestration (5 participants, 15.6%) and dactylitis (4 participants, 12.5%) were the most commonly reported events over that time period. It should be noted that, due to their age, medical history for some of the 6 months–1.99 years age group did not extend to 12 months before screening.

Numbers analysed

A total of 435/464 PK measurements from 32 study participants were used in the development of the final popPK model.

Outcomes and estimation

For the paediatric study INV543 modelling and simulation analyses, once the base model was developed, the influence of covariates (such as age, weight, sex, geographic region, study site, and laboratory endpoints) on model parameters were fully investigated. Systemic exposure (secondary PK) parameters were determined through simulations of the final model.

The analysis of population PK involved pooling data from all study participants and analysing simultaneously using a non-linear mixed effects modelling approach. The time course data of hydroxycarbamide in plasma of children enrolled in study INV543 was successfully described with a two-compartment population PK model with allometric body weight scaling on CL, Q and V1, V2. Only bodyweight was identified as a significant covariate and its inclusion reduced interindividual variability in clearance to 14.5% CV. Following a single 15 mg/kg dose of hydroxycarbamide, a marginal increase in Cmax and AUC(0-inf) with age was estimated.

The response of HbF in INV543 was in alignment with what has been reported in other studies of hydroxycarbamide in children with SCA and was consistent throughout the age range of 6 months to 18 years. Overall, the PK profile of hydroxycarbamide in this study population of children aged 6 months to 18 years was relatively uncomplicated with only weight being identified as an influential covariate. A robust HbF response was observed on treatment in all age categories.

PK Parameters:

The qualified final popPK model was used to estimate individual post-hoc PK parameters which in turn were used to calculate, through simulation, the following secondary PK parameters for each child in the PK study population after a single dose of 15 mg/kg:

- C_{max}: maximal plasma concentration.
- T_{max}: time of maximal plasma concentration.
- $AUC_{(0\text{-inf})}$: area-under-the-plasma-concentration-time curve from time 0 to infinity.
- $T_{1/2}$: half-life of elimination estimated by linear regression of the semi-logarithmic plot of simulated plasma concentrations versus time, taking only concentrations from 8 h to 24 h into account in 1-hour increments.

A summary of estimated PK parameters, stratified by age groups, is given in Table 7. Results indicate a marginal increase in C_{max} and $AUC_{(0\text{-inf})}$ and reduction in T½ with increasing age.

Table 7: Paediatric Study INV543 Summary Statistics of Secondary PK Parameters Stratified by Age Group

Age group	Statistic	C_{max} [µg/mL]	T_{max} [h]	$AUC_{(0\text{-}inf)}$ [h·µg/mL]	$T_{1/2}$ [h]
6 months to 1.99 years	n	6	6	6	6
	Minimum	11.3	0.79	56.1	3.82
	Maximum	14.8	1.58	79.7	4.34
	Median	12.5	1.4	58.5	4.09
	Mean	12.8	1.27	62.5	4.11
	Standard deviation	1.4	0.322	9.02	0.187
	Coefficient of variation [%]	10.9	25.4	14.4	4.55
2 years to 5.99 years	n	16	16	16	16
	Minimum	10	0.5	53	3.46
	Maximum	16.7	2.19	75.3	4.3
	Median	13.4	1.16	62	3.96
	Mean	13.1	1.24	62.9	3.95
	Standard deviation	1.94	0.455	7.37	0.257
	Coefficient of variation [%]	14.8	36.8	11.7	6.51
6 years to 17.99 years	n	10	10	10	10
	Minimum	9.29	0.85	57.1	3.16
	Maximum	15	2.08	94.4	4.04
	Median	14.1	1.12	69.6	3.66
	Mean	13.4	1.27	68.9	3.63
	Standard deviation	1.71	0.423	11.6	0.268
	Coefficient of variation [%]	12.8	33.4	16.9	7.38

CL = clearance; IIV = inter-individual variability; KA = oral absorption rate constant; SE = standard error; TAD = time after most recent dose; V1 = apparent volume of distribution of the central compartment after oral dosing; V2 = apparent Volume of distribution of the peripheral compartment after oral dosing

Age Effects on PK

A number of PK studies have been reported in the literature for adults and children, and the available evidence suggests that age does not influence hydroxycarbamide PK (de Montalembert et al. 2006, Dong et al. 2016, Estepp et al. 2016, Rogers et al. 2005, Wiczling et al. 2014).

The influence of age on PK was further investigated in paediatric study INV543 by simulating steady-state exposure following repeated daily dosing of hydroxycarbamide in children of the age groups 6 months up to 2 years, 2 years and up to 6 years, 6 years and up to 18 years. These simulations were facilitated by sampling age-appropriate body weights for children from the NHANES III. For each age group, 1000 virtual patients were simulated following 8 weeks of 15 mg/kg/day dosing of hydroxycarbamide. The median simulated hydroxycarbamide PK time courses and corresponding 90% prediction interval (PI) for each age group were plotted against time after most recent dose, following their 8 weeks of dosing (Figure 8). In addition, the distributions of maximum concentration (Cmax) and AUC(0-inf) were compared (Figure 9 and Figure 10).

Due to the allometric scaling of body weight on clearance (CL) in the final popPK model, following 8 weeks of dosing of 15 mg/kg/day, predicted hydroxycarbamide AUC(0-inf) increases with age (and body weight). The median AUC(0-inf) increases from 61.8 h*µg/mL, for children aged between 6 months and 2 years, to 70.6 h*µg/mL, for children aged between 2 and 6 years, and to 93.1 h*µg/mL, for children aged between 6 and 18 years. The distribution of AUC(0-inf) exposures overlapped considerably across the age categories. The influence of age on Cmax is less pronounced with the median Cmax increasing from 13.4 µg/mL, for children aged between 6 months and 2 years, to 13.9 µg/mL for children aged between 2 and 6 years, and to 14.7 µg/mL for children aged between 6 and 18 years. These results suggest no age-related dosage adjustments are necessary and weight-based

dosing results in similar systemic exposures (although acknowledging that the higher average exposure in children aged 6 – 18 years could be avoided if doses were not related linearly to body weight, but exponentially with an exponent of 0.75).

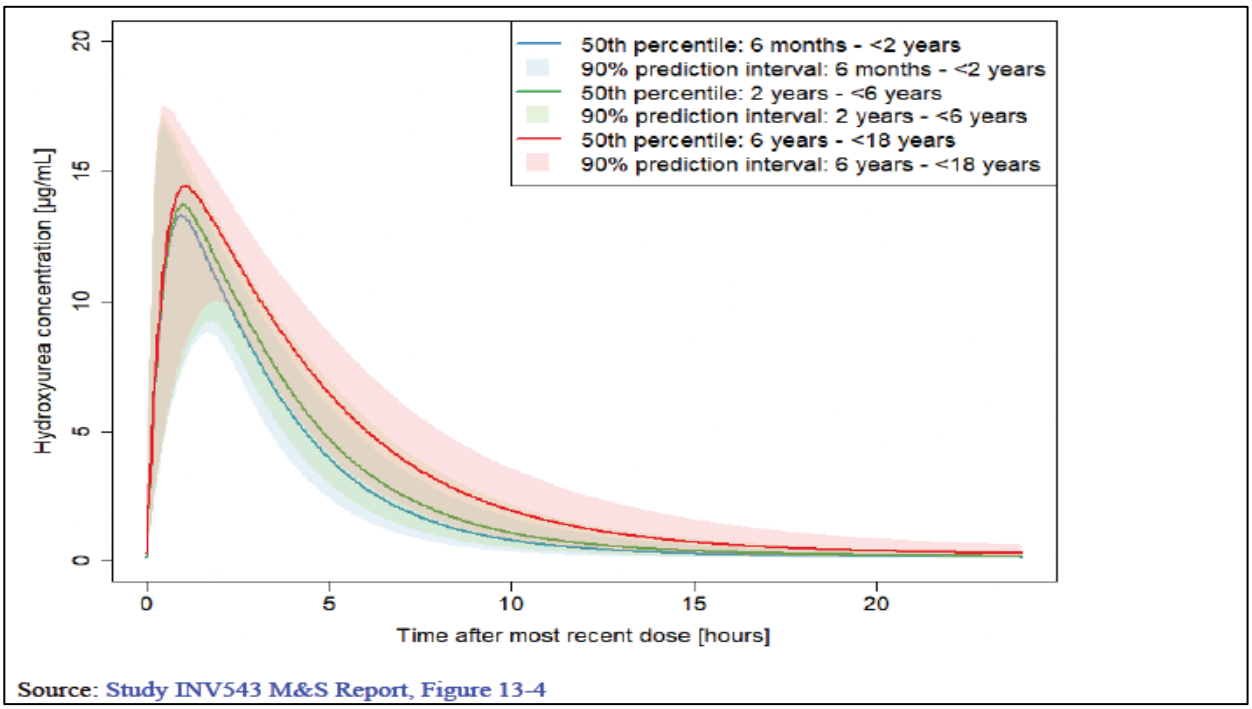
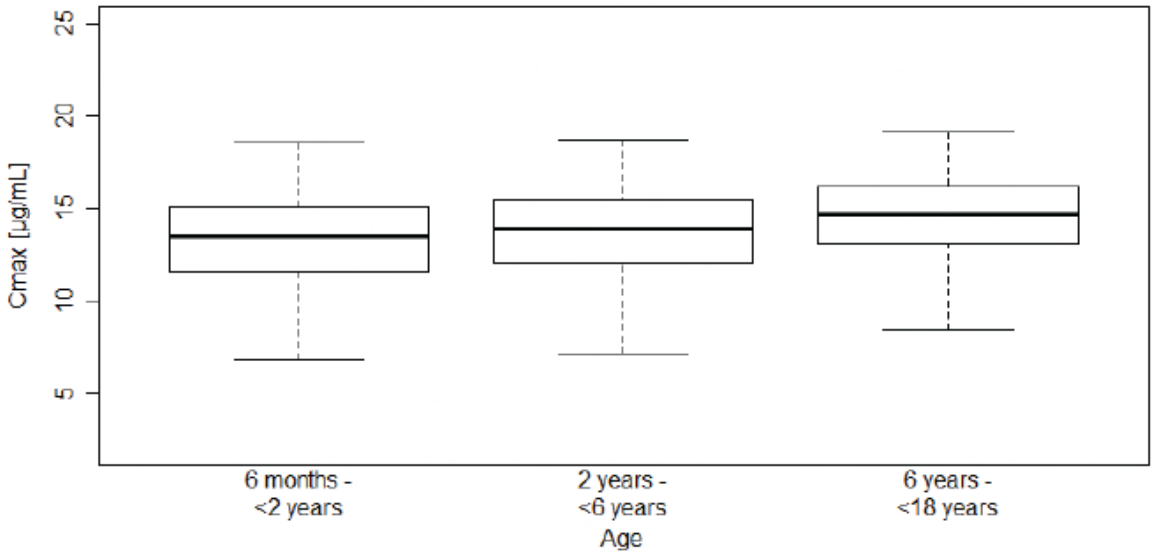
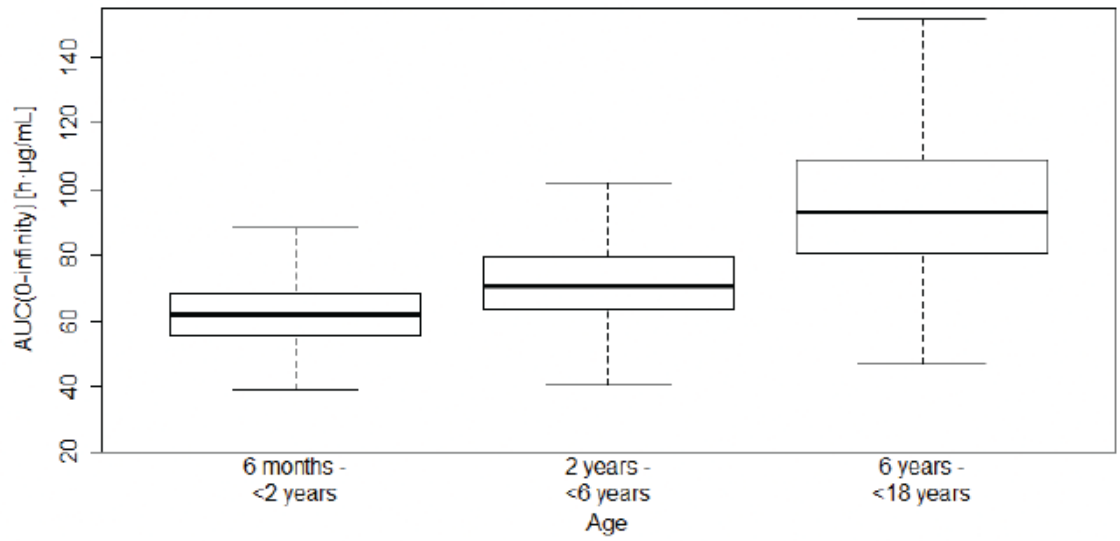


Figure 8: Paediatric Study INV543 Simulated Hydroxyurea PK Profiles after 8 Weeks of 15 mg/kg/day Stratified by Age Group



Source: Study INV543 M&S Report, Figure 13-5
C_{max} = maximum plasma concentration
Box-and-whisker plots are stratified by age group. Each box covers the interquartile range (IQR), with the median as the vertical black line inside the box, and with the whiskers extending to the last data point within the 1.5 times the IQR. 1000 virtual patients were simulated for each age group.

Figure 9: Paediatric Study INV543 Boxplot of Simulated Hydroxyurea C_{max} after 8 Weeks of 15 mg/kg/day Stratified by Age Group



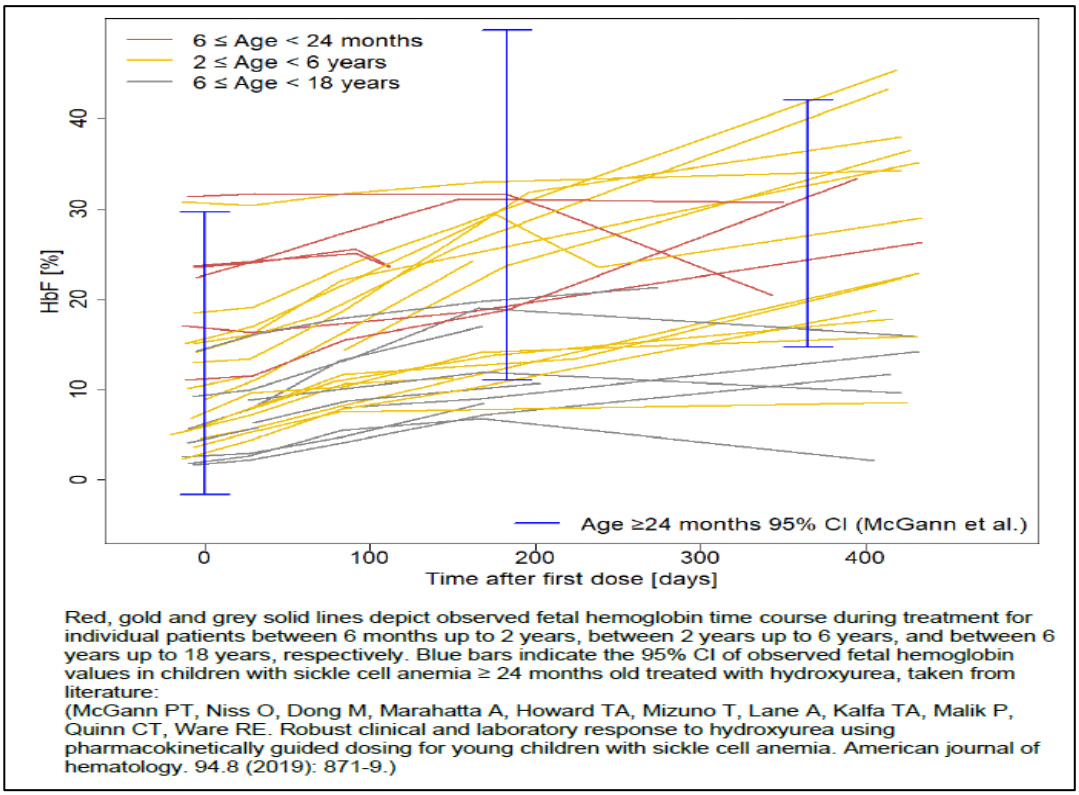
Source: Study INV543 M&S study report, Figure 13-6
AUC = area under the curve
Box-and-whisker plots are stratified by age group. Each box covers the interquartile range (IQR), with the median as the vertical black line inside the box, and with the whiskers extending to the last data point within the 1.5 times the IQR. 1000 virtual patients were simulated for each age group.

Figure 10: Paediatric Study INV543 Boxplot of Simulated Hydroxyurea $AUC_{(0\text{-}inf)}$ After 8 Weeks of 15 mg/kg/day Stratified by Age Group

Key efficacy Biomarker HbF

A spaghetti plot of foetal haemoglobin, showing trajectories for each individual and colored by age category, is shown in Figure 11. A second plot, this time showing locally weighted smoothing (LOESS) lines for each age category is given in Figure 12.

Both plots demonstrate the foetal haemoglobin response to hydroxyurea. Furthermore, the consistent response across the full age range of 6 months to 18 years is demonstrated.



Red, gold and grey solid lines depict observed fetal hemoglobin time course during treatment for individual patients between 6 months up to 2 years, between 2 years up to 6 years, and between 6 years up to 18 years, respectively. Blue bars indicate the 95% CI of observed fetal hemoglobin values in children with sickle cell anemia ≥ 24 months old treated with hydroxyurea, taken from literature:
(McGann PT, Niss O, Dong M, Marahatta A, Howard TA, Mizuno T, Lane A, Kalfa TA, Malik P, Quinn CT, Ware RE. Robust clinical and laboratory response to hydroxyurea using pharmacokinetically guided dosing for young children with sickle cell anemia. American journal of hematology. 94.8 (2019): 871-9.)

Figure 11: Spaghetti Plot of Individual Foetal Haemoglobin (HbF) Versus Time on Treatment

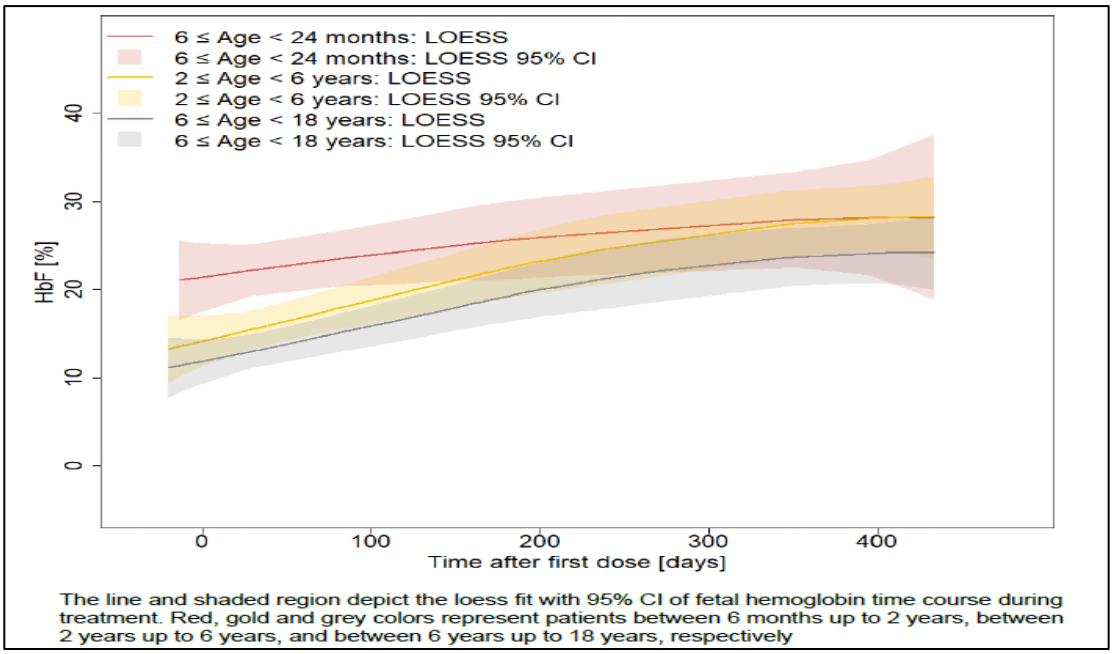


Figure 12: Loess Line Plot of Foetal Haemoglobin (HbF) Versus Time on Treatment

Additional simulations were requested using

- an adjusted popPK model with a maturation function on clearance.
- a newly developed indirect popPK-PD model for HbF with influence of age on the basal production rate of HbF.
- exposure data derived from relevant publications to confirm the model predictions in children <2 years of age.
- a newly developed popPK-PD model describing the influence of hydroxycarbamide PK on absolute neutrophil count (ANC) to assess the impact of hydroxycarbamide exposure on safety.

Simulations of systemic exposure variables using the popPK model with maturation function suggest that both AUC and Cmax are similar between children aged 6 months to < 2 years, 2 to < 6 years and 6 to <18 years of age. Indeed, even at the maximum 35mg/kg/day dose, exposure in infants 6 months to <2 years does not substantially differ from older children and adolescents.

Simulations of AUC(0-24)ss, Cmax,ss and HbF after 60 weeks of treatment stratified by age group and dosing regimen are provided in Figures below. Summary statistics are provided in Table 8. The results suggest that an increase in exposure corresponds to an increase in HbF irrespective of age.

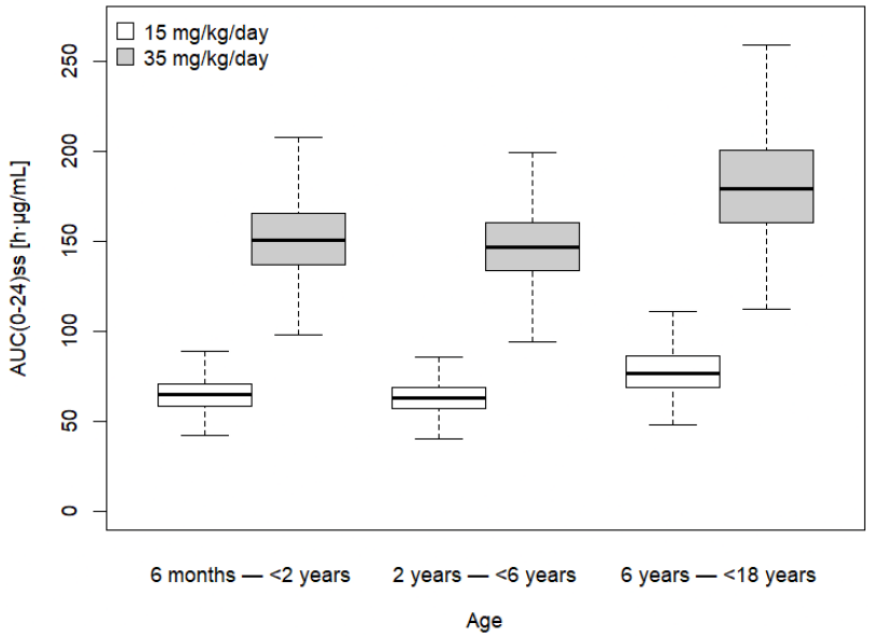


Figure 13: Boxplot of Simulated Hydroxycarbamide AUC(0-24)ss via the Adjusted popPK Model with Maturation Function Stratified by Age Group

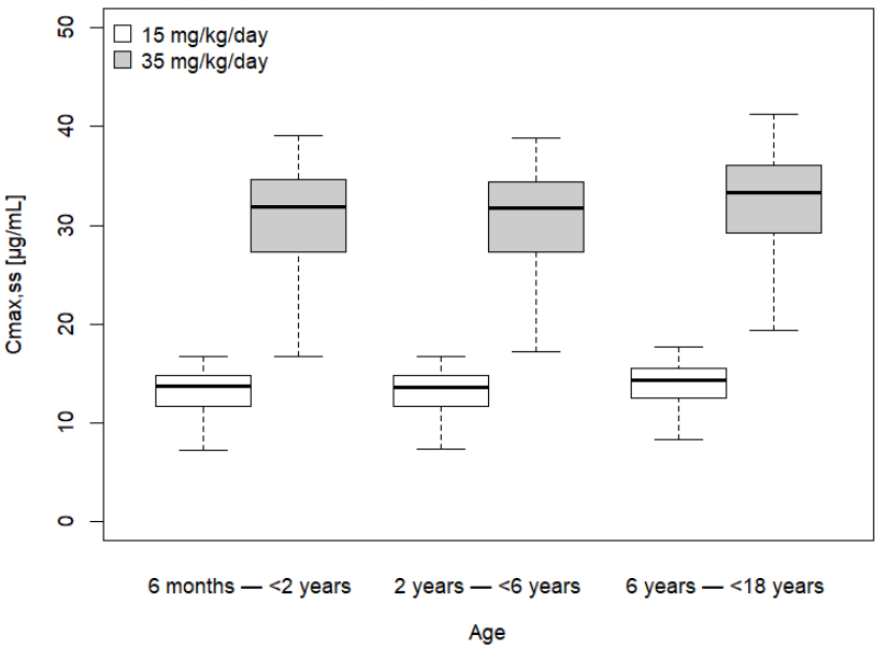
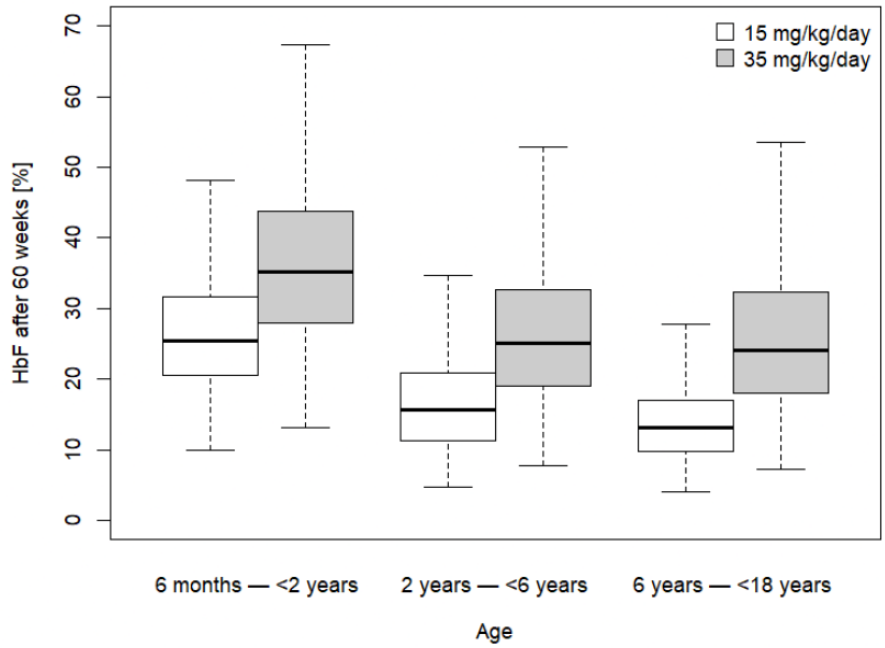


Figure 14: Boxplot of Simulated Hydroxycarbamide $C_{max,}$ss Via the Adjusted popPK Model with Maturation Function Stratified by Age Group



Box-and-whisker plots are stratified by age group. Each box covers the interquartile range (IQR), with the median as the vertical black line inside the box, and with the whiskers extending to the last data point within 1.5 times the IQR. 1000 virtual patients were simulated for each age and dosing group.

Table 8: Summary statistics of AUC (0-24)ss and HbF after 60 weeks of treatment via the final popPK-PD model for HbF (run731) stratified by age group

Age group	Dose per day	Measure[a]	5th perc.	Median	Arith. Mean	Geo. Mean	95th perc.
6 months – <2 years	15 mg/kg	AUC(0-24)ss	50.51	64.68	64.97	64.31	80.74
6 months – <2 years	15 mg/kg	HbF at 60 weeks	14.68	25.49	27.01	25.58	43.95
6 months – <2 years	35 mg/kg	AUC(0-24)ss	117.9	150.9	151.6	150.1	188.4
6 months – <2 years	35 mg/kg	HbF at 60 weeks	21.18	35.25	37.34	35.38	62.11
2 – <6 years	15 mg/kg	AUC(0-24)ss	50.46	62.91	63.37	62.78	78.05
2 – <6 years	15 mg/kg	HbF at 60 weeks	7.42	15.64	17.52	15.64	34.07
2 – <6 years	35 mg/kg	AUC(0-24)ss	117.7	146.8	147.9	146.5	182.1
2 – <6 years	35 mg/kg	HbF at 60 weeks	12.85	25.04	27.6	25.16	51.56
6 – <18 years	15 mg/kg	AUC(0-24)ss	58.34	76.83	77.82	76.79	99.16
6 – <18 years	15 mg/kg	HbF at 60 weeks	6.504	13.1	14.35	13.08	26.51
6 – <18 years	35 mg/kg	AUC(0-24)ss	136.1	179.2	181.6	179.2	231.3
6 – <18 years	35 mg/kg	HbF at 60 weeks	11.78	24.11	26.75	24.29	51.89

[a]AUC(0-24)ss units: h·µg/L. HbF at 60 weeks units: %.

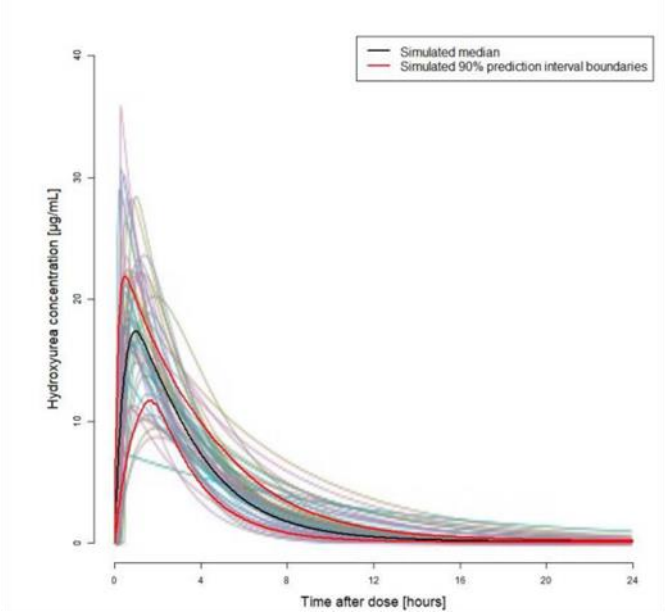


Figure 15: Final popPK Model Simulation Results Overlaid on PK Profiles of McGann *et al* (2019)

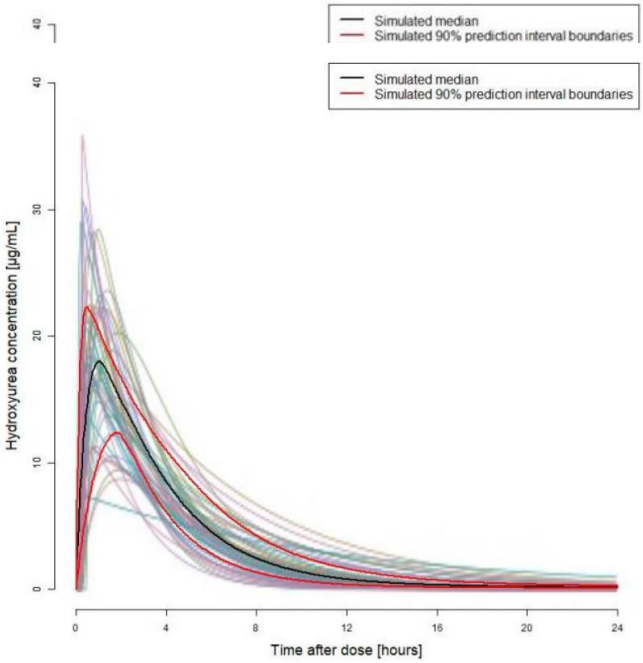


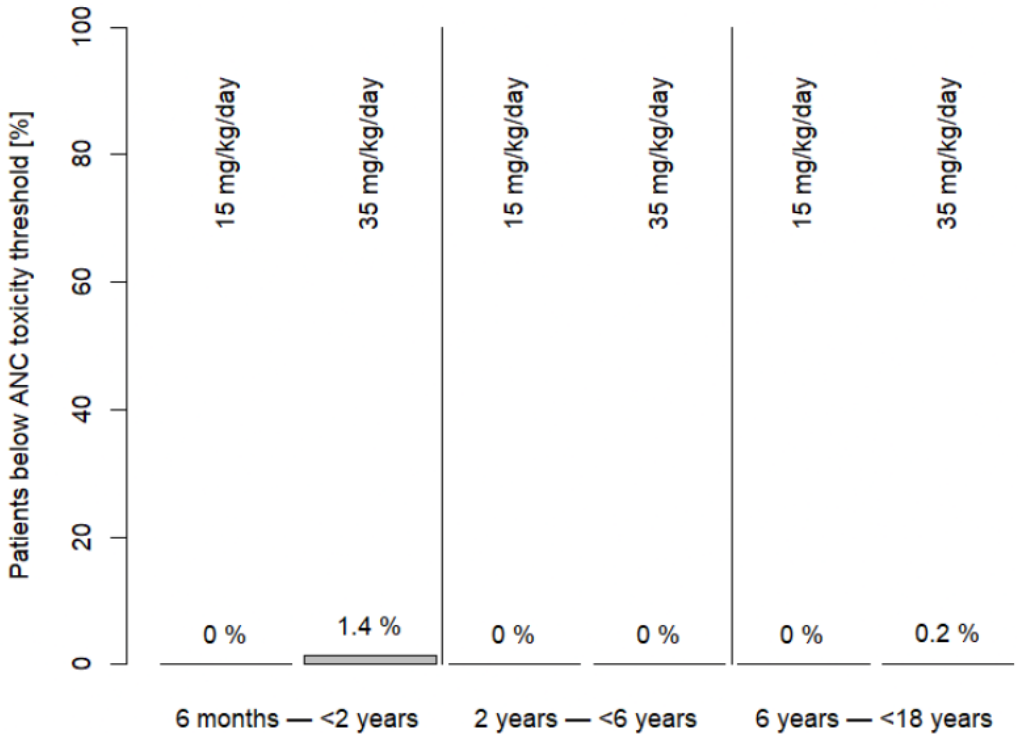
Figure 16: Maturation popPK Simulation Results Overlaid in PK Profiles of McGann *et al* (2019)

Figure 15 shows that the final popPK model produces a small underestimation of the median hydroxyurea concentration in this sample. This underestimation is improved by the addition of the maturation function in Figure 16, particularly in the 4 – 12 hours post-dose region where the median profile is roughly in the centre of the literature profiles. Overall, the simulations appear to display

similarity in the PK characteristics of the under 2 year old infants in this study population and that reported in the literature by McGann et al (2019).

Key Safety Biomarker ANC

Simulations of ANC after 60 weeks of treatment, summarized as percentage of patients that fall below the toxicity threshold of 1×10^9/L at any time, stratified by age group and dosing regimen are provided in Figure 17. Simulated AUC(0-24)ss distributions are visually identical to those in Figure 13. Summary statistics of AUC(0-24)ss and ANC levels at 60 weeks are provided in Table 9. The results suggest that although there is a statistically significant relationship between increasing exposure and decreasing ANC, the slope of this relationship is very shallow and the number of patients that drop below the toxicity threshold is rare (<1.5% across all dosing and age categories).



Bar plots are stratified by age group and dosing regimen. Bars (and text) represent percentage of simulated patients with an ANC value below $1\times10_9$ (toxicity threshold) following 60 weeks of treatment.

Figure 17: Simulated Percentage of Patients that Reach Toxicity Threshold via the Final popPK-PD model for ANC(run833) Stratified by Age Group

Table 9: Summary statistics of AUC(0-24)ss and ANC after 60 weeks of treatment via the final popPK-PD model for ANC (run833) stratified by age group

Age group	Dose per day	Measure[a]	5th perc.	Median	Arith. Mean	Geo. Mean	95th perc.
6 months – <2 years	15 mg/kg	AUC(0-24)ss	51.3	64.35	65.14	64.47	81.94
6 months – <2 years	15 mg/kg	ANC at 60 weeks	1.651	2.537	2.626	2.536	3.976
6 months – <2 years	35 mg/kg	AUC(0-24)ss	119.7	150.2	152	150.4	191.2
6 months – <2 years	35 mg/kg	ANC at 60 weeks	1.143	1.86	1.93	1.854	2.945
2 – <6 years	15 mg/kg	AUC(0-24)ss	50.13	63.23	63.52	62.95	77.8
2 – <6 years	15 mg/kg	ANC at 60 weeks	2.264	3.43	3.512	3.4	5.145
2 – <6 years	35 mg/kg	AUC(0-24)ss	117	147.5	148.2	146.9	181.5
2 – <6 years	35 mg/kg	ANC at 60 weeks	1.597	2.529	2.603	2.514	3.853
6 – <18 years	15 mg/kg	AUC(0-24)ss	59.33	76.28	77.33	76.35	98.73
6 – <18 years	15 mg/kg	ANC at 60 weeks	2.719	4.083	4.223	4.091	6.097
6 – <18 years	35 mg/kg	AUC(0-24)ss	138.5	178	180.4	178.2	230.3
6 – <18 years	35 mg/kg	ANC at 60 weeks	1.713	2.762	2.827	2.722	4.24

[a] AUC(0-24)ss units: h·µg/L. ANC at 60 weeks units: 10^9/L.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 10: Summary of Efficacy for trial INV543

Title: A Prospective Open Label, Pharmacokinetic Study of an Oral Hydroxyurea Solution in Children with Sickle Cell Anaemia			
Study identifier	INV543		
Design	A prospective open label, PK study of oral HU solution administered to study participants aged from 6 months to 17.99 years (i.e. to the day before 18th birthday) (n=6 participants aged 6 months to 1.99 years, n=16 participants aged 2 to 5.99 years and n=11 participants aged 6 to 17.99 years), with a 12- to 15-month treatment period for each participant. The study treatment duration was for 6 months at the maximum tolerated dose (MTD), which was usually reached by 6 months after initiation of treatment. For study participants in whom time to MTD was longer than 6 months or not achieved at all, the maximum duration of study treatment was 15 months. All children with sickle cell anaemia (SCA) initiating oral HU therapy were eligible for recruitment into the study. All study participants started on an oral dose of 15 mg/kg HU once daily. The dose was escalated by 5 mg/kg/day every 8-12 weeks until the MTD was achieved (defined as occurrence of hematological toxicity, an ANC of 1-3 ×109/L, or a maximum dose of 35 mg/kg/day). Once the MTD was established, treatment was maintained for a maximum of 12-15 months. Doses were calculated based on most current bodyweight (measured at each in-clinic visit). Doses were rounded where necessary to the nearest 10 mg. The PK of oral HU solution was evaluated on two PK days: Day 1 and ~6 months later. Additional single PK samples were taken at interim clinic visits where feasible. Safety endpoints mirrored those of current standard care where possible, with participants evaluated at 2- to 4-week intervals for the first 2 months, then 4- to 12-week intervals thereafter (up to 12 weeks maximal between in-clinic visits, 4 weekly safety telephone calls were mandatory between in-clinic visits), with a combination of in-clinic and telephone visits. Palatability and acceptability were assessed once after 8 weeks.		
	Duration of main phase:		12 to 15 months (or 6 months after MDT reached) 03 JAN 2019–12 APR 2022
Hypothesis	N/A		
Treatments groups	N/A		This was a single arm study and no placebo was used.
Endpoints and definitions	Primary endpoint	open label	To determine the pharmacokinetics (PK) of oral hydroxyurea (HU) solution (a population PK [popPK] approach was adopted to characterize the PK in this population)
	Secondary endpoint	open label	To further evaluate the safety of oral HU solution. Safety endpoints included the incidence of adverse events (AEs).
	Secondary endpoint	open label	To investigate the effects of HU dose escalation on laboratory parameters: To assess effects on foetal haemoglobin (HbF), haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count and differentials, absolute neutrophil count (ANC), absolute reticulocyte count (ARC), platelets, bilirubin, cystatin C and lactate dehydrogenase (LDH)
	Secondary endpoint	open label	To investigate the effects of HU dose escalation on clinical parameters: To assess effects on pain, transfusions, hospitalizations, and acute chest syndrome (ACS)
	Secondary endpoint	open label	To assess the acceptability and palatability of oral HU solution

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Results and Analysis		
Analysis description	**Primary and Secondary Analysis**	
Analysis population and time point description	*Number of study participants (planned and analyzed):* • Number of study participants planned: 35 (male and female) • Number of study participants analyzed: 33 enrolled, 32 initiated treated • Number of study participants withdrawn: 9 • Number of study participants completed: 24 *Diagnosis and Main Criteria for Inclusion:* 1. Male or female aged from 6 months to 17.99 years of age (i.e. to the day before their 18th birthday). 2. Diagnosis of SCA (HbSS and HbSβ 0 genotype). 3. Parent(s)/legal guardian were able and willing to provide written informed consent for the child to take part in the study. 4. Where applicable, the study participant assented to undergoing blood sampling for PK and biochemistry purposes and to allowing physiological measurements to be made. *Doses:* 15 mg/kg once daily (oral HU 100mg/mL solution). Escalated by 5 mg/kg/day every 8-12 weeks until maximum tolerated dose achieved.	
Descriptive statistics	Treatment group	N/A (This was a single arm study and no placebo was used)
	Number of subjects	32 (n=6 participants aged 6 months to 1.99 years, n=16 participants aged 2 to 5.99 years and n=11 participants aged 6 to 17.99 years) [36 children were screened for the study of whom 33 were enrolled as study participants and 32 received at least one dose]
	Primary endpoint: PK Data Analysis	The data from all participants taking part in the study were pooled and analysed simultaneously to avoid excessive blood sampling. Population PK parameters were estimated using a non-linear, mixed effects modelling approach. In the population approach, all data from different individuals were fitted simultaneously using a non-linear, mixed effects model and post hoc individual kinetic parameters were calculated. An appropriate software package (NONMEM) was used to conduct the analysis. One interim analysis was planned; when all study participants completed approximately 9 months of the study (i.e. when the last study participant reached their Week 40 visit). The interim analysis was to include all study endpoints described in the Statistical Analysis Plan (SAP).
	Secondary endpoint: Safety Analyses	Safety analyses included summaries of physical examinations, clinical laboratory results (where possible in-clinic), and AE reports. Adverse events were Medical Dictionary for Regulatory Activities (MeDRA) coded and presented by relatedness, severity, and body system. Serious AEs (SAEs) were listed in detail, describing the timing of each event, the nature, severity, seriousness, and relatedness of the event. Additional analyses could be conducted if the number of events permitted.
Effect estimate	Primary endpoint: AUC	The median AUC(0-inf) increased from 61.8 h*µg/mL, for children aged between 6 months and 1.99 years, to 70.6 h*µg/mL, for children aged between 2 and 5.99 years, and to 93.1 h*µg/mL, for children aged between 6 and 17.99 years. However, the distribution of AUC(0-inf) exposure overlapped considerably across age groups.

	Primary endpoint: Cmax	The influence of age on Cmax was less pronounced with median Cmax increasing from 13.4 µg/mL for children aged between 6 months and 1.99 years, to 13.9 µg/mL, for children aged between 2 and 5.99 years, and to 14.7 µg/mL, for children aged between 6 and 17.99 years.
	Primary endpoint: popPK model	Further simulations using the final popPK model following 8 weeks of 15 mg/kg/day HU demonstrated that systemic exposure predicted with the novel oral liquid formulation were comparable with values reported in the literature by Dong et al. 2016 from 96 paediatric patients.
	Secondary endpoint: laboratory parameters	%HbF (HbF as a proportion of HbF+HbS) increased in all age groups during treatment. In addition total Hb, MCV and MCH increased with time, while the platelet, ARC, WBC, ANC counts, LDH and bilirubin levels all decreased. Other secondary safety laboratory parameters (aspartate aminotransferase [AST], alanine aminotransferase [ALT], gamma glutamyl transferase [GGT], alkaline phosphatase [ALP]) showed no appreciable change over the course of the study.
	Secondary endpoint: hospitalizations	Overall, a marked numerical reduction in hospitalizations was observed over the 12 months following first dose of investigational medicinal product (IMP) compared with the 12 months prior to treatment.
	Secondary endpoint: palatability	Overall mean palatability scores were over 80% for smell and taste, and the mean (standard deviation) overall visual analogue scale aftertaste score was 62.1 (35.07) mm. Aftertaste scores in the 6 months–1.99 ears and 2–5.99 years age groups should be treated with caution as only one study participant in each group responded that they still taste the drug minutes after taking it.
	Secondary endpoint: time-averaged mean velocity (TAMV)	Any change noted in maximum time-averaged mean velocity (TAMV) transcranial Doppler category was a downgrading of abnormality.
	Secondary endpoint: safety	All except one of the 32 study participants in the Safety Population experienced at least one TEAE, which was expected given the serious and debilitating nature of SCA. There were 28 related TEAEs in 9 participants, the most frequent of which were isolated and transient occurrences of hematological toxicity, which were typically associated with recent or concurrent illness (viral and upper respiratory tract infections). All SAEs and most of the Grade $\geqslant$3 AEs were considered unrelated to IMP and were indicative of the typical complications of SCA. No study participants died during the study and only one study participant (03-007) was discontinued permanently from IMP due to an unrelated AE (Principal investigator discretion to allow use of HU off-protocol). Laboratory results, vital signs and physical examination results were unremarkable except for isolated occurrences of hematological toxicity which were an expected result of dose titration.

Supportive studies

The applicant submitted several published clinical studies that support the efficacy of hydroxycarbamide in paediatric SCD patients.

The randomized controlled studies that include children under age 2 which were submitted were Wang et al. 2011 (BABY HUG), Thornburg et al. 2012 (BABY HUG follow-up) and Opoka et al. 2017 (NOHARM).

BABY HUG was the first randomized, double blind, multicenter, placebo-controlled trial in infants aged 9-18 months. 193 infants with mean age of 13,6 months (SD 2.7) participated, with 24-month follow-up, in 13 centers in USA, and even though the study did not show prevention of reduction in splenic function, it showed improved clinical results in the treated group compared to the placebo group.

The findings in the Baby Hug trial can be summarised as follows: 96 patients received hydroxycarbamide and 97 placebo, of whom 83 patients in the hydroxycarbamide group and 84 in the placebo group completed the study. Significant differences were not seen between groups for the primary endpoints (19 of 70 patients with decreased spleen function at exit in the hydroxycarbamide group vs 28 of 74 patients in the placebo group, p=0·21; and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1·73 m(2), p=0·84). Hydroxycarbamide decreased pain (177 events in 62 patients vs 375 events in 75 patients in the placebo group, p=0·002) and dactylitis (24 events in 14 patients vs 123 events in 42 patients in the placebo group, p<0·0001), with some evidence for decreased acute chest syndrome, hospitalisation rates, and transfusion. Hydroxyurea increased haemoglobin and foetal haemoglobin, and decreased white blood-cell count. Toxicity was limited to mild-to-moderate neutropenia.

However, hudroxyurea was given as a fixed dose of 20 mg/kg/day of the oral solution and the lower age limit was from 9 months of age.

NOHARM was a randomized, double blind, placebo-controlled trial in 207 children aged 1-4 years old, with 12-month follow-up, in Uganda, which showed improved secondary outcomes in the treated group compared to the placebo group. However, hudroxyurea was given as a fixed dose of 20±2.5 mg/kg/ day, the age limit was 12 months of age and the primary outcome was incidence of clinical malaria, and not efficacy/safety endpoints related to SCD.

The reviews which according to the applicant provide evidence of benefit in MTD dosing in infants under 2 Years and were submitted were George & Tran (2020) and Karkoska et al (2021).

George & Tran (2020) conducted a retrospective chart review of infants under the age of 2 years with HbSS or HbS β0 thalassemia. 97 patients continued treatment with the intention of advancement to an MTD, and 86 successfully reached this level of therapy. Among patients escalated to MTD, the mean dose was 22.0 ± 4.8 mg/kg/day. Thus, the mean MTD of 22 mg/kg is considered very comparable to the fixed dose of BABY HUG (20 mg/kg) and is not considered indicative of the superiority of MTD vs fixed dose.

Furthermore, as the applicant has already mentioned, comparisons between the cohort of patients in this study and the BABY HUG hydroxycarbamide treatment arm are not considered feasible, because of the difference in patient populations, time of analysis, and study procedures between the 2 groups.

Karkoska et al (2021) is a retrospective review exhibiting a trend to prescribe HU earlier in children after 2014 in accordance to published guidelines (NHLBI 2014). It is stated that >90% of children have already started HU at the age of 11 months compared to only 10% of children younger than 6 years before 2013. The exact number of patients <2 years is not stated. Only IQR 8-17 is mentioned. Only 3 children 6 months - 2 years of age participated in the review for the whole period and the youngest participant was 10 months old. Furthermore, this retrospective review reflecting change of policy in a single center was not designed to evaluate safety and efficacy, and even though it was associated to a reduction in SCD-related admissions, it does not provide robust data for an extension of indication to children from 6 months of age.

2.4.3. Discussion on clinical efficacy

Xromi is approved for the prevention of vaso-occlusive complications of sickle cell disease in patients older than 2 years of age. The present application requested the extension of indication to patients older than 6 months of age. The applicant provided results from study INV543 which is a non-comparative, not randomized, open-label, PK efficacy and safety study. Considering that the primary objective of the study INV543 was PK and the fact that only 6 patients in the proposed new age range (6 months-2 years) were included in the study while no patient was <10 months of age, a potential approval of the extension of the indication has to be based on extrapolation of efficacy and safety from older children and adults.

The applicant was requested

1. to discuss if the disease is sufficiently similar in children aged 6 months-9 months and 9 months-2 years, respectively, compared to older children/adults to support a PK/PD extrapolation approach.
2. to justify the therapeutic rationale of the use of HU in the age population of 6-9 months with SCD, taking into account disease characteristics and HbF levels in this age group, based on available literature data.

Although SCD has similar underlying pathophysiological processes regardless of age, the manifestation of the disease is not the same in all age groups of SCD patients. The applicant claimed that major differences do not appear between the 6-9 month age group compared to 9 month-2 year age group, plus the pathophysiological processes of SCD which result in serious complications later in childhood seem to begin early at around 6 months of age as HbF dissipates (from around 80% at birth to 30-40% by 6 months of age and to less than 10% by 1 year). Based on these claims of the applicant, levels of HbF of 30-40% at 6 months of age are a lot higher than the level of around 20% which is associated with reduced clinical symptoms (Estepp et al, 2017) and can prevent complications of SCD (Steinberg et al, 2014).

Various literature sources describe cases of SCD clinical symptom manifestations (pain crises, dactylitis, anaemia) as early as 6 months of age and even below, but the data on the very young children <9 months is very limited and only a subset of SCD patients present disease manifestation this early. Even though it is agreed that the data is scarce (due to the disease rarity), it suggests that early intervention might be needed in some cases of severe disease. Further, some publications suggest that uncontrolled sickle haemoglobin polymerization might take place already with HbF<30-35%. Further, the decline trajectories of HbF with age might differ substantially between individuals.

Early intervention might be needed in some cases of severe disease and some authors suggest the possibility of starting from 6 months (Schuchard SB et al, 2019; Ware RE et al, 2019; Elenga N et al, 2022). However, as data available for a strong recommendation in this sense are not yet available, it will have to be evaluated on a case-by-case basis.

Furthermore, in study INV543 there were no patients <10 months of age. The small number of patients included in the pivotal study could have been overcome provided clear conclusions could be drawn from PK/PD data and clinical extrapolation in children below 9 months of age, however, this is not the case as per assessment of the responses provided by the MAH, failing to demonstrate clinical relevance, PK/PD extrapolation and adequate posology definition.

For the age group of 9 months to 2 years of age, the proposed maximum tolerated dose (MTD) of 35 mg/kg/day can be considered acceptable based on the adjusted popPK-PD model with maturation function, on popPK-PD modelling for HbF and on popPK-PD modelling for ANC, and on the extrapolation of data from older children.

Furthermore, the fact that the proposed posology is based on titration on an individual basis, with initiation at the lowest dose of 15mg/kg/day and incrementally increasing by 5mg/kg/day every 8 weeks until a mild myelosuppression is achieved (i.e. ANC 1.5 to 4 $\times 10^9$/L, whilst maintaining platelet count > 80 $\times 10^9$ /L), or a maximum dose of 35 mg/kg/day is achieved, while laboratory safety monitoring is conducted initially every month for 2 months and then every 2- 3 months once a MTD is achieved, is considered the best option for the treatment of children of this age.

As far as secondary efficacy endpoints in study INV543 are concerned, there was a difference after the treatment with hydroxycarbamide in subjects between 6 months and 2 years of age in the secondary efficacy endpoints of some laboratory parameters. The increase in %HbF relative to baseline was modest for the 6 months–1.99-year age group (mean [SD] increase relative to baseline: 43.17% [84.593%]), the final proportion was numerically similar to that observed for the 2–5.99-year age group (mean [SD] final level: 26.32% [4.893%]). However, there was no difference in this age group concerning the secondary efficacy endpoints of frequency of acute complications and hospitalizations, frequency of infections, and clinical symptoms. The observed decline in average time-averaged mean velocity (TAMV) which shows decreased stroke risk was -1 in this age group (standard deviation could not be calculated).

PK/PD extrapolation to the younger subjects <9 months, including posology, does not seem possible due to a) the lack of PK/PD data, b) unknown ontogeny of metabolizing enzymes, c) change in renal clearance of HU and d) potential impact of the high HbF levels on the needed dose in these young subjects.

Additionally**,** in literature data provided by the applicant, the number of patients below 9 months of age who participated in the studies is either not defined or very small and that's why these studies are inadequate to provide robust data on efficacy and safety of hydroxycarbamide in this age group (for example, only 2 patients <9 months in Thomas et al, 2019, number of patients starting from 8.1 months of age not defined in George et al [12.0 ± 3.9 months of age, n=24]). On the other hand, in various studies in a significant number of children > 9 months of age (including HUSOFT, BABY HUG, Thomas et al, 2019, George et al, 2020), hydroxycarbamide showed clinical benefit in several clinical outcomes (decrease in pain, dactylitis, ACS syndrome, hospitalization).

Considering that both adequate clinical data in the age group of 6-9 months from literature are not yet available and there is absence of observed PK and PD data in the age group of 6-9 months from study INV 543 to support extrapolation of efficacy and safety, the B/R in the age group of 6-9 months of age is considered negative and the applicant was requested to narrow the indication to children from 9 months of age.

2.4.4. Conclusions on the clinical efficacy

Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age. The clinical data support the extension of the above indication to patients over 9 months of age.

The following recommendation was agreed to address issues related to efficacy:

A PASS study was agreed :

"A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study To evaluate the long-term two-year comparative safety and efficacy of hydroxycarbamide oral solution 100 mg/ml (Xromi) administered to children under 2 years of age for the prevention of complications of Sickle Cell Disease)

2.5. Clinical safety

Introduction

Xromi has been approved as a hybrid medicinal product with Hydrea as the reference medicinal product.

The safety profile for hydroxycarbamide in people with SCD is derived from 3 RCTs that enrolled 517 people and almost 50 observational studies that enrolled more than 3,000 people. In addition, in patient populations other than SCD, toxicity evidence is derived from 21 RCTs that enrolled more than 4,800 individuals and 35 observational studies that enrolled more than 7,500 individuals (NIH Expert Panel Report 2014). The safety profile of Xromi is described in detail in the EPAR of the product. According to the SmPC of the product, bone-marrow suppression is the major toxic effect of hydroxycarbamide and is dose related. At lower doses, mild, transient and reversible cytopenias are commonly reported in Sickle Cell Disease patients which is expected based on the pharmacology of hydroxycarbamide. Hydroxycarbamide affects spermatogenesis, and hence oligospermia and azoospermia are very commonly reported. Other commonly reported adverse effects also include nausea, constipation, headache, and dizziness. Adverse reactions affecting the skin and subcutaneous tissue such as darkening of the skin and nail beds, dry skin, skin ulcers, and alopecia tend to occur following several years of long-term daily maintenance therapy. Rarely leg ulcers and very rarely systemic lupus erythematosus have been reported. There is also a serious risk of leukaemia and in the elderly, skin cancer, although the frequency is not known. In the event of bone marrow suppression, haematological recovery usually occurs within two weeks of withdrawal of hydroxycarbamide. Gradual dose titration is recommended to avoid more severe bone marrow suppressions. The macrocytosis caused by hydroxycarbamide is not vitamin B12 or folic acid dependent. The anaemia commonly observed has mainly been due to an infection with Parvovirus, splenic or hepatic sequestration, renal impairment. Weight gain observed during treatment with hydroxycarbamide may be an effect of improved general conditions. Oligospermia and azoospermia caused by hydroxycarbamide are in general reversible, but have to be taken into account when fatherhood is desired (see section 5.3). These disorders are also associated with the underlying disease.
Xromi is contraindicated in severe hepatic impairment (Child-Pugh classification C), severe renal impairment (CrCl < 30 ml/min), breastfeeding, pregnancy and concomitant anti-retroviral medicinal products for HIV disease. Hydroxycarbamide is unequivocally genotoxic in a wide range of test systems. Hydroxycarbamide is presumed to be a trans-species carcinogen.

Safety results for Paediatric Study INV543 are presented in this report. The study objective for safety included an assessment of the incidence of adverse events (AEs). AEs were coded using MedDRA version 23.1. Treatment-emergent adverse events (TEAEs) were evaluated by relatedness to study drug and by severity according to Common Terminology Criteria for Adverse Events (CTCAE) criteria. The safety population (N=32), which included all enrolled study participants who received at least 1 dose of study medication, was used for all analyses of baseline characteristics, secondary and exploratory outcomes, as well as all safety outcomes.

Patient exposure

Paediatric Clinical Study INV543 in Children with SCA

Xromi dosing and treatment compliance for Study INV543 are summarized briefly herein. The starting dosage for all 32 study participants was 15 mg/kg/day. If dose escalation was warranted based on clinical and laboratory findings, it was to be increased in 5-mg/kg/day increments every 8-12 weeks,

until an MTD was reached or to a maximum of 35 mg/kg/day. Doses were calculated based on most current bodyweight (measured at each in-clinic visit) and were rounded to the nearest 10 mg. The Xromi dose escalation criteria are detailed in Study INV543 Table 11 below.

Table 11: Hydroxyurea Dose Escalation Criteria

Starting dosage for all study participants: 15 mg/kg/day

- Complete blood count (CBC) with WBC differential and ARC were monitored about every 4 weeks when adjusting dosage
- The target ANC was 1-3 x 10^9/L; however, with a platelet count >80 x 10^9/L
- If hematological toxicity occurs as defined by:
  - Neutropenia (ANC <1.0 x 10^9/L)

If ANC was <1.5 x 10^9/L, CBC was to be repeated in a week if there were no concerns about toxicity, maintained at the same dose

- In the event of the following CBC results, HU dosing was to be stopped temporarily and CBC with WBC differential monitored weekly until toxicity resolved:
  - Thrombocytopenia (platelets <80 x 10^9/L)
  - Absolute reticulocyte count <80 x 10^9/L, unless Hb concentration >9.0 g/dL,
  - A 20% decrease in Hb concentration from baseline, or Hb <4.5 g/dL.
- If hematological toxicity resolved in 1 week HU was to be restarted at the same dose.
- If hematological toxicity persisted for >1 week or occurred twice in a 3-month period, the HU dose was to be withheld until recovery and then reduced by about 2.5 mg/kg/day, or at a dose of 2.5-5.0 mg/kg/day lower than the dose given before the onset of cytopenias.
- If a dose escalation was warranted based on clinical and laboratory findings, typically failure to achieve mild neutrophil and reticulocyte suppression, guidance recommended to proceed as follows:
  - Dose increased by 5 mg/kg/day increments every 8-12 weeks at in-clinic visits.
  - Give until mild myelosuppression (ANC of 1-3 x 10^9/L) was achieved.
    - However, if ARC remained high (>200 x 10^9/L), dose escalation could continue if clinically indicated, to achieve the optimal dosing.
- Dose was not to exceed a maximum dose of 35 mg/kg/day.
- Once a stable dose had been established, laboratory safety monitoring included CBC with WBC differential, ARC, platelet count and blood chemistry every 4-12 weeks *(C** extended to up to a maximum of 12 weeks during active pandemic periods at Investigator discretion when safe to do so).*
  - *C** As the period between in-clinic safety review could be up to 12 weeks at Investigator discretion, 'stable' study participants showing trends towards toxicity could be treated proactively to ensure study participant safety until the study participants next in-clinic safety review (including dose reductions or temporary halts, as applicable).*

ANC, absolute neutrophil count; ARC, absolute reticulocyte count; CBC, complete blood count; Hb, hemoglobin; HU, hydroxyurea; WBC, white blood cell.

For the starting dose of 15 mg/kg/day, mean Xromi dose rose to 25.82 (SD 5.681) mg/kg/day at study completion/withdrawal. MTD was achieved by 20 (62.5%) participants overall. For many participants, dose titration occurred against a backdrop of stringent hospital regulations and procedures designed to minimize risk associated with the global COVID-19 pandemic. This limited the number of in person visits that were required to provide data for the safety of dose escalations. The highest proportion of study participants achieving MTD was in the 6-months – 1.99-years age group (5/6 participants; mean [SD] MTD: 23.5 [8.944] mg/kg/day) and the lowest was in the 2 – 5.99-year group (9/16 participants; mean [SD] MTD: 26.11 [5.465]). Under more normal circumstances and without the pandemic-related reduced frequency of study visits, MTD may have been achieved sooner and in more study participants.

The median number of participant-reported missed doses over the time preceding each visit was 0, until the Week 52-60/end of study visit when there was a median of 4 missed doses. There were 69 protocol deviations related to dosing of study drug reported for 24 (72.7%) study participants. Despite the ongoing pandemic resulting in study participants being considered "clinically vulnerable," all participants who wished to remain in the study were kept on drug, albeit with minor dosing irregularities in some cases and with adaptations to reduce the requirement for in clinic visits in line with standard care.

Adverse events

Overall, all study participants, except 1 in the 2 – 5.99 age category, experienced at least 1 AE. There were 339 AEs in 31 study participants in Study INV543, all of which were TEAEs with 28 events (in 9 participants) assessed to be at least possibly related to study drug. There were 7 Serious adverse events (SAEs) (in 6 study participants), and no deaths. AEs were distributed roughly in proportion to the number of study participants in each age group, with TEAEs determined to be at least possibly related to study drug more frequent in the <2-year-old age group (29.2%) (**Table 12**).

Table 12: Paediatric Study INV543 Overview of Adverse Events (Safety Population)

	6 Months – 1.99 years		2 – 5.99 years		6 – 17.99 years		Overall	
	Participants (N=6)	**Events (N=65)**	**Participants (N=16)**	**Events (N=148)**	**Participants (N=10)**	**Events (N=126)**	**Participants (N=32)**	**Events (N=399)**
Any AEs (n [%])	6 (100)	65 (100)	15 (93.8)	148 (100)	10 (100)	126 (100)	31 (96.9)	339 (100)
All TEAEs	6 (100)	65 (100)	15 (93.8)	148 (100)	10 (100)	126 (100)	31 (96.9)	339 (100)
Related to study drug	4 (66.7)	19 (29.2) *	4 (25.0)	5 (3.4)	1 (10.0)	4 (3.2)	9 (28.1)	28 (8.3)
*Leading to treatment discontinuation**	1 (16.7)	6 (9.2)	0	0	0	0	1 (3.1)	6 (1.8)
Serious	0	0	3 (18.8)	3 (2.0)	3 (30.0)	4 (3.2)	6 (18.8)	7 (2.1)
Fatal outcome	0	0	0	0	0	0	0	0

AE, adverse event; TEAE, treatment-emergent AE.
*1 participant in the 6 months – 1.99 years age category accounted for 13 of these TEAEs related to study drug and all 6 of those lead to treatment discontinuation, of which only 1 unrelated TEAE was ultimately deemed the reason for withdrawal.

Analysis of Adverse Events by Organ System

In paediatric study INV543 in children with SCA, the SOCs of TEAEs reported most frequently were Infections and infestations [n=99 TEAEs (29.2%) in 26 participants (81.3%)], Blood and lymphatic disorders [n=61 TEAEs (18.0 %) in 22 participants (68.8%)], Respiratory, thoracic and mediastinal disorders [38 TEAEs (11.2%) in 17 participants (53.1%)], and Gastrointestinal disorders [29 TEAEs (8.6%) in 17 participants (53.1%)] (Study INV543 Table 12-2). These TEAEs are largely reflective of the complications of SCA.

Overall the TEAEs occurring most frequently in study INV543 participants were SCA with crisis (53 events in 18 participants), upper respiratory tract infection (43 events in 17 participants), pyrexia (16 events in 9 participants), cough (7 events in 7 participants), vomiting (27 events in 6 participants), and abdominal pain (7 events in 6 participants) (Table 13 below).

Table 13: Paediatric Study INV543 Summary of Treatment-Emergent Adverse Events (≥ Study Participants) by System Organ Class and Preferred Term (Safety Population)

Primary system organ class (n [%]) *Dictionary-derived term*	6 Months - 1.99 years		2 years – 5.99 years		6 years – 17.99 years		Overall	
	Participants (N=6)	Events (N=65)	Participants (N=16)	Events (N=148)	Participants (N=10)	Events (N=126)	Participants (N=32)	Events (N=339)
Blood and lymphatic system disorders	4 (66.7)	5 (7.7)	10 (62.5)	17 (11.5)	8 (80.0)	39 (31.0)	22 (68.8)	61 (18.0)
Neutropenia	2 (33.3)	2 (3.1)	0	0	0	0	2 (6.3)	2 (0.6)
Sickle cell anaemia with crisis	1 (16.7)	1 (1.5)	9 (56.3)	13 (8.8)	8 (80.0)	39 (31.0)	18 (56.3)	53 (15.6)
Thrombocytopenia	1 (16.7)	2 (3.1)	1 (6.3)	1 (0.7)	0	0	2 (6.3)	3 (0.9)
Gastrointestinal disorders	3 (50.0)	6 (9.2)	9 (56.3)	16 (10.8)	5 (50.0)	7 (5.6)	17 (53.1)	29 (8.6)
Abdominal pain	2 (33.3)	2 (3.1)	4 (25.0)	5 (3.4)	0	0	6 (18.8)	7 (2.1)
Constipation	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Diarrhoea	2 (33.3)	2 (3.1)	2 (12.5)	3 (2.0)	0	0	4 (12.5)	5 (1.5)
Gastritis	0	0	0	0	2 (20.0)	2 (1.6)	2 (6.3)	2 (0.6)
Vomiting	1 (16.7)	1 (1.5)	3 (18.8)	3 (2.0)	2 (20.0)	2 (1.6)	6 (18.8)	6 (1.8)
General disorders and administration site conditions	4 (66.7)	9 (13.8)	7 (43.8)	15 (10.1)	3 (30.0)	3 (2.4)	14 (43.8)	27 (8.0)
Influenza like illness	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Pyrexia	4 (66.7)	8 (12.3)	4 (25.0)	7 (4.7)	1 (10.0)	1 (0.8)	9 (28.1)	16 (4.7)
Infections and infestations	5 (83.3)	16 (24.6)	14 (87.5)	50 (33.8)	7 (70.0)	33 (26.2)	26 (81.3)	99 (29.2)
Body tinea	0	0	0	0	2 (20.0)	2 (1.6)	2 (6.3)	2 (0.6)
Conjunctivitis	0	0	2 (12.5)	2 (1.4)	1 (10.0)	1 (0.8)	3 (9.4)	3 (0.9)
Lower respiratory tract infection	1 (16.7)	1 (1.5)	3 (18.8)	3 (2.0)	1 (10.0)	1 (0.8)	5 (15.6)	5 (1.5)
Nasopharyngitis	1 (16.7)	2 (3.1)	2 (12.5)	2 (1.4)	0	0	3 (9.4)	4 (1.2)
Otitis media	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Rhinitis	3 (50.0)	4 (6.2)	0	0	0	0	3 (9.4)	4 (1.2)
Sinusitis	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Tonsillitis	0	0	2 (12.5)	2 (1.4)	1 (10.0)	1 (0.8)	3 (9.4)	3 (0.9)
Upper respiratory tract infection	1 (16.7)	1 (1.5)	10 (62.5)	27 (18.2)	6 (60.0)	15 (11.9)	17 (53.1)	43 (12.7)
Urinary tract infection	0	0	2 (12.5)	3 (2.0)	0	0	2 (6.3)	3 (0.9)
Viral infection	1 (16.7)	2 (3.1)	2 (12.5)	2 (1.4)	2 (20.0)	3 (2.4)	5 (15.6)	7 (2.1)
Viral upper respiratory tract infection	1 (16.7)	1 (1.5)	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	3 (9.4)	3 (0.9)
Injury, poisoning, and procedural complications	1 (16.7)	1 (1.5)	2 (12.5)	3 (2.0)	4 (40.0)	7 (5.6)	7 (21.9)	11 (3.2)
Skin laceration	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Soft tissue injury	0	0	0	0	2 (20.0)	2 (1.6)	2 (6.3)	2 (0.6)
Investigations	3 (50.0)	16 (24.6)	2 (12.5)	4 (2.7)	2 (20.0)	4 (3.2)	7 (21.9)	24 (7.1)
Haemoglobin decreased	1 (16.7)	2 (3.1)	1 (6.3)	1 (0.7)	0	0	2 (6.3)	3 (0.9)
Neutrophil count decreased	1 (16.7)	1 (1.5)	1 (6.3)	1 (0.7)	0	0	2 (6.3)	2 (0.6)
Platelet count decreased	2 (33.3)	3 (4.6)	1 (6.3)	1 (0.7)	0	0	3 (9.4)	4 (1.2)
Vitamin D decreased	1 (16.7)	1 (1.5)	0	0	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Metabolism and nutrition disorders	0	0	2 (12.5)	2 (1.4)	1 (10.0)	1 (0.8)	3 (9.4)	3 (0.9)
Vitamin D deficiency	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Musculoskeletal and connective tissue disorders	1 (16.7)	1 (1.5)	2 (12.5)	2 (1.4)	6 (60.0)	9 (7.1)	9 (28.1)	12 (3.5)
Pain in extremity	1 (16.7)	1 (1.5)	1 (6.3)	1 (0.7)	3 (30.0)	3 (2.4)	5 (15.6)	5 (1.5)
Nervous system disorders	1 (16.7)	1 (1.5)	2 (12.5)	7 (4.7)	2 (20.0)	2 (1.6)	5 (15.6)	10 (2.9)
Headache	0	0	2 (12.5)	6 (4.1)	2 (20.0)	2 (1.6)	4 (12.5)	8 (2.4)
Respiratory, thoracic and mediastinal disorders	4 (66.7)	9 (13.8)	9 (56.3)	21 (14.2)	4 (40.0)	8 (6.3)	17 (53.1)	38 (11.2)
Acute chest syndrome	0	0	3 (18.8)	5 (3.4)	2 (20.0)	2 (1.6)	5 (15.6)	7 (2.1)
Allergic sinusitis	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Asthma	0	0	2 (12.5)	7 (4.7)	0	0	2 (6.3)	7 (2.1)
Bronchospasm	0	0	1 (6.3)	2 (1.4)	1 (10.0)	1 (0.8)	2 (6.3)	3 (0.9)
Cough	4 (66.7)	4 (6.2)	3 (18.8)	3 (2.0)	0	0	7 (21.9)	7 (2.1)
Rhinitis allergic	0	0	2 (12.5)	2 (1.4)	1 (10.0)	2 (1.6)	3 (9.4)	4 (1.2)
Skin and subcutaneous tissue disorders	1 (16.7)	1 (1.5)	5 (31.3)	9 (6.1)	3 (30.0)	5 (4.0)	9 (28.1)	15 (4.4)
Eczema	0	0	2 (12.5)	2 (1.4)	0	0	2 (6.3)	2 (0.6)
Pruritus	0	0	1 (6.3)	1 (0.7)	2 (20.0)	2 (1.6)	3 (9.4)	3 (0.9)
Rash	1 (16.7)	1 (1.5)	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	3 (9.4)	3 (0.9)
Rash papular	0	0	1 (6.3)	1 (0.7)	1 (10.0)	1 (0.8)	2 (6.3)	2 (0.6)
Urticaria papular	0	0	2 (12.5)	2 (1.4)	0	0	2 (6.3)	2 (0.6)

Source: Study INV543 Table 14.3.1.2

The % of participants was calculated based on the total number of participants within each cohort and the % of events was calculated based on the total number of event records within each cohort. Adverse events were coded using MedDRA version 23.1

Summary of Adverse Events by Severity

Severity of TEAEs in Study INV543 was assigned via NCI CTCAE toxicity grade. Overall, there were 19 Grade 3 TEAEs in 12 study participants and no Grade 4 or higher events reported (Table 14 below). The only events reported in more than 1 participant were SCA with crisis (7 events in 4 study participants) and ACS (4 events in 3 study participants).

Table 14: Paediatric Study INV543 Treatment-emergent Adverse Events Graded ≥3 Using the National Cancer Institute Common Terminology Criteria for Adverse Events

Primary System Organ Class (n [%]) *Dictionary-Derived Term*	6 Months – 1.99 years		2 – 5.99 years		6 – 17.99 years		Overall	
	Participants (N=6)	Events (N=65)	Participants (N=16)	Events (N=148)	Participants (N=10)	Events (N=126)	Participants (N=32)	Events (N=339)
Any System Organ Class	4 (66.7)	4 (6.2)	5 (31.3)	8 (5.4)	3 (30.0)	7 (5.6)	12 (37.5)	19 (5.6)
Blood and Lymphatic System Disorders	2 (33.3)	2 (3.1)	2 (12.5)	3 (2.0)	2 (20.0)	5 (4.0)	6 (18.8)	10 (2.9)
Anaemia	0	0	1 (6.3)	1 (0.7)	0	0	1 (3.1)	1 (0.3)
Neutropenia	2 (33.3)	2 (3.1)	0	0	0	0	2 (6.3)	2 (0.6)
Sickle Cell Anaemia with Crisis	0	0	2 (12.5)	2 (1.4)	2 (20.0)	5 (4.0)	4 (12.5)	7 (2.1)
Congenital, Familial, and Genetic Disorders	0	0	0	0	1 (10.0)	1 (0.8)	1 (3.1)	1 (0.3)
Sickle Cell Anaemia	0	0	0	0	1 (10.0)	1 (0.8)	1 (3.1)	1 (0.3)
Infections and Infestations	1 (16.7)	1 (1.5)	0	0	0	0	1 (3.1)	1 (0.3)
Viral Upper Respiratory Tract Infection	1 (16.7)	1 (1.5)	0	0	0	0	1 (3.1)	1 (0.3)
Investigations	1 (16.7)	1 (1.5)	1 (6.3)	1 (0.7)	0	0	2 (6.3)	2 (0.6)
Haemoglobin Decreased	1 (16.7)	1 (1.5)	0	0	0	0	1 (3.1)	1 (0.3)
Neutrophil Count Decreased	0	0	1 (6.3)	1 (0.7)	0	0	1 (3.1)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders	0	0	0	0	1 (10.0)	1 (0.8)	1 (3.1)	1 (0.3)
Pain in Extremity	0	0	0	0	1 (10.0)	1 (0.8)	1 (3.1)	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	0	0	3 (18.8)	4 (2.7)	0	0	3 (9.4)	4 (1.2)
Acute Chest Syndrome	0	0	3 (18.8)	4 (2.7)	0	0	3 (9.4)	4 (1.2)

Source: Study INV543 Table 12-4 and Table 14.3.1.4.

The % of participants was calculated based on the total number of participants within each cohort and the % of events was calculated based on the total number of event records within each cohort. Adverse Events were coded using MedDRA version 23.1.

Summary of Adverse Events by Causality

Twenty-eight TEAEs in 9 study participants were considered at least possibly related to study drug. The most common of such events were thrombocytopenia/platelet count decreased (6 events in 3 study participants) and neutropenia/neutrophil count decreased (4 events in 4 study participants each).

Other than 1 study participant (in whom decreases in Hb, HCT, ARC, erythrocytes were also noted and an associated iron deficiency ultimately diagnosed), all were associated with concurrent or recent viral or other infection or splenomegaly. There were no study participants with combined neutropenia and thrombocytopenia. All events associated with haematological toxicity were transient and resulted in temporary dose interruption on 4 occasions; there was no change in dose on 4 occasions and dose reduction on 2 occasions. One study participant (in the < 2-years age group) accounted for 13 events. Six TEAEs were associated with permanent discontinuation. At subsequent follow up, 1 unrelated event (severe iron deficiency anaemia/low Hb) was determined to be the reason for withdrawal.

Table 15: Paediatric Study INV543 Treatment-emergent Adverse Events (≥2 Study participants) Considered at Least Possibly Related to Study Treatment, by System Organ Class and Preferred Term (Safety Population)

Primary System Organ Class (n [%]) *Dictionary Derived Term*	6 Months – 1.99 years		2 years – 5.99 years		6 years – 17.99 years		Overall	
	Participants (N=6)	Events (N=19)	Participants (N=16)	Events (N=5)	Participants (N=10)	Events (N=4)	Participants (N=32)	Events (N=28)
Any System Organ Class	4 (66.7)	19 (100.0)	4 (25.0)	5 (100.0)	1 (10.0)	4 (100.0)	9 (28.1)	28 (100)
Blood and Lymphatic System Disorders	3 (50.0)	4 (21.1)	2 (12.5)	2 (40.0)	0	0	5 (15.6)	6 (21.4)
*Neutropenia**	2 (33.3)	2 (10.5)	0	0	0	0	2 (6.3)	2 (7.1)
*Thrombocytopenia**	1 (16.7)	2 (10.5)	1 (6.3)	1 (20.0)	0	0	2 (6.3)	3 (10.7)
Investigations	2 (33.3)	14 (73.7)	1 (6.3)	1 (20.0)	1 (10.0)	1 (25.0)	4 (12.5)	16 (57.1)
*Neutrophil Count Decreased**	1 (16.7)	1 (5.3)	1 (6.3)	1 (20.0)	0	0	2 (6.3)	2 (7.1)
*Platelet Count Decreased**	2 (33.3)	3 (15.8)	0	0	0	0	2 (6.3)	3 (10.7)
Skin And Subcutaneous Tissue Disorders	0	0	1 (6.3)	2 (40.0)	1 (10.0)	3 (75.0)	2 (6.3)	5 (17.9)
Rash Papular	0	0	1 (6.3)	1 (20.0)	1 (10.0)	1 (25.0)	2 (6.3)	2 (7.1)

Source: Study INV543 Table 12-3 and Table 14.3.1.3

Only those events where relationship to the treatment was marked as 'probable', 'possible', or 'definite' were included in this table. The % of participants was calculated based on the total number of participants within each cohort and the % of events was calculated based on the total number of event records within each cohort. Adverse Events were coded using MedDRA version 23.1.

* The AE terms for neutropenia/ neutrophil count decreased and thrombocytopenia/platelet count decreased can be considered together, as they have been used interchangeably by the Investigators to indicate toxicity in accordance with the protocol definition where Neutropenia (ANC<1.0x10^9L), Thrombocytopenia (Platelets 80x10^9L) and ARC <80x10^9L unless Hb concentration ≥ 9.0g/dL, with the exception of 1 low platelet count/Hb for participant 03-02 (2-5.99 age group).

Overall, in paediatric Study INV543, values for haematology, clinical chemistry, and urinalysis parameters were generally within normal ranges for this patient population and showed little change over the course of the study; the exception to this was estimated glomerular filtration rate (eGFR) values, which were high (but stable throughout). Low 25-hydroxyvitamin D was the most common abnormality (10 events in 7 study participants). Of the 4 TEAEs of neutropenia/neutrophil count decreased, all were isolated events: 3 were in the under-2-years age group (in 3 participants) and 1 was in the 2-5.99-years age group.

Physical examination results and vital signs assessments were unremarkable, and no apparent pattern could be discerned in terms of abnormal results.

Serious adverse event/deaths/other significant events

Deaths: No deaths occurred in paediatric clinical study INV543.

Serious Adverse Events: A total of 7 SAEs occurred during paediatric study INV543 in children with SCA. All of the 7 SAEs reported in 6 study participants in study INV543 were considered unrelated to Xromi, and all study participants recovered from the event and continued participating in the study. Dosing of Xromi was temporarily suspended for 2 participants (dose: 15 mg/kg/day, suspended for 3 days before being restarted at the same dose) and (dose: 15 mg/kg/day, suspended for 13 days before being restarted at the same dose). Dosing of Xromi was maintained throughout the event for all other SAEs.

In accordance with the protocol, unrelated hospitalizations were only reported as an SAE in this trial if it was for a period >7days; this is due to the frequency of hospitalizations in this population because of their underlying disease condition. If a more standard definition of SAE were to be used, the number of

SAEs overall would increase to 15 (in 10 study participants), all of which were also determined to be unrelated to Xromi.

Laboratory findings

Overall, in paediatric study INV543, values for haematology, clinical chemistry, and urinalysis parameters were generally within normal ranges for this patient population and showed little change over the course of the study; the exception to this was estimated glomerular filtration rate (eGFR) values, which were high (but stable throughout). Low 25-hydroxyvitamin D was the most common abnormality (10 events in 7 study participants).

Haematological toxicity

Protocol INV543 defined haematological toxicities as follows:

- neutropenia or low neutrophils (ANC) count of $<1.0x10^9L$
- thrombocytopenia or low platelet count of $<80x10^9L$
- low absolute reticulocytes count (ARC) $<80x10^9L$ with a Hb <9g/dL

Haematological toxicity meeting the above protocol definition was reported in 14 separate TEAEs in 6 participants and determined to be at least possibly related to drug toxicity in line with the protocol during the course of the trial, (see above in section *Summary of Adverse Events by Causality*). Although 'Neutrophil count decreased' and 'Platelet count decreased' were coded separately (under SOC Investigations) to 'neutropenia' and 'thrombocytopenia', the absolute values in all these events was considered when discussing the protocol stipulated criteria of neutropenia and thrombocytopenia for haematological toxicity.

- Of the 4 TEAE's of neutropenia/neutrophil count decreased, all were isolated events: 3 were in the under-2-years age group (in three participants) and 1 was in the 2-5.99-years age group.
    - o In 3 out of the 4 children, isolated neutropenia was associated with documented viral illness.
    - o In the under-2-years age group, 2 of these cases were associated with a viral illness (either concurrently or one month prior to the low neutrophil count).
    - o In the 2-5.99-years age group, one participant had a recurrent upper respiratory tract infection and a painful crisis in the months prior, and splenomegaly was identified at screening on-going throughout the trial.
- Of the 6 TEAE's of thrombocytopenia/ platelet count decreased, 5 were in the under-2-years age group (in 2 participants) and 1was in the 2-5.99-years age group.
    - o In the 6 months–1.99 age group, 3 of these cases were associated with a 1 participant who also had a viral illness (either concurrently or the week prior to the low platelet count) and a fungal rash. The other 2 cases were in another participant (discussed in the last bullet).
    - o In 1 participant a single event of thrombocytopenia was associated with splenomegaly.
- Of the 2 instances of protocol defined toxicity due to low ARC and associated low Hb, this was reported as 4 separate TEAEs (2 for low reticulocytes and 2for low Hb) in the same participant, who was in the 6 months-1.99 years age group. This participant was later diagnosed with severe iron deficiency anaemia and these Hb TEAEs in follow up were determined to be unrelated to the study drug.

Thirteen of the 28 TEAEs determined as at least possibly related to the study drug by the Investigator were reported in a single participant, and in whom the TEAEs were transient and recovered following a temporary halt of Xromi, with the exception of the low Hb which was diagnosed as severe iron deficiency anaemia and unrelated to the study drug. The Investigator's decision was to withdraw the participant from the study to allow off protocol management with oral hydroxycarbamide, as the participant was unlikely to achieve the required return to >20% Hb baseline levels or >4.5 g/dL, which was the protocol requirement for the restart of the study drug.

Vital Signs, Physical Findings, ECGs Findings

In paediatric Study INV543, physical examination included the following: ear/nose/throat (tonsils), dermatological, cardiovascular, respiratory, gastrointestinal, lymph nodes, musculoskeletal, hepatomegaly and splenomegaly, ophthalmological and central nervous system.

Vital signs assessments included supine systolic and diastolic blood pressure, pulse and body temperature, and respiratory rate. Other evaluations could be performed as deemed necessary by the Investigator. ECGs were not required per the protocol.

Physical examination results and vital signs assessments were unremarkable, and no apparent pattern could be discerned in terms of abnormal results.

Safety in special populations

Age

All safety analyses in paediatric clinical study INV543 were conducted in 3 age subgroups of 6 Months–1.99 years, 2–5.99 years and 6–17.99 years (Table 16 below).

Table 16: Paediatric Study INV543 Participant Age Distribution

Age Group	N	Mean (years)	SD (years)	Min, Max (Years)
6 Months–1.99 Years	6	0.97	0.068	0.8, 1.0
2–5.99 Years	16	3.06	0.929	2.0, 5.0
6–17.99 Years	11 [a]	10.09	3.506	6.0, 16.0
Overall	33	5.03	4.251	0.8, 16.0

Source: Study INV543 Table 14.1.1.2

[a] Note that N=10 participants in the 6-17.99 age group were included in the Safety Analysis Set.

N=1 study participant underwent pre-dose blood sampling but was discontinued prior to receiving treatment by the Investigator as they were unwilling to commit to the study. The participant was classified as 'enrolled' but subsequently withdrawn and hence excluded from the safety population.

Although nearly all study participants experienced at least 1 TEAE, the 6 months – 1.99-years age group reported the highest proportion of participants with a TEAE related to study drug (4 participants [66.7%]), compared to 4 participants [25.0%] among 2-5.99 years participants, and 1 participant [10.0%] among 6-17.99 years participants. The highest frequency of related TEAEs in the 6 months – 1.99 years age group was in the 'Blood and lymphatic system disorders' and 'Investigations' SOC. A single participant from this age category accounted for 13 of the 19 related TEAEs in this age group and in whom there was an underlying severe iron deficiency causing anaemia. The reported cytopenias were typically isolated, transient, and benign and associated with recent or concurrent respiratory or viral illness. Transient cytopenia induced by viral infections is commonly observed in young infants and children (Alexandrapoulou et al. 2015, Fettah et al. 2017).

None of the participants in the youngest age group experienced a serious TEAE compared to 3 (18.8%) 2-5.99 years participants, and 3 (30.0%) 6-17.99 years participants.

Among all TEAEs, other than increased frequency of SCA crises, ACS, and pain in the older age categories (a reflection of disease progression), the frequency of other AEs was relatively unremarkable. The prevalence of headache increased with age. Conversely, incidence of pyrexia, gastrointestinal disorders and cough decreased in prevalence with increasing age.

Sex: Males and females are diagnosed in equal numbers with SCD, and no sex differences with hydroxycarbamide therapy have been noted in the prescribing information of marketed hydroxycarbamide products. In paediatric study INV543, 51.5% of children with SCA were female. No obvious differences by sex were noted in the study. With regard to the impact of sex on the safety of hydroxycarbamide, the prescribing information for marketed hydroxycarbamide products include information on the risk of hydroxycarbamide use in pregnant women and information about the potential impact to fertility.

Race: In paediatric study INV543, 31 of the 33 children (93.9%) were Black or African American, 1 identified as "Caribbean" and 1 as "Black British." Because of the uniformity of each study population, no subgroup analyses of safety parameters by race could be performed. No impact of race on the safety of hydroxycarbamide in patients with SCA is noted in the prescribing information of marketed products.

Genotype: In paediatric study INV543, 1 participant was of the HbSβ^0 genotype and the remaining 31 were of the HbSS genotype and, therefore, subgroup analyses were not feasible.

Females and Males of Reproductive Potential: No pregnancies occurred in patients enrolled in paediatric clinical study INV543 and no pregnancies were reported in partners of enrolled patients.

Overdose: No overdose occurred in paediatric clinical study INV543.

Drug Abuse: No evidence of abuse of Xromi in paediatric clinical study INV543 was reported.

Safety related to drug-drug interactions and other interactions

No drug-drug interactions and other interactions were reported.

Discontinuation due to adverse events

In paediatric study INV543, 1 study participant in the 6-months to 1.99-years age group experienced 6 TEAEs leading to permanent discontinuation of Xromi, although ultimately 1 unrelated TEAE was deemed responsible for withdrawal from the study. Study drug was initiated at a dose of 15 mg/kg/day. A first TEAE of low platelet count was reported on Study Day 116 (noted as resolved on Study Day 210), followed by low reticulocyte count, low HCT, low Hb, low RBC count and low neutrophils, all first reported on Study Day 158 (all noted as resolved on Study Day 184). The dose of Xromi was first reduced to 10 mg/kg/day on Study Day 215 due to drug toxicity, then titrated to 15 mg/kg/day on Study Day 296 since platelet count had returned to acceptable levels. On Study Day 317 a TEAE of low Hb was reported, and Xromi was temporarily interrupted on Study Day 318. A diagnosis of severe iron deficiency anaemia was made locally on Study Day 336, which was assessed by the Investigator as unrelated to the study drug. The participant's Hb did not recover >20% of baseline or >4.5 g/dL and, therefore, in accordance with the protocol, the study drug was not restarted. However the investigator wished to continue off-protocol treatment with hydroxycarbamide while providing iron supplementation, so the participant was withdrawn from the study. Xromi was permanently discontinued on Study Day 384. The clinical database AE log was not updated with the final relatedness assessment prior to database lock.

Post marketing experience

Xromi was first authorized in the EU and European Economic Area (EEA; Iceland, Norway and Lichtenstein) by the centralized procedure on July 1, 2019. Xromi is now approved in the U.K. independently of the EU.

Xromi (100 mg/mL) oral solution is indicated for the prevention of vaso-occlusive complications of SCD in patients >2 years of age and is currently marketed in the U.K. (since March 23, 2020), Germany (June 12, 2020), and Ireland (since August 1, 2020).

The cumulative exposure was estimated to be between 48,529 and 82,650 patient-months or between 4,044 and 6,887 patient-years since approval. No exposure data were available regarding age, gender, indication or dose.

No exposure data are available regarding post-authorization use in special populations, e.g., the elderly population or in pregnant/lactating women; patients with hepatic and/or renal impairment, other relevant comorbidity or disease severity different from that studied in clinical trials; or in subpopulations carrying relevant genetic polymorphisms or in patients of different racial and/or ethnic origins.

No exposure data are available regarding other post-authorization use, e.g., overdose, abuse, misuse or use beyond the recommendations in the Reference Safety Information (i.e., off-label use).

During the reporting period of July 1, 2019 to Sept 31, 2022, a total 151 adverse drug reactions (ADRs) were reported in 60 cases. There were 6 cases with fatal outcome; 4 were in relation to COVID-19, 1 was a case of intracranial haemorrhage, and 1 was off-label use in a patient with myeloproliferative neoplasia with eosinophilia. Of the 151 ADRs reported, 76 were serious and 75 were non-serious. The most commonly reported spontaneous adverse drug reactions were Condition aggravated (n=6), COVID-19 (n=5), Headache (n=5), and Off-label use (n=24).

2.5.1. Discussion on clinical safety

Xromi is approved for the prevention of vaso-occlusive complications of sickle cell disease in patients from older 2 years of age. The safety profile for this indication is extensively described in the EPAR of Xromi. The present application requested the extension of indication to patients older than 6 months of age. It is supported by published data for study BABY HUG (Wang et al. 2011) and results from PK study INV543 and a PK/PD model.

Safety data from the BABY HUG trial in very young children with SCD from 9 months to 18 months of age showed that, there were no adverse effects on growth or other anthropomorphic measures during 2 years of hydroxycarbamide therapy in fixed dose of 20 mg/kg/day (Rana et al. 2014). The safety data from study BABY HUG also showed that infants treated with HU did not have significant differences from those treated with placebo in rates of severe neutropenia ANC, thrombocytopenia, anaemia (Hb), reticulocytopenia (ARC), or abnormal tests of liver function (alanine aminotransferase [ALT], bilirubin). According to Rodgers et al. 2022, these are among the most compelling evidence that moderate-dose HU is better well tolerated and may not require the same degree of close laboratory monitoring as maximum-tolerated-dose HU.

The applicant provided also results from study INV543 which is a non-comparative, not randomized, open-label, PK efficacy and safety study and a PK/PD model. An exploratory model-free analysis of several efficacy and safety markers were conducted. Key safety biomarkers explored included absolute neutrophil count (ANC), platelets, absolute reticulocyte count (ARC), and liver function tests. Plots of safety markers WCC, ANC, platelets, ARC, ALP, GGT, AST and ALT revealed behaviour in alignment

with what has been reported in literature and did not identify new safety concerns. Safety results from paediatric study INV543 are consistent with data from the published literature on the use of hydroxycarbamide in children with SCD.

According to the applicant in paediatric study INV543 as well as literature reported randomized clinical trials and other studies in infants, few unexpected treatment-related SAEs and few dose limiting toxicities have been observed (e.g., Wang et al. 2011, Wang et al. 2001, Hankins et al. 2005, George and Tran. 2020, Schuchard et al. 2019). Frequencies of cytopenias were not noted to be appreciably different between infants and older children and reports of recurrent or persistent or severe cytopenias are not common. AEs associated with hydroxycarbamide are well recognized in the literature and product labelling. The findings from paediatric study INV543 are consistent with those seen in populations of patients throughout Europe and the rest of the world taking hydroxycarbamide, and consistent with the decades long safe and efficacious use of hydroxycarbamide in children with SCD.

It is important to underline the fact that in study INV543 only 6 patients between 6 months and 2 years old were included in the pivotal study, 5 subjects achieved MTD (maximum tolerated dose) in this age group (mean MTD: 23.5 mg/kg/day) All of the 5 subjects were females and black/African-american and the MAH claims that demographic characteristics do not have an impact on the endpoints of the study. Three subjects discontinued the study and the applicant was requested to fully clarify the reasons for these withdrawals. The one of the withdrawals concerned a study participant in the 6-Month to 1.99-year age group who experienced six Treatment-Emergent Adverse Events (TEAEs), one of which led to permanent treatment discontinuation (haemoglobin decreased/severe iron deficiency anaemia). The number of 5 subjects is considered too low to establish efficacy and safety of hydroxycarbamide in children below 2 years of age with SCD based on study INV543, especially since 1 of two withdrawals was due to safety reasons. In this case, the B/R balance could only be assessed only based on the PK model and extrapolation of the available clinical data.

In the popPK/PD model for ANC, a trend for higher frequency of AEs in the age group of 6 months to 2 years is observed, as it was also observed in study INV543. Regarding the TEAEs in study INV543 the applicant was requested to justify why TEAEs determined to be at least possibly related to study drug more frequent in the <2-year-old age group (29.2%). According to the applicant there were a total of 65 TEAEs (6 [100%] study participants) in the < 2 years group, of which 19 TEAEs (29.2%) were possibly related to study drug. Acknowledging the small sample size within each age category, this frequency of related TEAEs is higher than the 2-6 years (3.4%) and 6-18 years group (3.2%). It was clarified however, that 13 of the related TEAEs in the < 2 years group were recorded in a single participant. This subject had incidences of neutropenia, thrombocytopenia, low absolute reticulocytes, low MCV, low Hb. This can possibly skew the data in the <2 year age group to some extent. It is acknowledged that the number of participants in this age group is considered very small to draw any definite conclusions on safety of HU in this age group.
Furthermore considering that even if short term safety could potentially be extrapolated from older children, there are uncertainties on long term safety in younger children the applicant was asked to submit a proposal on generation of long-term safety data in children below 2 years of age.

The applicant proposed to conduct a comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age. Although the 2-year follow up was considered rather short to fully assess effects on growth and maturation (especially effects on fertility and risk of malignancies) due to the fact that the medicinal product already has an indication in children from 2 years of age, the CHMP sees no value in pursuing a longer follow up period, since its feasibility is also doubtful. Upon request the MAH has provided a more comprehensive clinical extrapolation plan to support the characterization of the safety profile of hydroxycarbamide in

the sought population and agreed to also include in primary objectives other factors associated to changes in growth (body weight and size, organ weight), organ function, and clearance. An exploration of sickle genotype to see if it influences the safety and efficacy endpoints, even if according to the applicant it is likely to lack statistical power.

The applicant has also submitted data on the number of cases of SCD population in the EU for each genotype of SCD. The total number (%) of cases by genotype estimated in the listed EU countries are: SS 19947 (58.0), Sβ 9279 (27.0), SC 3776 (11.0), other/unspecified/unknown 1368 (4.0), and it is evident that the SS and Sβ genotype dominate in terms of absolute numbers.

As explained in section 2.4.3 considering that both adequate clinical data in the age group of 6-9 months from literature are not yet available and there is absence of observed PK and PD data in the age group of 6-9 months from study INV 543 to support extrapolation of efficacy and safety, the B/R in the age group of 6-9 months of age is considered negative and the applicant was requested to narrow the indication to children from 9 months of age which was accepted. More data are expected from the recommended and agreed PASS study.

2.5.2. Conclusions on clinical safety

The safety profile of hydroxycarbamide is well described in the literature and product labelling. However it was acknowledged that although short term safety could potentially be extrapolated from older children there are uncertainties on long term safety in younger children below 2 years of age. To overcome these uncertainties it was recommended and accepted that the MAH performs the PASS study below:

"A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age"

2.6. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.7. Risk management plan

The MAH submitted/was requested to submit an updated RMP version 4.4 with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 4.4 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 4.4.

