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PASS information

Title	ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study
Protocol version identifier	V4.0
Date of last version of protocol	19 September 2023
EU PASS Registry number (internal reference)	Study not registered (SIK-EU-20-1)
Active substance	L01XX05, hydroxycarbamide/hydroxyurea (HU)
Medicinal product	Siklos® (Hydroxycarbamide/hydroxyurea)
Product reference	*Siklos 100 mg film-coated tablets:* EU/1/07/397/002; *Siklos 1000 mg film-coated tablets:* EU/1/07/397/001
Product number	EMEA/H/C/000689
Marketing authorization holder(s)	Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France Phone: +33 (0)1 72 69 01 86 https://www.theravia.com
Joint PASS	No
Research question and objectives	As part of the registration dossier for Siklos® (hydroxycarbamide/hydroxyurea [HU]), the Marketing Authorization Holder (MAH) committed to initiate a non-interventional study (ESCORT-HU) with the main goal of collecting safety information upon administration of Siklos® in patients with Sickle Cell Disease (SCD), as well as long-term follow-up data after treatment with HU. Most of the objectives of ESCORT-HU study have been fulfilled as regards the collection of information on the most common safety concerns associated with the administration of HU in patients with SCD. However, for some safety concerns, the cumulative data were not sufficient to draw meaningful conclusions. As safety information pertaining to the long-term use of HU remains incomplete in spite of the first safety study (ESCORT-HU), an extension of the latter is proposed. ESCORT-HU Extension study aims at evaluating the long-term safety of Siklos® focusing on some questions regarding its safety when used in current practice in adults and paediatric patients treated with Siklos® and followed for up to 5 years. **Primary objective** • To determine the long-term safety profile of Siklos® focusing on risks which are poorly documented or unknown (unknown meaning: nature and frequency of serious adverse events [SAEs] causally related to Siklos® which are not listed in the product information). **Secondary objectives** • To document changes in fertility status in males and females;

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	in particular, to determine and document the management of male fertility through the use of semen cryopreservation in adults but also in children having started Siklos® in early childhood, • To monitor the outcome of pregnancies following exposure to Siklos® at the time of conception or at any time during the pregnancy (in participant and participant's partner), • To provide more information about the potential barriers to the compliance to the prescription, • To determine how the switch or combination with new SCD treatments is made. • To describe complications linked to SCD • To document the quality of life of SCD adult patients
Country(-ies) of study	France, Italy, Greece and Germany.
Author	Laura THOMAS-BOURGNEUF

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Marketing authorization holder

Marketing authorization holder (MAH)	Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France Phone: +33 1 72 69 01 86 Fax: +33 1 73 72 94 13 E-mail : pv@theravia.com
MAH contact person	Laura THOMAS-BOURGNEUFTheravia 16 rue Montrosier; 92200 Neuilly-sur-Seine,France Phone: +33 1 72 69 01 86 Fax: +33 1 73 72 94 13 E-mail : laura.thomas-bourgneuf@theravia.com

Confidentiality

This document is confidential. The acceptance of this document commits the addressee not to communicate or publish any information, apart from the information dedicated to the patients included in the study. This also applies to the persons who work with the addressee or with the institutional review committee, if applicable.

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Sponsor representative signature

Study Title: ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study

Sponsor: Theravia

EU PASS Registry number:

Date of the protocol (version): 19 September 2023

I hereby confirm that I have read and approved the present protocol study:

Sponsor Representative: Christophe Pompon

Signature: Directeur Développement Clinique, Theravia

Date: DocuSigned by: Christophe Pompon 23BD1149B6164EF...
20/12/2023 | 15:31 CET

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European Coordinating Investigator signatures

Study Title: ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study

Sponsor: Theravia

EU PASS Registry number:

Date of the protocol (version): 19 September 2023

I hereby confirm that I have read and approved the present protocol study:

Adults Coordinating Investigator: Pr. Frédéric GALACTEROS

Signature: DocuSigned by: Frédéric Galactéros D1BF6A7FECF4443...

Date: 2/1/2024 | 03:59 PST

Paediatrician Coordinating Investigator: Pr. Mariane de MONTALEMBERT

Signature: DocuSigned by: Mariane de Montalembert 48C96600CB9343C...

Date: 19/12/2023 | 07:31 PST

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European Qualified person in pharmacovigilance (EUQPPV) signature

Study Title:	ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study
Sponsor:	Theravia
EU PASS Registry number:	
Date of the protocol (version):	19 September 2023

I hereby confirm that I have read and approved the present protocol study:

EUQPPV: Dr. Corinne DUGUET

Signature: DocuSigned by: Corinne Duguet 43C966C2FE64479...

Date: 20/12/2023 | 10:05 CET

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2. List of abbreviations

AE	Adverse Event
CI	Confidence Interval
CRA	Clinical Research Associate
e-CRF	Electronic Case Report Form
CRO	Contract Research Organization
EC	European Commission
EU	European Union
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ESCORT-HU	European Sickle Cell Disease Cohort - Hydroxyurea
EUQPPV	European Qualified Person Responsible for Pharmacovigilance
HAS	Haute autorité de santé
GEP	Good Epidemiology Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good pharmacoVigilance Practice
HU	Hydroxyurea
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
MAH	Marketing Authorisation Holder
MedDRA	Medical dictionary for Regulatory Activities
NA	Not Applicable
PASS	Post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
QC	Quality Control
QPPV	Qualified Person for Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SCD	Sickle Cell Disease
SmPC	Summary of Product Characteristics

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3. Responsible parties

Sponsor Representative	Laura THOMAS-BOURGNEUF Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France +33 (0) 1 49 70 95 85
EUQPPV:	Dr. Corinne DUGUET Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France pvcc.medical@gmail.com
Project Manager	Nesrine FLISSI Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France +33 (0)1 49 70 95 83
Main author of the protocol	Laura THOMAS-BOURGNEUF Theravia 16 rue Montrosier; 92200 Neuilly-sur-Seine, France +33 (0) 1 49 70 95 85
European Coordinating Investigators:	
Adult population	Pr. Frédéric GALACTEROS Hôpital Henri Mondor 51 avenue du Maréchal de Lattre de Tassigny 94000 Créteil, France
Paediatric population	Pr. Mariane de MONTALEMBERT Hôpital Necker-Enfants Malades 149 rue de Sèvres 75015 Paris, France
Contract Research Organization (CRO) Trial management, data collection on-site, quality control, biostatistics, medical writing, data management	ICTA PM 11 rue du Bocage 21121 Fontaine les Dijon, France +33 (0)3 80 53 40 00

Contact details and the list of all investigators will be detailed in the stand-alone document listed in Annex 1 and available upon request.

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4. Abstract

TITLE OF STUDY	ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study Version 4.0, (19 September 2023) Laura THOMAS-BOURGNEUF, Clinical Operations Manager, Theravia
RATIONALE AND BACKGROUND	Siklos® (Hydroxycarbamide/hydroxyurea [HU]) was approved in 2007 in Europe for the prevention of symptomatic vaso-occlusive crises including acute chest syndrome in sickle cell disease (SCD) patients. As part of the Siklos® Risk Management Plan, a first study named ESCORT-HU was initiated to evaluate the use of Siklos® in real-life conditions. A total of 1906 patients in 62 centres (Germany, Greece, Italy and France) were enrolled between January 2009 and June 2017. At the time of ESCORT-HU Extension original protocol development, data collection for ESCORT-HU was complete. The main objectives of ESCORT-HU have been fulfilled as regards the collection of data for the most common safety concerns associated with the use of HU in patients with SCD: myelosuppression, child growth, concomitant administration of live vaccines, safety in population with renal and hepatic impairment and frequency of SCD events (painful crises, acute chest syndrome, stroke, acute splenic sequestration, infections, blood transfusions and hospitalisations). However, due to the late access to the market in France and the absence of significant sales in the United Kingdom, both countries counting for the largest population of SCD patients in Europe, less than 200 patients had been enrolled by the end of 2012. The majority of the participants of ESCORT-HU have been included from January 2013. Therefore, long-term follow-up data are still lacking, and the following concerns still need to be addressed: • Drug-induced malignancies: the mean exposure in the cohort of ESCORT-HU study was 30 months, for a cumulative exposure of 2835.8 patient-years by 29 June 2018. Only one myelodysplastic syndrome has been reported in the cohort to date. It is possible that the duration of exposure was too short to estimate the incidence of this risk; therefore, further long-term exposure data are required. • Leg ulcers: the number of events and duration of exposure were not sufficient to provide discriminating criteria between leg ulcer related to the disease and HU-induced leg ulcer. Further data are needed to define such discriminating criteria. • Male fertility: consequences on male fertility when HU is started before puberty, sometimes in very young children, are not well documented. Therefore, one of the objectives of the ESCORT-HU Extension study is to gain knowledge on how clinicians manage this concern. • Pregnancies: number of pregnancies with documented outcomes was too limited to allow for meaningful assessment of foetal outcome following exposure to Siklos® during pregnancy. Additional data should be collected. • Potential barriers to the compliance to the prescription of Siklos®: more information needs to be provided. • New SCD treatments, in combination with Siklos® or not, are or will be soon available. How does Siklos® fit in the management of SCD within this new environment? A feasibility study for ESCORT-HU Extension was performed during summer 2018 showing that almost all centres participating in ESCORT-HU study were willing to

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	continue the surveillance of their patients through ESCORT-HU Extension. It is expected that more than 60% of patients included in ESCORT-HU study will give their consent to continue the surveillance thus allowing collection of data over a period of up to 15 years in total. Therefore, ESCORT-HU Extension study will be initiated in the same countries as ESCORT-HU. New patients in additional SCD reference centres in France, Italy and Germany, may also be included. ESCORT-HU Extension is thus expected to cover almost all SCD reference centres and to ensure the follow-up of more than 50% of the patient population eligible for Siklos® treatment in these centres.
RESEARCH QUESTION AND OBJECTIVES	As safety information regarding the use of Siklos® on long-term remains incomplete despite a first safety study (ESCORT-HU), an extension of the latter is proposed. The ESCORT-HU Extension study aims at evaluating the long-term safety of Siklos® when used in current practice in adults and paediatric patients treated with Siklos® and followed for up to 5 years. **Primary objective** The primary objective of the study is to determine the long-term safety profile of Siklos® focusing on risks which are poorly documented or unknown (unknown meaning: nature and frequency of serious adverse events [SAEs] causally related to Siklos® which are not listed in the product information). **Secondary objectives** • To document changes in fertility status in males and females; in particular, to determine and document the management of male fertility through the use of semen cryopreservation in adults but also in children having started HU in early childhood, • To monitor the outcome of pregnancies following exposure to Siklos® at the time of conception or at any time during the pregnancy (in participant and participant's partner), • To provide more information about the potential barriers to the compliance to the prescription of Siklos®, • To determine how the switch or combination with new SCD treatments is made. • To describe complications linked to SCD • To document the quality of life of SCD adult patients
STUDY DESIGN	Multicentre, prospective, non-interventional cohort study in SCD patients treated with Siklos®. Participants and parents or legal guardians of children already enrolled in ESCORT-HU will be informed by the investigator about this extension study and the possibility for a longer follow up period. New eligible patients in already existing centres or new centres will also be asked to participate. Participants will be evaluated in hospital at inclusion, then at least once a year according to usual monitoring of the disease and to the recommendations in Siklos® product information. Temporary discontinuation of Siklos® will not lead to interruption of data collection, however, in case of permanent stop[1], the data will no longer be collected and the participant will be withdrawn from the study. A **Steering Committee**, composed of medical experts from all involved countries and sponsor representatives, will oversee the conduct and reporting of the study, to ensure expert clinical guidance and a high standard of scientific quality. Member of the Steering Committee will meet at least once a year unless unscheduled meetings are

[1] A permanent stop could be defined in case of bone marrow transplantation, gene therapy and treatment discontinuation longer than 12 months. Of note, a stop longer than 12 months due to the wish of being parent has to be considered as a temporary stop.

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	needed.
POPULATION	The study population will include male or female patients, aged ≥ 2 years old, with symptomatic SCD, treated with Siklos®. Only patients having been informed of the study by the investigator and consenting to participate in the study or whose parents or legal guardians have been informed and given permission for their child to participate will be included. In addition, children mature enough to understand the study and what they are expected to do will be asked to give their assent. Only patients with at least one of the following criteria will be considered for enrolment: • Participants previously enrolled in ESCORT-HU and who agree to participate in the extension study, • New participants: o with history of HU treatment for more than 5 years, or o children who have not completed puberty aged more than 10 years for girls and more than 13 years for boys at enrolment (possibility to follow them at least until the end of puberty and for boys to increase the number of patients with potential therapeutic window/stop to do the semen cryopreservation), or o with leg ulcers history, or o being pregnant women without interruption of Siklos® 3 months before the beginning of the pregnancy, or o being males treated with Siklos® whose partner is pregnant and without discontinuation of Siklos® 3 months before the beginning of the pregnancy.
VARIABLES	**Primary objective assessment** • Occurrence of malignancies, leg ulcers, male fertility impairment (oligospermia, azoospermia) and serious unexpected AEs (meaning SAEs which are not listed in the product information) according to the causal relationship with Siklos® or not and main features of these events. **Secondary objectives assessments** • Mean age at first periods for females, mean age of puberty for males and contraception, • Incidence of the use of cryopreservation for the purpose of paternity, management of semen cryopreservation (age of performance compared to the age of occurrence of puberty/ stop of HU treatment) and semen analysis, • Management of Siklos® during pregnancy (number of pregnancies, HU treatment interruption, mean exposure time to HU during the entire pregnancy, mean exposure time to HU per week during pregnancy) and outcome of pregnancy following exposure at the time of conception (in participant and participant's partner) or at any time during the pregnancy, • Frequency and reason for temporary (>15 days) or permanent discontinuations of Siklos® duration of interruption, daily dose of Siklos at the time of discontinuation, reoccurrence of vaso-occlusive crisis, • Switch or combination with alternative treatment (erythrocytapheresis,

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	Hydrea®, blood transfusion, bone marrow transplantation and/or other), • Complications linked to SCD at enrolment and occurring during follow-up, • Quality of life for adults SCD patients
DATA SOURCES	Data from participant's medical records and results from routine visits available in hospitals will be entered in the electronic case report form (eCRF) by the investigator or delegated data entry specialists. Data to be retrieved from ESCORT-HU will also be reported in the e-CRF of ESCORT-HU Extension. Data entered in the eCRF will be sent to a central database via a secure transfer. Electronic forms will be used to transmit information collected during the study to Theravia and regulatory authorities, as applicable. For participants already included in ESCORT-HU, data and medical history at last visit in ESCORT-HU study will be collected retrospectively at enrolment visit and data between last visit in ESCORT-HU study and first visit in ESCORT-HU extension study will be collected retrospectively at follow-up 1 visit. Main data collected at baseline will include demographic baseline characteristics of the participant, SCD history, SCD treatment history, history of malignancies, leg ulcers, male fertility impairment (oligospermia, azoospermia), and fertility status. Then, the following data will be collected at least annually during a follow-up visit: • Occurrence of malignancies, leg ulcers, male fertility impairment (oligospermia, azoospermia) and serious unexpected AEs causally related to Siklos®, • Siklos® treatment stop (temporary stop > 15 days and permanent stop), reason for treatment stop and combination or alternative treatments, • Fertility status evolution, cryopreservation, (if any) and conditions of cryopreservation, occurrence of pregnancy and outcome. The quality of life of the adults' patients will be evaluated once or twice during the study.
STUDY SIZE	Around 2100 patients treated with Siklos® are expected to participate in this extension study. This sample size must allow the estimation with a sufficient precision of the rate of patients treated with Siklos® experiencing any of the events of interest (malignancies, leg ulcers, male fertility impairment (oligospermia, azoospermia) and serious unexpected adverse events causally related to Siklos®) (primary objective of ESCORT-HU Extension study). A sample size of 2100 patients will allow for an estimation of rates of events as low as 0.5% with a precision of 0.3%.
DATA ANALYSIS	Primary and secondary endpoints will be analysed on all enrolled patients and on the safety population consisting of all enrolled participants having received at least one dose of Siklos® and meeting all inclusion criteria. The analyses will be mainly descriptive and no formal statistical testing will be carried out. Statistical evaluation will be performed using Statistical Analysis System (SAS)®. Parameters will be presented in terms of mean, median, standard deviation, range for continuous data and counts or percentage for categorical data. Two-sided 95% confidence intervals (95%CI) will be presented where appropriate. Descriptive statistics will be used to: • Report the prevalence of primary and secondary variables, • Describe the global population and the sub-groups of interest, where relevant.

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	Appropriate multivariate analyses will be used to describe the determinants of the observed events, if the number of observed events is sufficient.
MILESTONES	Starting date (First Patient First Visit): Q3 2020 Regular periodic review for periodic safety documents: annually End of inclusions (Last Patient Included): Q1 2024 End of follow-up (Last Patient Last Visit): Q3 2025 Annual interim reports; End of Q3, each year, from 2021 to 2024 Final analysis: estimated 2026

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5. Amendments and updates

Protocol Version / Date	Type of Amendment	Amendment Rationale	Sections Affected	Summary of Amendment / Changes to the Protocol
v1.0 (15 Jan 2020)	n.a	n.a	n.a	n.a
v2.0 (30 Oct 2020)	Non substantial	Deletion of Siklos SmPC from annexes and minor corrections and precisions	Section 9.2. Setting Section 9.3.1. Inclusion visit and section 9.3.2. Follow-up visit Section 9.3.2. Follow-up visit and Annex 2 Section 9.7.1. Analysis set	Precisions regarding data collection for patient who previously participate o ESCORT-HU study were added. Addition of data collected in eCRF that were not mentioned in the protocol Deletion of Siklos SmpC from annex 2 and replacement by the sentence “SmPC of Siklos effective at the time of the event” in order to take into account all future modifications of the SmPC. In the statistical part, study populations (Enrolled population and Reference population) were combined into a single population called Safety population
v3.0 (06 April 2022)	Non substantial	Clarification of study objective and endpoints Precision of an inclusion criteria Addition of data collected in the database but not present in these section Minor clarifications	Section 8. Research question and objectives 9.2.1.1. Inclusion criteria 9.3.1. Inclusion Visit and 9.3.2 Follow up visits 9.7.1. Analysis sets	Endpoints have been detailed in order to take into account all the data collected and to be more accurate. The pubertal status of the patients has been clarified The pubertal status of the patients has been clarified and all data collected in the database have been added Minor clarifications have been added

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		Precision regarding events reported in medical history	11.2. Adverse event collection and reporting	Events reported in medical history section will not be analysed as adverse events
V4.0 (19 September 2023)	Non substantial	Change of Sponsor Name and address	Section 3. Responsible parties Section 11.2 Adverse event collection and reporting	Name/address of Sponsor contacts and logo have been modified.
		Change of end of inclusions and sample size	Section 4. Abstract Section 9.2.1 Study population Section 9.5 Study size Section 9.9.1 Selection bias	Sample size has been changed to 2100 patients as inclusions will end at Q1 2024.

6. Milestones

Milestone	**Planned date**
Start of data collection	Q3-2020
End of data collection	Q3 2025
Annual interim report	Q3-each year, from 2021 to 2024
Final report of study results	Estimated 2026

7. Rationale and background

The efficacy and long-term effectiveness of hydroxycarbamide/hydroxyurea (HU) in the prevention of painful crises and in the decrease of mortality and morbidity in sickle cell disease (SCD) patients has been established (Charache et al. 1992; Halsey et al. 2003). As a post marketing commitment to the European Medicinal Agency (EMA) following granting of the marketing authorization for Siklos® in Europe, the non-interventional prospective ESCORT-HU study was conducted as part of the Risk Management Plan to evaluate the use of Siklos® in real-life conditions and to collect information on the long-term safety of Siklos® when used in current practice for the prevention or treatment of symptomatic complications in patients with SCD.

A total of 1906 patients were enrolled in the ESCORT-HU study in 62 centres (Germany, Greece, Italy and France) between January 2009 and June 2017. As planned in the protocol, the follow-up was closed in Q1 2019. The main objectives of ESCORT-HU have been fulfilled as regards the collection of data on the most common concerns associated with the use of HU in

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SCD patients: myelosuppression, child growth, concomitant administration of live vaccines, safety in population with renal and hepatic impairment and frequency of SCD events (painful crises, acute chest syndrome, stroke, acute splenic sequestration, infections, blood transfusions and hospitalizations).

However, due to the late access to the market in France and the absence of significant sales in the United Kingdom, both counting for the largest population of SCD patients in Europe, less than 200 participants had been enrolled in ESCORT-HU by the end of 2012. The majority of the participants have been enrolled from January 2013. Therefore, long-term follow-up data are still lacking and the following concerns still need to be addressed:

- Drug-induced malignancies: the mean exposure in the cohort of ESCORT-HU study was 30 months, for a cumulative exposure of 7310 patient-years by 01 July 2019. Only one myelodysplastic syndrome has been reported in the cohort to date. It is possible that the duration of exposure to HU was too short to fully estimate the incidence of this risk; therefore, further long-term exposure data are required.

- Leg ulcers: the number of events and duration of exposure were not sufficient to provide discriminating criteria between leg ulcer caused by the disease and HU-induced leg ulcer. Further data are needed to define such discriminating criteria.

- Male fertility: different publications report the deleterious effect of HU on spermatozoa count (Berthaut et al. 2017, Jones et al. 2009, Smith-Whitley et al. 2014) and reversibility has been observed after HU treatment stop (Elalfy et al. 2018, Sahoo et al. 2017). The consequences on male fertility when HU is started before puberty, sometimes in very young children, are still not very well documented. Therefore, one of the objectives of the ESCORT-HU Extension study is to gain knowledge on how clinicians manage this concern: What is the fertility potential in patients treated with HU when HU is started before puberty? Is it possible to temporarily stop HU to allow for sperm cryopreservation and document the time to reverse HU lesions? Which alternative SCD treatment is appropriate during this HU-free period? Do the deleterious effects reoccur?

- Pregnancies: to date, there is a limited number of pregnancies with documented outcome. Despite no adverse effects on pregnancy or on the health of the foetus/newborn have been registered (Siklos® summary of product characteristics [SmPC]), a careful follow-up should be considered in case of female pregnant patients or pregnant partners of male patients exposed to HU. Therefore, since an increase of the number of pregnancies with documented outcomes will allow for meaningful assessment of foetal outcome following exposure to Siklos® during pregnancy, additional data should be collected.

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- Although its efficacy in the clinical management of SCD has been demonstrated, HU is often underutilised. Potential barriers to the adherence of HU have been identified at patient, provider and system levels (Brandow et al. 2010, Brawley et al. 2008). Lack of knowledge on the therapeutic potential of HU represents a barrier at the 3 above mentioned levels. Moreover, it is well known that the fear of side effects and constant laboratory monitoring are 2 factors which hinder patients to fully adhere to the treatment. Additional data will help to better apprehend the potential barrier to patient's compliance to HU. In this regard, patients' decision to discontinue their treatment has to be distinguished from a discontinuation decided by the physician and perceived as necessary to ensure the safety and well-being of patients.

- Finally, new SCD treatments, in combination with HU or not, are or will be soon available. How does HU fit in the management of SCD within this new environment?

The data collected in this study extension will supplement data from ESCORT-HU study on specific safety concerns when using Siklos® in routine clinical practice in adult and paediatric patients treated for SCD. Patients giving their consent to participate in the study or whose parents or legal guardians have been informed and given permission for their child to participate will be followed for up to 5 (additional) years or until discontinuation of Siklos®. Of note, children mature enough to understand the study and what they are expected to do will be asked to give their assent.

8. Research question and objectives

As safety information regarding the use of HU on long-term remains incomplete despite a first safety study (ESCORT-HU), an extension of the latter is proposed. The ESCORT-HU Extension study aims at evaluating the long-term safety of Siklos® when used in current practice in adults and paediatric patients treated with Siklos® and followed for up to 5 years.

Objectives	Endpoints
Primary	
• To determine the long-term safety profile of Siklos® focusing on risks which are poorly documented or unknown (unknown meaning: nature and frequency of serious adverse events [SAEs] causally related to Siklos® which are not listed in the product information).	• Occurrence of malignancies, leg ulcers, male fertility impairment (oligospermia, azoospermia) and serious unexpected AEs (meaning SAEs which are not listed in the product information) according to the causal relationship with Siklos® or not and main features of these events.
Secondary	
• To document changes in fertility status in males and females; in particular, to determine and document the management of male fertility through the use of semen cryopreservation in adults but also in	• Mean age at first periods for females, mean age of puberty for males and contraception,

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children having started HU in early childhood.	
Secondary (continued)	
• To monitor the outcome of pregnancies following exposure to Siklos® at the time of conception or at any time during the pregnancy (in participant and participant's partner).	• Incidence of the use of cryopreservation for the purpose of paternity, management of semen cryopreservation (age of performance compared to the age of occurrence of puberty/ stop of HU treatment) and semen analysis,
• To provide more information about the potential barriers to the compliance to the prescription.	• Management of Siklos® during pregnancy (number of pregnancies, HU treatment interruption, mean exposure time to HU during the entire pregnancy, mean exposure time to HU per week during pregnancy) and outcome of pregnancy following exposure at the time of conception (in participant and participant's partner) or at any time during the pregnancy,
• To provide more information about the potential barriers to the compliance to the prescription of Siklos®,	• Frequency and reason for temporary (>15 days) or permanent discontinuations of Siklos®, duration of interruption, daily dose of Siklos at the time of discontinuation, reoccurrence of vaso-occlusive crisis,
• To determine how the switch or combination with new SCD treatments is made.	• Switch or combination with alternative treatment (erythrocytapheresis, Hydrea®, blood transfusion, bone marrow transplantation and/or other).
• To describe complications linked to SCD	• Complications linked to SCD at enrolment and occurring during follow-up
• To document the quality of life of SCD adult patients	• Quality of life questionnaire: 12-Item Short-Form Health Survey (SF-12)

9. Research methods

9.1. Study design

This is a multicentre, prospective, non-interventional cohort study in adult and paediatric patients treated with Siklos® purposed to deepen the current knowledge on low incidence and indeterminate risks including secondary cancers, leg ulcers, serious unexpected adverse events related to Siklos® and fertility issues. A feasibility study for ESCORT-HU Extension was performed during summer 2018 showing that almost all centres participating in ESCORT-HU study were willing to continue the surveillance of their participants treated by Siklos® through ESCORT-HU Extension study. In addition, approximately 10 additional SCD reference centres are expected to participate in ESCORT-HU Extension study. The ESCORT-HU Extension

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study is thus expected to cover almost all SCD reference centres in France and to ensure, as detailed below (section 9.2), the follow-up of more than 50% of the patient population eligible for Siklos® treatment in the participating centres.

9.2. Setting

ESCORT-HU Extension study will be initiated in the same countries as ESCORT-HU (France, Italy, Germany and Greece).

Investigators will be recruited among physicians experienced in SCD management who are the only ones authorised to initiate Siklos® treatment hence to enrol and to follow up the participants. Investigators who are already participating in ESCORT-HU study will be asked to participate in the extension study. In addition, the study will be proposed to other physicians experienced in SCD management in France, Germany, Greece, and Italy in order to open new sites motivated to participate in the ESCORT-HU Extension study.

Investigators will have to fulfil the following criteria:

- Be able to enrol a minimal number of SCD patients who are potentially likely to be treated by Siklos® (minimal number of patients per investigator: 3),
- Have the adequate resources for collecting (through a web-based electronic case report form [eCRF]) and transmitting medical data and all the results of the assessments performed during the entire study,
- Have the possibility to be in contact with the participant and other medical staff to prevent loss to follow-up or to collect additional medical information.

During the study, the participating investigator will be free to determine the appropriate therapy for each participant and make treatment choices as deemed clinically necessary and according to current clinical practice.

Participants will be followed for up to 5 years. The follow-up will be strictly observational and will fit within routine clinical monitoring without any controlled treatment, specific examination, investigation or modification of follow-up. Participants will be evaluated in hospital at inclusion. Due to the observational nature of the study, investigators will be free to determine the frequency of the visits of the participant although at least one follow-up visit per year will be entered in the eCRF containing all data from the previous visit.

Both retrospective and prospective data will be collected in order to well document SCD history and Siklos® exposure. For participants already included in ESCORT-HU, data and medical history at last visit in ESCORT-HU study will be collected retrospectively at enrolment visit and data between last visit in ESCORT-HU study and first visit in ESCORT-HU extension study will be collected retrospectively at follow-up 1 visit. Investigator's will be asked to enter data in the eCRF at inclusion, and to complete a follow-up visit in the eCRF at least every year.

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The investigator will report in each follow-up visit of the eCRF patient's relevant medical information collected within the last visit. Each investigator will be included in the database and a reminder will be sent regularly (every 12 months) in case of missing follow-up data capture for a given participant. Temporary discontinuation of Siklos® will not lead to interruption of data collection, however, in case of permanent stop, data will no longer be collected and the participant will be withdrawn from the study (Section 9.2.2.).

9.2.1. Study Population

Patients will be recruited over a 3.5-year period, from Q3 2020 to Q1 2024 with an end of follow-up at Q3 2025. In addition to patients already involved in ESCORT-HU, new at-risk patients might be added in additional centres in France, Italy and Germany, such as 1/ patients with a long history of HU exposure (at least 5 years, to allow a long-term follow-up), 2/ children who have not completed puberty aged more than 10 years for girls and more than 13 years for boys (in order to document puberty and cryopreservation) and 3/ patients with a history of leg ulcers, 4/ pregnant women without interruption of Siklos® 3 months before the beginning of the pregnancy, 5/ males treated with Siklos® whose partner is pregnant and without discontinuation of Siklos® 3 months before the beginning of the pregnancy.

During the recruitment period, patients fulfilling the inclusion criteria will be informed by their initiating physician about the ESCORT-HU Extension study and enrolled in case they agree to participate.

It is expected that more than 60% of participants included in ESCORT-HU study (i.e. approximately 1200 patients) will be treated by Siklos® at the time of the inclusion in the ESCORT-HU Extension study and will give their consent to continue the surveillance allowing thus collection of data over a period of up to 15 years in total. Taken into account the patients recruitment rate in the ESCORT-HU study, approximately 1200 new patients are expected to be recruited by the ESCORT-HU centres over the 5-year duration of the study. In addition, at least 10 participants in each of the 10 additional SCD reference centres are expected to participate in ESCORT-HU Extension study. In total, around 2100 patients treated with Siklos® are expected to participate in this extension study.

In centres already involved in ESCORT-HU, all participants and parents or legal guardians of children already enrolled in ESCORT-HU and still treated by Siklos® and fulfilling the eligibility criteria for ESCORT-HU extension will be informed by the investigator about this extension study and the possibility for a longer follow-up period. Participants will be included only upon given informed consent according to local regulations. For patients <18 years old, parents or legal guardians will be informed and have to give permission for their child to participate. In addition, children mature enough to understand the study and what they are expected to do will be asked to give their assent. Patients turning 18 years old during the follow-up period, will be asked to give their consent upon their majority.

All new eligible patients in already existing centres and new centres will also be asked to

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participate according to local regulations and will be enrolled after given informed consent.

9.2.1.1. Inclusion criteria

In order to enter the study, participants must fulfil all the eligibility criteria reported below:

- Male or female patients with symptomatic SCD,
- ≥ 2 years old,
- Treated with Siklos® (initiation of treatment before inclusion in the study or on the day of inclusion),
- Having been informed of the study by the investigator and consenting to participate, or whose parents or legal guardians are consenting for their child to participate.

In addition, children mature enough to understand the study and what they are expected to do will be asked to give their assent.

- To allow risk evaluation, participants must belong at least to one of the subpopulations defined below:
    - Participants previously enrolled in ESCORT-HU who agree to participate in ESCORT-HU Extension study,
    - New participants with any of the following criteria:
        - history of HU treatment for more than 5 years, or
        - children who have not completed puberty over 10 years of age for girls and 13 years of age for boys at enrolment (possibility to follow them until the puberty and increase the number of patients with possible therapeutic window/stop to perform the semen cryopreservation), or
        - with history of leg ulcer, or
        - pregnant women without interruption of Siklos® 3 months before the beginning of the pregnancy, or
        - males treated with Siklos® whose partner is pregnant and without discontinuation of Siklos® 3 months before the beginning of the pregnancy.

9.2.2. Withdrawal from study and termination of study criteria

A participant may withdraw from the study at any time without prejudice.

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If the investigator decides it is in the best interest of the participant to permanently discontinue Siklos®, the participant should be withdrawn from the study.

In case of withdrawal, the following data are to be reported in the participant's medical file:

- Date of withdrawal,
- Reasons for permanent discontinuation and/or premature withdrawal. If there are several reasons, the main reason should be reported.

The reasons for permanent discontinuation of treatment and/or premature withdrawal from the study should be documented in the e-CRF and may include (not exhaustive):

- Death
- Toxicity due to hydroxycarbamide,
- Inefficacy,
- Alternative treatment (erythrapheresis, switch to Hydrea, Transfusion, Bone marrow transplantation…),
- Patient's/parents' will
    - Lost to follow-up
    - Other reason

  Of note, a stop longer than 12 months due to the wish of being parent has to be considered as a temporary stop.

Lost to follow-up: In case the participant leaves the participating centre, every effort must be made by the centre to determine whether the participant continued the treatment and if not the reason for the discontinuation. If all these attempts to contact the participant fail, the investigator can then declare the participant "lost to follow-up". The investigator should document all these attempts in the corresponding participant's medical file.

In case of premature withdrawal from the study due to toxicity, the event must be reported to the competent authority by the investigator.

9.2.3. Steering Committee

A **Steering Committee**, formed by medical experts from all the countries involved in the cohort and sponsor representatives, will oversee the conduct and reporting of the study, to ensure expert clinical guidance and a high standard of scientific quality. Members of the Steering Committee will meet at least once a year unless additional unscheduled meetings are needed. A specific charter will be developed to define roles and responsibilities of the Steering Committee.

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9.3. Variables

Study assessments are detailed in Table 1 provided below:

Table 1Study assessments

	Inclusion visit	Follow-up visits	Termination visit[1]
Informed consent[2]	X		
Demographic data -Date of birth -Gender	 X X		
Haemoglobin genotype	X		
Biology (Hb, HbF, Neutrophils, MCV)	X	X	X
Treatments: -HU treatment history -Other SCD treatment -Siklos® treatment	 X X X	 X X	 X X
Medical history -Malignancy -Leg ulcer and other SCD complication -Male fertility impairment (oligospermia, azoospermia)	 X		
Malignancy		X	X
Leg ulcer and other SCD complication		X	X
Serious unexpected adverse event causally related to Siklos®		X	X
Male fertility impairment (oligospermia, azoospermia)		X	X
Fertility status and pregnancy	X	X	X
Quality of life questionnaire (SF-12 + additional questionnaire)	X[3]	X[3]	

[1]Termination visit may occur at the end of planned study period or at last visit prior to participant permanent discontinuation/withdrawal from the study.
[2]According to local regulations.
[3]One or two administrations during the study
AE: adverse event; HU: Hydroxyurea; SCD: Sickle cell disease;

9.3.1. Inclusion Visit

The informed consent (ICF) of the participant or of the parents or legal guardian of the participant must be obtained before enrolment in the study, in the modality foreseen by local regulations. Children mature enough to understand the study and what they are expected to do will be asked to give their assent.

During the inclusion visit, the following data will be collected:

Demographic characteristics:

- Date of enrolment (corresponding to date of consent),
- Demographic characteristics of the participant: date of birth and gender.

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SCD history:

- Haemoglobin Genotype (SS, SC, Sβ0, Sβ+, other S genotype when applicable), alpha gene defect, G6PD deficiency,

Treatments:

- HU treatment history
    - History of treatment with any specialty of hydroxycarbamide: start date of the first administration of any specialty of hydroxycarbamide, reason for initiation.
- Other SCD treatment
    - SCD treatment other than HU: treatment, start date, stop date and reason for initiation.

Laboratory results:

- Haemoglobin, Foetal Haemoglobin, Absolute Neutrophils Count, Mean Corpuscular Volume

Quality of life questionnaire (for adults patients only, not mandatory, to be performed once or twice during the study):

- 12-Item Short-Form Health Survey (SF-12)
- Additional questionnaire about patient's quality of life

Medical History

- History of malignancy:
    - Date of first diagnosis, organ, type of treatment, date of treatment, status of the malignancy at enrolment, history of malignancy in the family of the patient.
- History of leg ulcers:
    - Type of lesion, type of episode, location(s), status of leg ulcer at enrolment, causal relationship with HU.
- Type of complications linked to SCD

Fertility status

- Pubertal status (for female : age at first period, for males : age at Tanner V stage),
- For male, age at puberty, history of sperm cryopreservation, results of semen analysis

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if available, oligospermia, azoospermia (if applicable),

- For female, age at onset of periods, previous pregnancies and number of children (if applicable),

9.3.2. Follow-up Visit

During the follow-up visit, the following data will be collected:

Date of visit

Serious Unexpected AE causally related to Siklos®

The list of all AEs related to Siklos® by frequency of occurrence, is documented in the SmPC of Siklos effective at the time of the event.

Unexpected serious AEs not reported in the product SmPC which is applicable at the time of the event and considered as causally related to Siklos® should be collected in the context of ESCORT-HU Extension study. Oligospermia and azoospermia events will also be collected. For each of these events, the information listed below will be collected and reported in dedicated forms as detailed in Section 11.

- Event type, date of onset, date of end, seriousness criteria, change of Siklos® treatment, corrective treatment, severity and outcome, declaration to competent authority.

Malignancy, Leg ulcer, SCD complications

- Malignancy: occurrence, reoccurrence, date of first diagnosis, organ, date of treatment, type of treatment, status of the malignancy and causal relationship with Siklos®.

- Leg ulcer: occurrence, reoccurrence or worsening, causal relationship with Siklos®, date of diagnosis, type of lesion, main location, treatment, status of leg ulcer, doppler and other exams results, predisposing factors.

- Complications linked to SCD: Type of complication

Siklos® treatment

- Daily dose of Siklos® at the visit,

- Temporary stop longer than 15 days, reason of stop, date of interruption, date of restart, dose of Siklos® at the stop, and occurrence of vaso-occlusive event during the treatment stop and number,

- Permanent stop,

- Other SCD treatment:

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- SCD treatment other than HU: treatment, start date, stop date and reason for initiation.

Laboratory results:

- Haemoglobin, Foetal Haemoglobin, Absolute Neutrophils Count, Mean Corpuscular Volume

Quality of life questionnaire (for adults patients only, not mandatory, to be performed once or twice during the study):

- 12-Item Short-Form Health Survey (SF-12)
- Additional questionnaire about patient's quality of life

Male fertility status

- Pubertal status: Age at puberty if it occurs within the previous year,
- For pubescent males: Sperm cryopreservation, age at sperm cryopreservation, Siklos® interruption, and semen analysis, oligospermia, azoospermia, relation to Siklos®
- For pubescent males: Partner pregnancy and outcome of pregnancy; date of pregnancy, use of cryopreserved semen, outcome of pregnancy, Siklos® treatment interruption, when applicable.

Female fertility status

- Pubertal status: Age at first periods, when applicable,
- For pubescent females: Contraception,
- For pubescent females: Pregnancy and outcome of pregnancy; date of pregnancy, outcome of pregnancy, Siklos® treatment interruption, when applicable, status of the baby.

Of note, patients turning 18 years old during the follow-up period, will be asked to give their consent upon their majority.

9.4. Data sources

Data from participant's medical records and results available from routine visits available at hospital level will be entered in the eCRF by the investigator or delegated data entry specialists. Data entered in the eCRF will be sent to a central database via a secure transfer. The electronic forms will be used to transmit information collected during the study to Theravia and Regulatory Authorities, as applicable.

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9.5. Study size

The total number of patients expected to be enrolled in the ESCORT-HU Extension study over a 3.5-year period, from Q3 2020 to Q1 2024 is estimated to be of 2100:

- According to the results of a feasibility study performed during Summer 2018, it is estimated that more than 60% of the participants enrolled in ESCORT-HU (that is about 1200 patients) will be still treated by Siklos® (and will accept a follow-up in ESCORT-HU Extension
- Based on the patients' recruitment rate in the ESCORT-HU study, approximately 1200 new patients are expected to be recruited by the ESCORT-HU centres over the 3.5-year enrolment period of the study
- In addition, at least 10 participants in each of the 10 additional SCD reference centres are expected to participate in ESCORT-HU Extension study

This sample size must allow the estimation with a sufficient precision of the rate of patients treated with Siklos® experiencing any of the events of interest (malignancies, leg ulcers, male fertility impairment (oligospermia and azoospermia) or serious unexpected adverse events) causally related to Siklos® (primary objective of ESCORT-HU Extension study). The rates of these events are expected to be low, being ≤ 5 %. They will be estimated using two-sided 95% Confidence Interval (95%CI). The precision *e* in the estimation of a rate *p* for a given sample size *n* is calculated using the following sample size:

$$e = \sqrt{\frac{1.96^2 p(1-p)}{n}}$$

The table below provides the precision of the estimation with n=2100 patients to estimate rates from 0.5% to 5%

Expected rate of the events of interest	**Precision in the estimation with n=2100 patients**
p=5%	e=0.93%
p=2,5%	0.67%
p=1%	0.42%
p=0,5%	0.30%

This will allow for an estimation of frequencies of events as low as 0.5% with a precision of 0.3%.

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9.6. Data Handling

9.6.1. Case report form

An electronic data capture system will be used for this study.

In order to ensure confidentiality and security of the data, usernames and passwords will be used to restrict system access to authorized personnel only, whether resident within the Investigator's sites, Sponsor or third parties.

Data will be entered by the investigator or delegated data entry specialists in the eCRF once a year. Entered data will be sent to a central database via a secure transfer.

The eCRF will be reviewed periodically for completeness, legibility, and accuracy by Theravia personnel (or their representatives). The investigator or the delegated data entry specialist will make any necessary corrections to the eCRF.

After the last visit of the participant and before the lock of the eCRF, the Investigator must attest by entering his/her user name and password:

- the authenticity of the data collected in the eCRF,
- the coherence between the data in the eCRF and those in the source documents, with the exception of those data recorded directly in the eCRF and considered as source data.

9.6.2. Data management

A Contract Research Organization (CRO) appointed by the Sponsor will be responsible for management of collected data (setting up of a database and validation).

SAS® software version 9.2 or later is used for data management process and data are stored in the clinical database stored in a secure folder.

AEs will be coded to a Preferred Term and System Organ Class using the Medical Dictionary for Regulatory Activities (MedDRA). SCD treatments will be coded using the World Health Organization (WHO) Drug Dictionary. The latest validated version of MedDRA and WHO Drug Dictionary will be used for coding.

Access to the electronic data capture system will be provided to the CRO personnel responsible for data management for the duration of the trial through a password-protected method of internet access.

Quality assurance department representatives from Theravia and/or CRO may visit a study site to conduct quality assurance audit in order to ensure the study is conducted in compliance with protocol, standard operating procedures and all applicable legal requirements (Section9.8.).

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9.7. Data analysis

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP). The SAP will be written by the CRO in charge of the study and will be validated by the Sponsor prior to the database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

Being a safety study, the analyses will be mainly descriptive and no formal statistical testing will be carried out.

Statistical evaluation will be performed using Statistical Analysis System (SAS)® (version [9.4 or higher])

9.7.1. Analysis sets

All statistical analyses (i.e. patients disposition and characteristics, primary and secondary endpoints) will be performed on all enrolled patients and on the Safety Population, defined as all enrolled patients meeting all inclusion criteria who received at least one dose of Siklos®.

The list of inclusion criteria not respected will be defined by the CRO in charge of the Statistics activities in a dedicated document validated by the sponsor. This list will be reviewed with the Sponsor during the pre-analysis data review meeting.

9.7.2. Statistical /analytical methods

9.7.2.1. Descriptive statistics

All assessment data, including demographics, will be summarised using descriptive techniques. Summary statistics (n, mean, standard deviation, median, first and third quartiles (Q1 and Q3), minimum and maximum values) will be presented for quantitative variables. Absolute frequencies and percentages will be presented for qualitative variables. Where appropriate, Two-sided 95% confidence intervals (CIs) will be presented (Wald for the quantitative variables, Agresti-Coull for the categorical variables).

Where relevant, analyses will also be produced according to subgroups defined in section 9.7.2.4.

Individual patient listings to be provided will be detailed in the Statistical Analysis Plan.

9.7.2.2. Analysis of primary endpoints

The primary analysis will be based on the description of the following events of interest occurring during ESCORT-HU extension study follow-up period:

- malignancies,
- leg ulcers,
- serious unexpected adverse events related to Siklos®

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- male fertility impairment (oligospermia and azoospermia)

Events occurring during ESCORT-HU extension study follow-up period are those reported in follow-up visits. For participants previously enrolled in ESCORT-HU, only events with a date of onset > date of last visit in ESCORT-HU will be taken into account.

Serious unexpected adverse events related to Siklos® will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

The number and percentage of patients having presented at least one of the events of interest will be calculated and the corresponding two-sided Agresti-Coull 95%CI provided.

For serious unexpected adverse events related to Siklos®, the analysis will be performed overall and by MedDRA system organ class (SOC) and preferred term (PT). In this by-patient analysis, a patient having the same event more than once will be counted only once.

Detailed listings of the events of interest will be provided.

Moreover, appropriate multivariate analyses will be used to describe the determinants of the observed events of interest if the number of observed events is sufficient.

9.7.2.3. Analysis of secondary endpoints

Each of the secondary endpoints will be summarized using descriptive statistics overall and by subgroup, if relevant, as described in Section 9.7.2.1.

9.7.2.4. Subgroups analyses

All subgroups' analyses will be performed on the Safety population. As will be specified in the SAP, some statistical analyses will be stratified.

The following analyses will be performed as exploratory analyses of the primary endpoints:

- Number and percentages of patients having presented malignancies after inclusion in the ESCORT-HU Extension study according to the occurrence of malignancies before inclusion in the ESCORT-HU Extension study

- Number and percentages of patients having presented leg ulcers after inclusion in the ESCORT-HU Extension study according to the occurrence of leg ulcers before inclusion in the ESCORT-HU Extension study

- Number and percentages of male patients having presented fertility impairment after inclusion in the ESCORT-HU Extension study according to the occurrence of male fertility impairment before inclusion in the ESCORT-HU Extension study

If relevant, primary and secondary parameters will also be analysed according to:

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- The gender
- The patient age at the time of the inclusion in the study in category
- Prepubescent >10 years old for girls and >13 years old for boys
- The duration of the exposure to Siklos®/HU in category
- The country

No statistical comparison between groups will be done. A given analysis will be performed within a subgroup only if the subgroup is composed of sufficient number of participants. Further details will be provided in the SAP.

9.7.3. Handling of missing data

Methods of handling missing data will be drafted within the SAP, presented and discussed during the final pre-analysis data review meeting and then, if required, modified in the final version of the SAP.

By default, for patients who discontinue the study or miss a visit, missing data for quantitative variables will not be replaced, neither missing data on categorical variables. Missing data items will be indicated in all cases.

Regarding the primary endpoints a sensitivity analysis will performed. The proportion of patients having presented at least one event of interest and the proportions of patients having presented each individual event of interest will be performed in considering patients who stopped the study prematurely or lost to follow-up without having presented any of the event of interest as having presented the event (equivalent to a worst case method of imputation). Percentages will be based on the missing and non-missing data. The corresponding Agresti-Coull 95% CI will be computed and edited.

9.7.4. Interim analyses

Annual interim analyses will be performed in order to write annual report addressing the Pharmacovigilance Risk Assessment Committee (PRAC).

The annual report will present a general description of the population included and frequencies of all primary and secondary parameters on the global population and by subgroups.

9.8. Quality control (QC)

A monitor from the CRO mandated by the Sponsor will visit regularly the investigation centre, during the setting up and conduct of the study. Frequency of the visit will depend on the recruitment rate, agreement between the investigator and the monitor and the Sponsor’s specifications.

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Data QC will be performed in all sites in each country involved in the study. In each site, following an iterative approach, 5% of the participants will undergo QC. Each CRF page will be reviewed completely (100%) by the Clinical Research Associate (CRA) for accuracy and completion. If the control is not satisfying (% of error >5%), other 5% of participants will undergo QC.

It is the responsibility of the investigators to ensure that all data collected are recorded with minimum delay, accurately and legibly.

All study related material will be archived securely according to relevant internal procedures. A detailed archiving procedure will ensure that access to confidential information is limited and that the confidentiality of information about study participants is protected.

The archives should be maintained for the time defined by the local requirements after final report or first publication of study results, whichever comes first.

