Clinical trial results:
Evaluation of the impact of renal function on the pharmacokinetics of hydroxyurea (Siklos®) in patients with sickle cell disease with normal renal function, with hyperfiltration, or with renal failure.

Summary

EudraCT number	2014-005033-31
Trial protocol	FR
Global end of trial date	29 November 2016

Results information

Result version number	v1 (current)
This version publication date	07 November 2021
First version publication date	07 November 2021
Summary attachment (see zip file)	Pressiat 2020 (Pressiat 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	SIK-FR14-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02522104
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Addmedica SAS
Sponsor organisation address	37 rue de Caumartin, Paris, France, 75009
Public contact	Laura Thomas-bourgneuf, Project manager, Addmedica S.A.S, 0033 0172690186, laura.thomas-bourgneuf@addmedica.com
Scientific contact	Corinne Duguet, Medical director, Addmedica S.A.S, 0033 0149709585, corinne.duguet@addmedica.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 November 2016
Global end of trial reached?	Yes
Global end of trial date	29 November 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Comparison of the different pharmacokynetics parameters of hydroxyurea in sickle-cell patients with a renal condition (glomerular hyperfiltration and moderate renal) to those presenting a normal renal function.

Protection of trial subjects:

Informed consent of the patient

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 March 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited during the consultations by the investigator doctor at Henri Mondor hospital in France from September 2015 to November 2016.

Pre-assignment

Screening details:

A total of 40 patients were screened but PK evaluation was not performed for 10 of them. Main reasons were : Patient’s consent withdrawal, Technical issues: blood samples could not be taken, Adverse even, Suspicion of pregnancy, Blood transfusion, planned hospitalisation. 3 patients prematurely discontinued the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	NR group

Arm description:

Normal-renal function: 90 ≤ glomerular filtration rate (GFR) ≤ 130 mL/min/1.73m2 inwomen or 140 mL/min/1.73m2 in men.

Arm type	Active comparator
Investigational medicinal product name	Siklos
Investigational medicinal product code	
Other name	Hydroxycarbamide
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Siklos was administered by oral route, at the usual dosage (according to the SPC of Siklos® and as per routine prescription)

Arm title	MRF group

Arm description:

Moderate renal failure: 30 ≤ GFR ≤ 60 mL/min/1.73m2

Arm type	Experimental
Investigational medicinal product name	Siklos
Investigational medicinal product code	
Other name	Hydroxycarbamide
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Siklos treatment was administered by oral route, at the usual dosage (according to the summary of product characteristics [SPC] of Siklos®, as per routine dosage).

Arm title	GH group

Arm description:

Glomerular hyperfiltration: GFR > 130 mL/min/1.73m2 in women and GFR > 140mL/min/1.73m2 in men.

Arm type	Active comparator

Investigational medicinal product name	Siklos
Investigational medicinal product code	
Other name	Hydroxycarbamide
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Siklos treatment was administered by oral route, at the usual dosage (according to the summary of product characteristics [SPC] of Siklos® and as per routine dosage).

Number of subjects in period 1	NR group	MRF group	GH group
Started	13	12	15
Completed	10	5	12
Not completed	3	7	3
Consent withdrawn by subject	1	2	-
Adverse event, non-fatal	2	-	-
Pregnancy	-	-	1
technical issue	-	2	-
Protocol deviation	-	3	2

Baseline characteristics

Reporting groups	
Reporting group title	NR group
Reporting group description:	
Normal-renal function: 90 ≤ glomerular filtration rate (GFR) ≤ 130 mL/min/1.73m2 inwomen or 140 mL/min/1.73m2 in men.	
Reporting group title	MRF group
Reporting group description:	
Moderate renal failure: 30 ≤ GFR ≤ 60 mL/min/1.73m2	
Reporting group title	GH group
Reporting group description:	
Glomerular hyperfiltration: GFR > 130 mL/min/1.73m2 in women and GFR > 140mL/min/1.73m2 in men.	