Safety concerns

Table 17: Summary of Safety Concerns

Important identified risks	1. Effects on male fertility- Oligospermia and azoospermia with normal morphology and reduced semen volume
Important potential risks	1. Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes 2. The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development
Missing information	1. Long-term safety in children below 2 years of age

Pharmacovigilance plan

Table 18: Ongoing and Planned Additional Pharmacovigilance Studies

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
NA	NA	NA	NA	NA
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
NA	NA	NA	NA	NA
Category 3 – Required additional pharmacovigilance activities				
A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study)	**Primary objectives:** To compare rates of adverse events of special interest (AESIs): myelosuppression (requiring permanent or temporary discontinuation of therapy), raised liver function tests, skin disorders, weight and growth abnormalities, hospitalisations for sickle cell disease (vaso-occlusive crisis/pain crisis, acute chest syndrome, anaemia), blood transfusions and unforeseen AEs, in patients with SCD treated with hydroxycarbamide oral solution and in a comparator cohort. **Secondary objectives:** • To evaluate the effectiveness of hydroxycarbamide oral solution in children under the age of 2 years with sickle cell disease for the	To evaluate the long-term two-year comparative safety and effectiveness of hydroxycarbamide oral solution 100 mg/ml (Xromi) administered to children under 2 years of age for the prevention of complications of Sickle Cell Disease.	Milestones will be confirmed	Due dates will be confirmed

	clinical endpoints of special interest (including but not limited to: vaso-occlusive and painful crises, acute chest syndrome, stroke, priapism, acute splenic sequestration, hepatopathy and infections) and biochemical and physiological factors of specialist interest (HbF, Hb, MCV, LDH, Bilirubin, Transcranial Doppler Velocity), by comparing patients with SCD treated with hydroxycarbamide and the comparator cohort. • To evaluate rates and reasons for discontinuation of hydroxycarbamide oral solution in children under the age of 2 years with sickle cell disease. • The severity, seriousness, outcome and duration of the AESIs of hydroxycarbamide will be described. • Is safety dependent on whether maximum tolerated dose is reached? • Is effectiveness dependent on whether maximum tolerated dose is reached? • Subgroup analyses of safety and effectiveness will include age groups (6 -12 months and >12—24 months), sex, main types of SCD (HbSS, HbSC, HbS/b-0 thalassemia, HbS/b+ thalassemia), comorbidities. • To describe patient characteristics of patients initiating hydroxycarbamide and the comparator cohort.			

Abbreviations: NA = Not applicable; PASS = post authorisation safety study.

Risk minimisation measures

Table 19: Summary of pharmacovigilance and risk minimisation activities

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risk		
Identified Risk #1 **Oligospermia and azoospermia with normal morphology and reduced semen volume**	Routine risk minimisation measures: Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.6 (Fertility, pregnancy and lactation) and Section 4.8 (Undesirable effects). Please refer to the Section 2 of the Xromi 100 mg/mL oral solution PL: <u>Pregnancy, breastfeeding and fertility.</u> **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Male patients should be informed by their healthcare professionals about the possibility of sperm conservation (cryopreservation) before the start of therapy. This recommendation has been added to Section 4.6 of the Xromi 100 mg oral	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: All the reports of impaired fertility will be monitored closely and will be presented in the PSUR. Additional pharmacovigilance activities: None.

	solution SmPC and to Section 2 of the Xromi 100 mg/mL oral solution PL. Additional risk minimisation measures: A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance.	
Important Potential Risks		
Potential Risk #1 **Potential medication errors – Transfer of patients from capsule and tablet to liquid formulation and two dosing syringes**	Routine risk minimisation measures: Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and Method of Administration). Please refer to Section 3 of the Xromi 100 mg/mL oral solution PL where appropriate guidance is provided on taking the medicine along with instructional pictures: How to take Xromi Additional risk minimisation measures: A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: All reports of medication errors will be monitored closely and will be reviewed in the PSUR. Additional pharmacovigilance activities: None.
Potential Risk #2 **The effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development**	Routine risk minimisation measures: Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.3 (Contraindications) and Section 4.6 (Fertility, pregnancy and lactation) and PL Section 2. **Routine risk minimisation activities recommending specific clinical measures to address the risk:** The patient should be instructed to immediately contact a doctor in case of suspected pregnancy. Effective method of contraception for both male and female patients in reproductive age group. Discontinuation of Xromi 3 to 6 months before, if patient on treatment want to conceive. PL Section 2 instructions - Please contact your doctor immediately if you think you may be pregnant. Additional risk minimisation measures: A separate educational material for physician and patient/parent will be prepared to communicate this risk and provide further guidance.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Specific Follow-up Forms for Pregnancy and Breastfeeding All reports of the effect on embryogenesis, teratogenic potential, breastfeeding and post-natal development will be monitored closely and will be presented in the PSUR. Additional pharmacovigilance activities: None.
Important Missing Information		
Important Missing Information #1 **Long-term safety in children below 2 years of age**	Routine risk minimisation measures: Please refer to the following Sections of the Xromi 100 mg/mL oral solution SmPC: Section 4.2 (Posology and method of administration) and Section 4.8 (Undesirable effects) and Section 2 of the PL. Additional risk minimisation measures: Not applicable.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: All reports of hydroxycarbamide use in patients below 2 years of age will be monitored closely and will be presented in the PSUR. Additional pharmacovigilance activities: A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral

		solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study) will be conducted.

Abbreviations: PK = pharmacokinetic; PL = Package leaflet; PSUR = Periodic safety update report; SmPC = Summary of Product Characteristics; PASS = post authorisation safety study.

2.8. Update of the Product information

As a consequence of this extension of indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated in sections 1,2 and 3, accordingly.

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and was found acceptable for the following reasons:

"A User Readability Test was conducted on the Patient Information Leaflet (PIL) for Hydroxycarbamide Nova Laboratories 100 mg/ml oral solution (PIL User testing report, dated 28 November 2018) to support the initial Marketing Authorisation Application. The purpose of the test was to investigate whether the information on the leaflet was clear and easy to find. Test volunteers were recruited from a database of volunteers of both sexes, with males (36%) females (64%) participating and had a mean age of 46 years (range 17 to 73 years). The PIL passed all 3 stages of testing.

The approved indication for Xromi 100 mg/mL Oral Solution 'Xromi is indicated for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age' is proposed to be extended to patients over 6 months of age. The above PIL User Readability Test remains applicable to the proposed extended population."

CHMP agreed that the changes to the package leaflet were minimal and do not require user consultation with target patient groups.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Xromi is intended for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 2 years of age. The MAH has applied for the extension of indication to patients over 6 months of age. However CHMP approved the extension of the indication from 9 months of age.

3.1.2. Available therapies and unmet medical need

Management programs for paediatric patients with SCD include acute care, routine prevention (e.g. childhood vaccinations and monitoring of growth and development, and the treatment of complications [e.g. cardiac, respiratory, and renal]). Haematopoietic stem cell transplantation (HSCT) is the only recognised cure for SCD, and has been shown to have an 85– 90% success rate in certain paediatric

patient groups. The use of HSCT is restricted by the lack of fully matched sibling donors for many potentially eligible patients.

Currently there is no medicinal product authorized for children younger than 2 years old. Several publications support the use of hydroxyurea in infants and children.

3.1.3. Main clinical studies

This application is supported by a prospective open label, PK study of oral HU solution administered to 32 participants aged from 6 months to 18 years. The primary endpoint was to determine the pharmacokinetics (PK) of oral hydroxyurea (HU) solution ($AUC_{(0\text{-}inf)}$, C_{max}, T_{max}, $T_{1/2}$) and a population PK [popPK] approach was adopted to characterize the PK in this population. The secondary endpoints were: (i) to further evaluate the safety of oral HU solution (safety endpoints included the incidence of adverse events (AEs)) (ii) To investigate the effects of HU dose escalation on laboratory parameters: foetal haemoglobin (HbF), haemoglobin (Hb), haematocrit, mean corpuscular volume (MCV), white blood cell (WBC) count and differentials, absolute neutrophil count (ANC), absolute reticulocyte count (ARC), platelets, bilirubin, cystatin C and lactate dehydrogenase (LDH). (iii) To investigate the effects of HU dose escalation on clinical parameters: pain, transfusions, hospitalizations, and acute chest syndrome (ACS). (iv) To assess the acceptability and palatability of oral HU solution

A published clinical trial BABY HUG (Wang et al 2011) is also used to support this application. This was a phase III double-blinded, multi-centre, randomised, placebo-controlled study in infants aged 9 – 18 months. Subjects received oral liquid hydroxycarbamide 20 mg/kg/day without escalation, or placebo for two years. Infants were initially monitored every 2 weeks for adverse events and laboratory toxicities until tolerability of the dose was confirmed, then every 4 weeks. Primary study endpoints were splenic function (qualitative uptake on 99mTc spleen scan) and renal function (glomerular filtration rate by 99mTc-DTPA clearance). Additional evaluations included blood counts, HbF, chemistry profiles, spleen function biomarkers, urine osmolality, neurodevelopment, TCD ultrasonography, growth, and mutagenicity. Ninety-six subjects received hydroxycarbamide and 97 placebo; 86% completed the study.

3.2. Favourable effects

Utilizing the developed PK/PD models simulations of systemic exposure variables using the popPK model with maturation function suggest that both AUC and Cmax are similar between children aged 10 months to < 2 years, 2 to < 6 years and 6 to <18 years of age. Indeed, even at the maximum 35mg/kg/day dose, exposure in infants 10 months to <2 years does not substantially differ from older children and adolescents. A dose-response relationship of hydroxycarbamide with improvement in clinical markers of SCD in children has been established by clinical studies and is also evident in study INV543. Exploratory plots of other efficacy markers HbF, MCV, MCH, bilirubin and LDH broadly mirrored what has previously been reported in literature.

Study BABY-HUG: Regarding primary endpoints, 19 of 70 patients had decreased spleen function at exit in the hydroxycarbamide group vs 28 of 74 patients in the placebo group and a difference in the mean increase in DTPA glomerular filtration rate in the hydroxycarbamide group versus the placebo group of 2 mL/min per 1·73 m². Regarding secondary endpoints, the following were observed: 177 events of pain in 62 patients in the hydroxycarbamide group vs 375 events in 75 patients in the placebo group and 24 events of dactylitis in 14 patients in the hydroxycarbamide group vs 123 events in 42 patients in the placebo group. Haemoglobin and foetal haemoglobin increased in the hydroxyurea group compared to the placebo group, whereas the white blood-cell count decreased.

3.3. Uncertainties and limitations about favourable effects

A relatively small number of patients aged below 2 years old have been enrolled in study INV543 and no PK/PD data are available for children from 9 to 10 months of age. However additional data from published clinical trials counterbalance this uncertainty. Furthermore a comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study) will be conducted as an additional recommendation.

Regarding the BABY HUG study the difference in the endpoints between groups was not statistically significant and this is clearly stated in section 5.1 of the SmPC.

3.4. Unfavourable effects

There were 339 AEs in 31 study participants in Study INV543, all of which were TEAEs with 28 events (in 9 participants) assessed to be at least possibly related to study drug. There were 7 Serious adverse events (SAEs) (in 6 study participants), and no deaths. AEs were distributed roughly in proportion to the number of study participants in each age group, with TEAEs determined to be at least possibly related to study drug more frequent in the <2-year-old age group (29.2%). Overall the TEAEs occurring most frequently in study INV543 participants were SCA with crisis (53 events in 18 participants), upper respiratory tract infection (43 events in 17 participants), pyrexia (16 events in 9 participants), cough (7 events in 7 participants), vomiting (27 events in 6 participants), and abdominal pain (7 events in 6 participants).

Simulations utilizing the developed PK/PD model for ANC suggest that although there is a statistically significant relationship between increasing exposure and decreasing ANC, the slope of this relationship is very shallow and the number of patients that drop below the toxicity threshold is rare (<1.5% across all dosing and age categories). Exploratory plots of other safety markers WBC, platelets, ARC, ALP, GGT, AST and ALT also revealed behaviour in alignment with what has been reported in literature and did not identify new safety concerns.

Safety data from the BABY HUG trial (Wang et al. 2011) in very young children with SCD from 9 months to 18 months of age showed that, there were no adverse effects on growth or other anthropomorphic measures during 2 years of hydroxycarbamide therapy in fixed dose of 20 mg/kg/day (Rana et al. 2014). The safety data from study BABY HUG also showed that infants treated with HU did not have significant differences from those treated with placebo in rates of severe neutropenia ANC, thrombocytopenia, anaemia (Hb), reticulocytopenia (ARC), or abnormal tests of liver function (alanine aminotransferase [ALT], bilirubin). According to Rodgers et al. 2022, these are among the most compelling evidence that moderate-dose HU is better well tolerated and may not require the same degree of close laboratory monitoring as maximum-tolerated-dose HU.

3.5. Uncertainties and limitations about unfavourable effects

Long-term safety in children below 2 years of age has been added as missing information in the RMP.

A comparative observational study to evaluate the safety and effectiveness of Xromi (hydroxycarbamide oral solution 100 mg/ml) for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients under 2 years of age (PASS Study) will be conducted as an additional pharmacovigilance activity.

3.6. Effects Table

Not applicable.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Following the initial approval of XROMI it was accepted by the CHMP that uncertainty remained regarding the PK, safety and efficacy in young children under 2 years of age considering that hepatic and renal function may be still immature at that age. In addition, metabolism/excretion of hydroxyurea is not fully characterized and differences in PK in this age group cannot be excluded. Furthermore, according to the Scientific Advice EMA/CHMP/SAWP/187964/201 the lack of PK data in infants between 9 months and 2 years does represent an uncertainty, particularly in the case of dose escalation. These uncertainties precluded the extrapolation of the indication to children under 2 years of age. Thus, CHMP has asked the applicant for results from a clinical study involving patients above 9 month until 2 years and to expand the number of participants of this age via PK modelling.

Utilizing the developed PK/PD models simulations of systemic exposure variables using the popPK model with maturation function suggest that both AUC and Cmax are similar between children aged 9 months to < 2 years, 2 to < 6 years and 6 to <18 years of age. Indeed, even at the maximum 35mg/kg/day dose, exposure in infants 6 months to <2 years does not substantially differ from older children and adolescents. A dose-response relationship of hydroxycarbamide with improvement in clinical markers of SCD in children has been established by clinical studies and is also evident in study INV543. Exploratory plots of other efficacy markers HbF, MCV, MCH, bilirubin and LDH broadly mirrored what has previously been reported in literature. Exploratory plots of safety markers ANC, WBC, platelets, ARC, ALP, GGT, AST and ALT also revealed behaviour in alignment with what has been reported in literature and did not identify new safety concerns. These findings supported by published clinical data and particularly study Baby HUG allow the extrapolation of the indication to patients aged > 9 months.

3.7.2. Balance of benefits and risks

The overall B/R of Xromi is positive for the prevention of vaso-occlusive complications of Sickle Cell Disease in patients over 9 months of age.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the prevention of vaso-occlusive complications of sickle cell disease in children from 9 months to 2 years of age for Xromi, based on final results from the paediatric study INV543, listed as a category 3 study in the RMP; this is a single-arm, open-label, multi-center study in children with sickle cell anaemia over 9 months of age.
As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.4 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Xromi is not similar to Adakveo. Oxbryta and Casgevy within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.