Prior to the initiation of the study, each investigator and study coordinator at participating sites will be trained on the protocol and eCRF completion. This training may be provided via an investigator's meeting (face to face, virtual, or hybrid), or an onsite initiation visit performed by a CRA. Sites will be given a workbook (CRF completion guide) describing completion of eCRF.

During the QC visit, the investigator will allow the monitor to:

- Inspect the site and the facilities where the study will take place as well as the material used for the study in order to ensure compliance with the protocol requirements,
- Meet all members of their team involved in the study,
- Consult all the documents relevant to the study,
- Have access to the eCRF,
- Directly access source documents for comparison of data therein with the data in the eCRF,

The monitor will:

- Check that the eCRF have been filled out correctly,
- Verify that the study is carried out in compliance with the protocol and local regulatory requirements,
- Pay attention to patients becoming adult during the course of the study. For children, consent is under the decision of parents/legally acceptable representatives until the 18th birthday. At this time the investigator should discuss with the participant the

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possibility to continue with the study (during the first visit after 18th birthday) and consent should be obtained and documented in the participant's medical file.

After the QC visit, CRA will discuss with the investigator or delegated data entry specialist the reported findings and their resolution. If not possible on site, the list of findings will be communicated after the visit in a follow-up email.

If corrections cannot be obtained during the visit, written instructions should be given for data entry correction according to the findings.

If computerised medical files are used, the investigator may print the medical files of the participants and securely archive them.

The investigator will personally sign and date the first page of each print-out, indicating the total number of pages. During a monitoring visit, the investigator may provide print-outs of the participant's medical files to the monitor. Those print-outs have to remain on site after monitoring visit.

If the computer system used allows the tracking of the changes made to the medical files, the investigator will supply the monitor, at each visit, with a print-out of the medical files of the participants and the records of the changes made. Each print-out will be personally dated and signed, by the investigator on the first page. The number of pages will also be indicated by the investigator on the first page.

All information dealt with during these visits will be treated as strictly confidential.

The investigator must guarantee the safety of the study data in the medical files by implementing security measures to prevent unauthorised access to the data and to the computer system.

9.9. Limitation of the research methods

Being an observational study, ESCORT-HU Extension may be affected by sources of bias that result from participant/SCD specialist selection, data collection and other factors.

9.9.1. Selection bias

Selection bias could occur if the characteristics of the participants or the investigators (SCD specialist) are systematically different from those of the general population, thus reducing its representativeness.

Investigational sites of the ESCORT-HU Extension study will be referent sites in SCD management, the only ones authorised to initiate Siklos® treatment. Taken into account that all or almost all investigators having participated to the ESCORT-HU study are expected to participate to the Extension study and that new reference sites will complete the sample of investigators, in participating countries, the participating sites are expected to represent about

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99% of all referent centres. The characteristics of the investigators of the ESCORT-HU Extension study will be then similar to the characteristics of the population of physicians initiating Siklos® and managing SCD.

In order to limit bias in the selection of patients, participants already enrolled in ESCORT-HU and treated by Siklos® will be asked for their consent to participate in the ESCORT-HU Extension study and the investigators will attempt to consecutively include all new patients who consent (or for whom parents or legal guardians consent) and meet the selection criteria, regardless of demography, health status, or other considerations as applicable.

Of note that the sample of patients enrolled in ESCORT-HU Extension study will represent more than 60% of the population of patients treated by Siklos® in the participating countries. Indeed, it is estimated that about 4000 patients only are treated with Siklos® over the world. More specifically, 80% of participants to the study are expected to be recruited in France. According to the elements that appear in the opinion of the transparency Commission (HAS) dated on May 2018, in France, the population of patients treated with Siklos® is estimated not to exceed 2500 patients. The French population coverage is thus expected to reach 80% at a minimum.

However, by design, patients treated with Siklos® having been treated by HU for 5 years or more, patients with history of leg ulcers and prepubescent children aged more than 10 years for girls and 13 years for boys may be slightly overrepresented in the study sample with respect of the population of patients treated by Siklos®.

9.9.2. Information bias

Information bias, also called measurement bias, is related to the completeness or accuracy of data collected over the course of the study. Measurement bias could affect investigators and could be due to difference in sites' procedures. To limit this bias, investigator and study coordinator at different participating sites will be trained in the same way on the protocol and data collection tool standard methods to manage SCD will be adopted.

9.9.3. Confounding bias

Confounding bias may result from selective patients care or selective prescribing of a particular treatments combination to more severely affected patients. As a result of a higher background risk, reported event rate may be higher and give the appearance of an elevated risk related to the use of the studied treatment. The collection of retrospective and baseline information will help to identify the presence of elevated background risk, so that event rates can be compared through subgroup analysis to determine whether the elevated risk is likely to be related to background risk or use of study drug.

This bias is further controlled by the participation of all or almost all referent physicians in the SCD management as well as the systematic consecutive patient invitation to participate in the study.

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9.9.4. Attrition bias

The non-interventional nature of the study may complicate the collection of follow-up data and may result in missing data and patients lost to follow-up. Even if the number of lost to follow-up in this study will be limited since, by nature, the SCD management obliges the patients to be closely monitored by their referent physician, it will be the study monitors responsibility to verify investigator's efforts and means through which study participants are contacted in order to avoid lost to follow-up.

Because the follow-up duration will be up to 5 years, the proportion of patient withdrawals/discontinuations might be significant. Safety data collection will be stopped in case of permanent discontinuation of Siklos and switch to another therapeutic regimen excluding Siklos® or Bone marrow transplantation or Gene therapy because it will not be possible to define if any occurrence of any event of interest after Siklos® discontinuation is linked to the previous use of Siklos® or to the new therapy or procedure. However, in patients secondarily treated with Hydrea® or other HU presentation, long term risks using HU will be reported to the MAH of Hydrea®.

9.9.5. Missing data

Missing data may bias the statistical analyses of a study if there are not missing completely at random; and even in this case, missing data may impact the precision of the estimates. The use of an e-CRF by investigators (including drop down list, single entry option and online checks for missing information) will reduce the risk of missing data; and will ensure that missing data will limit non-existing information and exclude non-reported information.

The handling of missing data is of special importance in longitudinal studies and thereby statistical analyses; its management and the methodology will be further discussed in the statistical analysis plan (SAP).

9.10. Other aspects

Not applicable.

10. Protection of human subjects

10.1. Participant information and informed consent

The investigator or a person designated by him is to collect consent from each participant before his/her participation in the study according to local regulations. For participants <18 years old, consent of their parents or legal guardians will be collected before any inclusion. In addition, children mature enough to understand the study and what they are expected to do will be asked to give their assent and patients turning 18 years old during the follow-up period will be asked to give their consent upon their majority. Prior to this, the investigator or their delegate must inform each participant of the objectives, benefits, risks and requirements imposed by the study,

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as well as the nature of the study products.

The participant will be provided with an information letter in clear and simple language. He must be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study.

When a written consent is required by local regulations, 2 original consent forms must be completed, dated and signed personally by the participant and by the person responsible for collecting the informed consent. If the participant is unable to read, an impartial witness should be present during the entire informed consent process. The participant must give consent orally and, if capable of doing so, complete, sign and personally date the information and consent form. The witness must then complete, sign and date the form together with the person responsible for collecting the informed consent. Both parents (or legal guardian) and the patient, if old enough to understand, will sign the inform consent form after carefully read the patient information sheet about the investigational medical product and the study requirements. The participant will be given one signed original information and consent form; the second original will be kept by the investigator.

When the written consent is not required by local regulations, the day the information letter is provided to the participant and the day participant's oral consent is collected, will be reported in the medical dossier of the participant.

10.2. Ethical Conduct of the Study

The Sponsor and the investigator(s) agree that the study will be performed in accordance with the Directive 2001/83/EC, Regulation (EC) No 726/2004 for the authorization and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, as well as in accordance with Guideline on Good Pharmacovigilance Practices (GVP) - Module VIII - Post-authorization safety studies (Revision 3, 13 October 2017); Guide on Methodological Standards in Pharmacoepidemiology (Revision 7, July 2018);]) International Society for pharmacoepidemiology guideline for Good Pharmacoepidemiology Practices (GPP) (Revision 3, June 2015), Recommendations for Deontology and Good Practices in Epidemiology (Version France 2007), and the Declaration of Helsinki (World Medical Association, Fortaleza 2013).

The study protocol and any amendments will be reviewed and approved by an independent ethics committee or institutional review board, according to local regulations in each country concerned by the study.