Reporting group values	NR group	MRF group	GH group
Number of subjects	13	12	15
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	12	15
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	31.2	50.0	27.8
standard deviation	± 4.8	± 7.5	± 7.6
Gender categorical Units: Subjects			
Female	8	5	13
Male	5	7	2

Reporting group values	Total		
Number of subjects	40		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		

Adults (18-64 years)	40		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	26		
Male	14		

End points

End points reporting groups

Reporting group title	NR group
Reporting group description:	
Normal-renal function: 90 ≤ glomerular filtration rate (GFR) ≤ 130 mL/min/1.73m2 inwomen or 140 mL/min/1.73m2 in men.	
Reporting group title	MRF group
Reporting group description:	
Moderate renal failure: 30 ≤ GFR ≤ 60 mL/min/1.73m2	
Reporting group title	GH group
Reporting group description:	
Glomerular hyperfiltration: GFR > 130 mL/min/1.73m2 in women and GFR > 140mL/min/1.73m2 in men.	

Primary: AUC/D 0-24h

End point title	AUC/D 0-24h
End point description:	
Dose normalized area under the drug concentration-time curve calculated between 0 and 24 h	
End point type	Primary
End point timeframe:	
0 to 24 hours	

End point values	NR group	MRF group	GH group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	5	12	
Units: h*µM				
arithmetic mean (standard deviation)	1.23 (± 0.24)	2.17 (± 0.78)	1.30 (± 0.24)	

Statistical analyses

Statistical analysis title	comparison between the 3 groups
Statistical analysis description:	
Statistical tests were carried out for each parameter between the 3 groups. The results between the 3 groups showed statistical significant differences for normalized AUC0-24h (p = 0.006)	
Comparison groups	NR group v MRF group v GH group
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.006
Method	Kruskal-wallis

Primary: AUC/D 0-24h	
End point title	AUC/D 0-24h
End point description: Dose normalized area under the drug concentration-time curve calculated between 0 and 24 h	
End point type	Primary
End point timeframe: 0 to 24 hours	

End point values	NR group	MRF group	GH group	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	5	12	
Units: h*µM/mg				
geometric mean (standard deviation)	1.23 (± 0.24)	2.17 (± 0.78)	1.30 (± 0.24)	

Statistical analyses

Statistical analysis title	Kruskal-Wallis
Comparison groups	MRF group v NR group v GH group
Number of subjects included in analysis	27
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	= 0.006
Method	Kruskal-wallis
Parameter estimate	Geometric LSM
Point estimate	0.0058
Confidence interval	
level	90 %
sides	1-sided
lower limit	0

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of signature of the consent,
Throughout the duration of patient follow-upin the study,
Up to 7 days after the end of the participant's follow-up in the study

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	All patients included

Reporting group description: -

Serious adverse events	All patients included		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Sickle cell crisis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Aplastic anemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	All patients included		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)		
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pregnancy, puerperium and perinatal conditions			
Normal newborn			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	-Extension of inclusions period until end of July 2016 -Extension of the duration of participation of each patient until 1month after the planned date. -Possibility of inclusion patients with red cell exchange within the15 days before the inclusion -Take into consideration of GFR of the last 6 months beforeinclusion -Decrease of bonus at 50 euros in case of samples impossible -Payment of bonus within the 3 to 6 months after the end ofparticipation of the patient -Add 1 blood sample to determine percentage of dense red bloodcells -Change of one EDTA tube with an Anticoagulant Citrate DextroseSolution (ACD) tube for dosage of Fetal hemoglobin -Change of one tube with a container for urine parameters -Add of an additional sample 30 minutes after administration -Change of the method of dosage of hydroxyurea in blood and inurine -Change of volume of blood samples for each pharmacokineticsample 4mL instead of 7 mL
16 September 2016	Extension of inclusions period until 31st of December 2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported