STUDY PROTOCOL

STUDY TITLE:	A bioequivalence study to compare the pharmacokinetics of two formulations of Siklos® in healthy volunteers.
SPONSOR STUDY NUMBER:	SIK-FR-21-1
SIMBEC-ORION STUDY NUMBER:	RD 785.35321
EudraCT NUMBER:	2021-002786-18
NCT NUMBER	05025072
IRAS ID:	300499
VERSION AND DATE	V4.0, 11 August 2021
INVESTIGATIONAL MEDICINAL PRODUCT(s):	**Test:** Hydroxycarbamide dispersible tablets (20 x 50 mg) **Reference:** Siklos® (Hydroxycarbamide) 1000 mg film-coated tablet.
PRINCIPAL INVESTIGATOR:	Dr Annelize Koch Simbec-Orion Clinical Pharmacology, Merthyr Tydfil Industrial Park, Pentrebach, Merthyr Tydfil, CF48 4DR, United Kingdom (UK).
STUDY SPONSOR:	Addmedica SAS 37 rue de Caumartin 75009 Paris, France.

NAME OF COMPANY: Addmedica SAS

NAME OF INVESTIGATIONAL MEDICINAL PRODUCT (IMP):

- **Test:** Hydroxycarbamide dispersible tablets (20 x 50 mg)
- **Reference:** Hydroxycarbamide 1000 mg film-coated tablet

NAME OF ACTIVE INGREDIENT: Hydroxycarbamide

TITLE OF STUDY: A bioequivalence study to compare the pharmacokinetics of two formulations of hydroxycarbamide in healthy volunteers.

PRINCIPAL INVESTIGATOR: Dr Annelize Koch

STUDY CENTRE: Simbec-Orion Clinical Pharmacology
Merthyr Tydfil, CF48 4DR, UK.

CLINICAL PHASE: I

OBJECTIVES:

Primary: To determine the bioequivalence of the IMP, hydroxycarbamide dispersible tablets (20 x 50 mg) and the reference product, hydroxycarbamide film-coated tablets (1000 mg).

Secondary:

- To assess the PK profile of the IMP, hydroxycarbamide dispersible tablets (20 x 50 mg) in comparison to the reference product hydroxycarbamide film-coated tablet (1000 mg).
- To assess the safety and tolerability of the IMP, hydroxycarbamide dispersible tablets (20 x 50 mg) in comparison to hydroxycarbamide film-coated tablet (1000 mg).

METHODOLOGY:

This study is a Phase I, open-label, single-centre, randomised, two-period, single-dose crossover study to compare and assess the bioequivalence, safety, tolerability and pharmacokinetics of hydroxycarbamide dispersible tablets (20 x 50 mg) (test IMP) and hydroxycarbamide film-coated tablet (1000 mg) (reference IMP) following single-dose administration. Thirty (30) healthy male and female participants, between 18 and 50 years of age are planned to participate in the study.

The study will comprise of a pre-study screen, followed by 2 treatment periods (1 and 2) and an EOS visit.

Screening (Day -28 to Day -2): Screening assessments will be performed from Days -28 to Day -2, to ensure the eligibility of participants, within 28 days prior to the first administration of IMP. Participants will be selected for participation based on medical history, prior medication, informed consent, demographics, physical examination, vital signs, 12-lead electrocardiogram (ECG), laboratory safety testing and urine Drugs of Abuse (DOA) screen.

Eligible participants will be asked to return for the treatment periods. Continued eligibility will be assessed pre-dose during each treatment period.

Treatment Periods (Day -1 to Day 2): Eligible participants will receive a single dose of each of the following IMPs over 2 treatment periods (1 per period) according to a randomisation code produced by Simbec-Orion:

- **Test IMP:** a single dose of hydroxycarbamide dispersible tablets (20 x 50 mg)
- **Reference IMP:** a single dose of hydroxycarbamide film-coated tablet (1000 mg)

Each treatment period will be approximately 3 days duration, from the morning prior to dosing (Day -1) until 24 hours (h) post-dose (Day 2). During each treatment period, participants will arrive at the Clinical Unit on Day -1, the IMP will be administered on the morning of Day 1 fasted (after an overnight fast of at least 10 h) and participants will be discharged 24 h post-dose (Day 2). PK samples will be collected pre-dose and up to 24 h post-dose (Day 2) (14 samples) for the measurement of hydroxycarbamide. There will be at least 72 h between dose administrations in each treatment period.

EOS: Post-study assessments will be conducted 1 to 3 days after the last dose of IMP.

NUMBER OF PARTICIPANTS: Thirty (30) participants will be enrolled for twenty-eight (28) to complete the study.

MAIN INCLUSION CRITERIA:

1. Healthy male and female participants, between 18 and 50 years of age, inclusive.
2. Female participant of childbearing potential willing to use a highly effective method of contraception, if applicable from the first dose until 3 months after the last dose of IMP.
3. Female participant of non-childbearing potential. For the purposes of this study, this is defined as the participant being amenorrhoeic for at least 12 consecutive months or at least 4 months post-surgical sterilisation.
4. Female participant with a negative pregnancy test at Screening.
5. Male participant (and partner of child bearing potential) willing to use a highly method of contraception, if applicable from first dose until 3 months after last dose of IMP.
6. Participant with a BMI of 18-29.9 kg/m^2.
7. No clinically significant history of previous allergy / sensitivity to hydroxycarbamide or any of the excipients contained within the IMP(s).
8. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 28 days before the first dose administration of the IMP.
9. Participant with a negative urinary DOA screen test results, determined within 28 days before the first dose administration of the IMP.
10. Participant with negative human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) and hepatitis C virus antibody (HCV Ab) test results at Screening.
11. No clinically significant abnormalities in 12-lead ECG determined within 28 days before the first dose of IMP.
12. No clinically significant abnormalities in vital signs determined within 28 days before the first dose of IMP.
13. Participant must be available to complete the study.
14. Participant must satisfy an Investigator about his/her fitness to participate in the study.
15. Participant must provide written informed consent to participate in the study.

MAIN EXCLUSION CRITERIA:

1. A clinically significant history of gastrointestinal (GI) disorder likely to influence IMP absorption.
2. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days or 5 half-lives prior to the first dose of IMP.
3. Evidence of renal, hepatic, central nervous system, respiratory, cardiovascular, or metabolic dysfunction.
4. A clinically significant history of drug or alcohol abuse within the past two years.
5. Inability to communicate well with the Investigators.
6. Participation in a New Chemical Entity (NCE) clinical study within the previous 3 months or five half-lives whichever is the longest, or a marketed drug clinical study within the 30 days or five half-lives whichever is the longest, before the first dose of IMP.
7. Donation of 450 mL or more blood within the 3 months before the first dose of IMP.
8. Users of nicotine products i.e., current smokers or ex-smokers who have smoked within 6 months prior to Screening or users of cigarette replacements.
9. Female participants who are pregnant, breastfeeding or lactating.
10. Participants who have received any live or attenuated (including any of the approved COVID-19 vaccinations) vaccine within 28 days of the first dose of IMP, or who are planning to receive a vaccine up to 28 days after receiving the last dose of IMP in Treatment Period 2.

IMP ADMINISTRATION:

Each participant will receive the following IMPs over 2 treatment periods (1 per period) in accordance with the randomisation code:

- **Test IMP:** a single dose of hydroxycarbamide dispersible tablets (20 x 50 mg)
- **Reference IMP:** a single dose of hydroxycarbamide film-coated tablet (1000 mg)

The IMPs will be administered fasted (after an overnight fast of at least 10 h). The test IMP (hydroxycarbamide dispersible tablets (20 x 50 mg)) will be dispersed in 240 mL of water. The reference IMP (hydroxycarbamide

film-coated tablet (1000 mg)) will be administered with 240 mL of water. Participants must remain in an upright position for at least 1 h after each dose.
STUDY VARIABLES/ENDPOINTS: **PK:** ***PK Endpoints:*** The following PK endpoints will be derived from plasma hydroxycarbamide concentration-time data following administration of hydroxycarbamide dispersible tablets (test IMP) and hydroxycarbamide film-coated tablet (reference IMP): Maximum concentration (C_{max}), time to C_{max} (T_{max}), elimination rate constant (λ_z), terminal elimination half-life ($t_{1/2}$), area under the concentration-time curve (AUC) from time of dosing to last measurable concentration (AUC_{0-t}), AUC extrapolated to infinity (AUC_{0-inf}) and $AUC_{\%\ extrapolated}$ (residual area). **Safety:** ***Safety Endpoints:*** Incidence of AEs and vital signs (systolic/diastolic pressure (SBP/DBP), heart rate (HR), and oral temperature).
STATISTICAL METHODS: Please refer to SAP for details of the planned statistical methods of analysis for this study.

DURATION OF STUDY:	Approximately 7 weeks for each individual (from Screening to EOS).