10.3. Patient Confidentiality

In accordance with the General Data Protection Regulation (GDPR, Regulation EU 2016/679), every effort will be made to maintain confidentiality of participant's data. At the time of study inclusion, participant will be assigned with an identification number which will be used to

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identify the participant in the eCRF. In order to respect participant anonymity in the database, collected personal data allowing participant identification will be encrypted.

All study data will be stored in electronic databases that are confidential, password protected and access-restricted. Investigators selected to perform the study and the CRO personal implicated in the study conduct will have access to the database. Theravia and competent authorities will be allowed to access to the data recorded in case of audit. For each authorised person, a login and an encrypted password will be created. All these persons have a duty of confidentiality to the participant and will do their best to meet this duty.

11. Management and reporting of adverse events (AE)/adverse reactions

11.1. Definitions

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labelling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE.

If an AE meets any of the following criteria, it is considered a serious adverse event (SAE):

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. **This does not include an emergency room visit or admission to an outpatient facility**.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in foetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache,

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	nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalisation, but based on medical judgment may jeopardise the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalisation, prolongation of hospitalisation, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

11.2. Adverse event collection and reporting

The following AEs will be collected during the study:

- Leg ulcers,
- Malignancies,
- Male fertility impairment (oligospermia and azoospermia),
- Unexpected serious AEs (i.e., which are not listed in the product information) causally related to Siklos®.

The investigator will monitor each participant for clinical and laboratory evidence of AEs and other special situations (i.e., pregnancy, Section 11.3.) relevant to the selected safety concerns at the enrolment visit and on a routine basis throughout the study.

Events reported in the medical history section will not be analysed as adverse events.

The investigator must seek to obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE. If an AE assessed as related to Siklos® occurs, expedited reporting to Health Authorities by Theravia will follow local and international regulations, as appropriate.

For AE with a causal relationship to Siklos®, follow-up by the investigator is required until the event or its sequelae resolves or stabilises at a level acceptable to the investigator, and Theravia concurs with that assessment.

In addition, an investigator may be requested by Theravia to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that

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captured on the AE page of the CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided.

This protocol requires all leg ulcers, malignancies, male fertility impairment (oligospermia and azoospermia) pregnancy and serious AE causally related to Siklos® not listed in the product information, to be actively solicited. Other events will not be actively solicited as these events are not likely to contribute to the further understanding of the safety profile of the product. For AEs which are not systematically collected in this study, healthcare professionals and consumers have to report adverse reactions (for which they suspect a causal role of a medicine) to the MAH (Theravia) or to the concerned Competent Authority via the national spontaneous reporting system (Annex 2).

The resulting case report will be managed, classified and submitted as spontaneous by the notified competent authority or MAH. The address of the MAH is:

Theravia
16 rue Montrosier
92200 Neuilly-sur-Seine
France
Tel: +33 (1) 72 69 01 86
Fax: +33 (1) 73 72 94 13

Email: pv@theravia.com

Leg ulcers, malignancy, male fertility impairment (oligospermia and azoospermia) and serious unexpected AEs causally related to Siklos® not listed in the product information experienced by study participants already under Siklos®/HU before study enrolment, will be recorded as medical history.

11.3. Special situations: pregnancy

If a participant is found to be pregnant, the evaluation of the risk-benefit ratio will be made on an individual basis outweighing the respective risk of continuing Siklos® therapy against alternative therapy.
All pregnancies should be reported as soon as the investigator is aware of the event and will be followed up to final outcome, using the pregnancy follow-up form.

11.4. Timeframe

Theravia is to be notified without delay after becoming aware of the event by the investigator or delegated data entry specialist via the eCRF if occur:

- Serious leg ulcers, malignancies and male fertility impairment (oligospermia and

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azoospermia),
- Serious unexpected AEs.

This timeframe also applies to additional new information (follow-up) on previously forwarded reports as well as to the initial and follow-up reporting of in utero exposure cases. In case eCRF is not available during the study, the investigator can report AE directly to the address above.

In the rare event that the investigator does not become immediately aware of the occurrence of the above mentioned events: leg ulcers, malignancies, pregnancy and serious unexpected AEs, (e.g., if an outpatient subject initially seeks treatment elsewhere), the investigator or delegated is to report the event without delay after learning of it and document the time of their first awareness.

For all serious leg ulcers, malignancies, serious unexpected AEs and serious oligospermia, and azoospermia events, the investigator is required to seek information and forward them to Theravia in accordance with the timeframes for reporting specified above. This timeframe also applies to special situations (i.e., pregnancies) and to additional new information (follow-up) on previously forwarded reports

11.5. Reporting period

For AEs collected prospectively, the collection period for the AEs starts from the time that the participant provides consent to participate in the study as foreseen by local regulation, and includes 28 calendar days after the last administration of Siklos®.

A medical event that occurs after a participant discontinues the study, and that is considered to be related to the participant's exposure to Siklos®, will be reported via standard post-marketing reporting practices.

11.6. Severity Assessment

The investigator will use the adjectives mild, moderate, or severe to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

- **Mild:** Does not interfere with participant's usual function,
- **Moderate**: Interferes to some extent with participant's usual function,
- **Severe:** Interferes significantly with participant's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

11.7. Causality Assessment

For all leg ulcers, malignancies, male fertility impairment (oligospermia and azoospermia) and

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serious unexpected AEs, sufficient information should be obtained by the investigator to determine the causality of the event.

The following definitions will be used to assess the relationship of the above mentioned AE to the use of Siklos®:

- **Related**: an AE where there is evidence to suggest a causal relationship between the product and the AE,
- **Not related:** an AE where there is no evidence to suggest a causal relationship between the product and the AE.

In case of suspected causal relationship to Siklos®, follow-up by the investigator is required until the event or its sequelae resolve or stabilise at a level acceptable to the investigator and upon Theravia agreement with that assessment.

If the investigator's final determination of causality is unknown and the investigator does not know whether or not Siklos® may have contributed to the event, then the event will be handled as "related to Siklos®" for reporting purposes.

12. Plans for disseminating and communicating study results

As per EU pharmacovigilance legislation, the protocol, the abstract and the final study report of the present PASS study will be published in the EU post-authorization study (PAS) register.

Moreover, upon study completion, study results will be submitted for review and publication in an appropriate scientific journal and/or presented at national/international scientific congresses.

13. References

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Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1			Study Investigators List

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Annex 2. Reporting of AE to National Competent Authority

Country	Competent Authority
France	ANSM: https://www.ansm.sante.fr/Declarer-un-effet-indesirable/Votre-declaration-concerne-un-medicament/Votre declaration-concerne-un-medicament/(offset)/0
Italy	AIFA. http://www.aifa.gov.it/content/come-segnalare-una-sospetta-reazione-avversa
Germany	BfArM: https://www.bfarm.de/DE/Home/home_node.html
Greece	ΕΟΦ, EOF. http://www.eof.gr/web/guest/organization

AIFA: Agenzia Italiana del Farmaco; ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé; BfArM: Bundesinstitut für Arzneimittel und Medizinprodukte; ΕΟΦ: Εθνικός Οργανισμός Φαρμάκων, EOF: National Organisation for Medicines;

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Annex 3. ENCePP checklist for study protocols

ENCePP Checklist for Study Protocols (Revision 4)

Article I. Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: ESCORT-HU Extension: European Sickle Cell Disease Cohort – Hydroxyurea – Extension study

EU PAS Register® number: Study not yet registered **Study reference number (if applicable):**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	6
1.1.2 End of data collection[3]	☒	☐	☐	6
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

[2] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[3] Date from which the analytical dataset is completely available.

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Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.1 & 9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Article II.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4 & 9.6
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.3
4.2.2 Age and sex	☒	☐	☐	9.3

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Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☒	☐	☐	9.3
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

5.2 It has no incidence on the primary objective

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8 & 9.3.
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☐	☒	

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Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

6.4 It is not the purpose of the study

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☐	☐	☒	
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☐	☒	

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Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☐	☐	☒	
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☐	☒	
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4 & 10.3

Comments:

9.3.1 Concomitant medications will not be collected

Article III.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

10.2 Study size only. Statistical precision not available.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6 & 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.2.3

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Comments:

11.1 : Information on database maintenance and fraud protection not yet available

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.2

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Article IV.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

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Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____