Clinical trial results:
Efficacy of Nintedanib per os as a treatment for epistaxis in HHT disease
A national, randomized, multicenter phase II study

EPICURE

Summary

EudraCT number	2019-002593-31
Trial protocol	FR
Global end of trial date	24 February 2023

Results information

Result version number	v1 (current)
This version publication date	14 December 2024
First version publication date	14 December 2024

Trial information

Trial identification

Sponsor protocol code	69HCL19_0003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03954782
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospices Civils de Lyon
Sponsor organisation address	3 Quais des Célestins, Lyon, France, 69003
Public contact	Regulatory Project Manager, Hospices Civils de Lyon, +33 472406829, drci_promo@chu-lyon.fr
Scientific contact	Principal investigator, Hospices Civils de Lyon, +33 427856522, sophie.dupuis-girod@chu-lyon.fr

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	10 October 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 February 2023
Global end of trial reached?	Yes
Global end of trial date	24 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

evaluate efficacy, at the end of the treatment period, on epistaxis duration of nintedanib treatment per os (300 mg/day for 12 weeks) versus placebo in patients with HHT complicated by moderate to severe epistaxis.

Protection of trial subjects:

The trial was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Monitoring the safety of administration of the product, motivated by the iatrogenic risks, justifies the setting up of a specific independent monitoring and safety committee. The Data Safety Monitoring Board = DSMB) reviews the data and issues that may occur during the trial, especially the ones that are scientific, ethical and tolerance, which may change the benefit/risk ratio. Following this review, the DSMB shall provide recommendations to the sponsor, which may concern the continuation, modification or termination of the study.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	01 December 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	51
From 65 to 84 years	8
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

This study involved adult patients suffering from moderate to severe epistaxis related to HHT, which responsible for severe alterations in social functioning and quality of life. This parameter is evaluated with an Epistaxis Severity Score. It has been established that patients with epistaxis from moderate to severe, that is to say a score ESS> 4,

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

double-blind trial

Arms

Are arms mutually exclusive?	Yes
Arm title	NINTEDANIB

Arm description: -

Arm type	Experimental
Investigational medicinal product name	OFEV®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

the treatment tested is nintedanib commercialized as OFEV®, soft capsules containing 150 mg of nintedanib. The daily dose of 300 mg was administered per os by two capsules per day approximately 12 hours' appart, for 12 weeks. In case of intolerance, the dose is reduced at 200 mg per day (2x100mg).

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

the placebo are soft capsules containing a suspension of titanium dioxide as drug substance substitute. The final product is strictly identical as the study treatment.

Number of subjects in period 1	NINTEDANIB	Placebo
Started	30	30
Completed	30	30

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	60	60	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	51	51	
From 65-84 years	8	8	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	31	31	
Male	29	29	

Subject analysis sets	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:
all patients included who started the treatment.

Reporting group values	Full Analysis Set		
Number of subjects	60		
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)	51		
From 65-84 years	8		
85 years and over	1		

Gender categorical Units: Subjects			
Female	31		
Male	29		

End points

End points reporting groups

Reporting group title	NINTEDANIB
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Intention-to-treat
Subject analysis set description: all patients included who started the treatment.	

Primary: Proportion of patients reporting a response at the end of the treatment (based on nosebleeds, with a reduction of at least 50% on epistaxis monthly mean duration comparing the 8 weeks before treatment to the last 8 weeks of tre

End point title	Proportion of patients reporting a response at the end of the treatment (based on nosebleeds, with a reduction of at least 50% on epistaxis monthly mean duration comparing the 8 weeks before treatment to the last 8 weeks of tre
End point description:	
End point type	Primary
End point timeframe: 12 weeks after beginning of the treatment	

End point values	NINTEDANIB	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: number				
number (not applicable)	13	8		

Statistical analyses

Statistical analysis title	main analysis for primary outcome
Comparison groups	NINTEDANIB v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.279
Method	Fisher exact
Parameter estimate	Risk difference (RD)
Point estimate	16.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	16.4
upper limit	16.9

Secondary: relative change of Hemoglobin level between inclusion and enf of treatment

End point title	relative change of Hemoglobin level between inclusion and enf of treatment

End point description:

End point type	Secondary

End point timeframe:

12 weeks after beginning of the treatment vs at the beginning of the treatment

End point values	NINTEDANIB	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: g/L				
arithmetic mean (standard deviation)	0.11 (± 0.20)	0 (± 0.16)		

Statistical analyses

Statistical analysis title	Secondary outcome measure
Comparison groups	NINTEDANIB v Placebo
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.019
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events and severe adverse events observed during the 24 weeks (6 months) of the study were collected (at D14, D28, D56, D84 D168)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

Reporting groups

Reporting group title	Nintedanib
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Nintedanib	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	4 / 30 (13.33%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoalbuminaemia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Nintedanib	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	26 / 30 (86.67%)	19 / 30 (63.33%)	
Investigations			
Transaminases increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vascular disorders			
Haemorrhage			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hypertension			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Peripheral arterial occlusive disease			

subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 30 (23.33%)	3 / 30 (10.00%)	
occurrences (all)	9	6	
migraine			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
general disorders			
subjects affected / exposed	5 / 30 (16.67%)	2 / 30 (6.67%)	
occurrences (all)	5	2	
Toothache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Thyroid cyst			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gastroenteritis			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	8 / 30 (26.67%)	2 / 30 (6.67%)	
occurrences (all)	9	3	
Abdominal pain upper			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	11 / 30 (36.67%)	1 / 30 (3.33%)	
occurrences (all)	20	1	
Epigastric discomfort			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Faeces soft			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Flatulence			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Functional gastrointestinal disorder			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Gingival pain			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Haemorrhoids			

subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Melaena			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	9 / 30 (30.00%)	3 / 30 (10.00%)	
occurrences (all)	9	4	
Oral discomfort			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Proctalgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Reproductive system and breast disorders			
Intermenstrual bleeding			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 30 (6.67%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
sinusitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Rash			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			

Renal failure			
subjects affected / exposed	0 / 30 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Back pain			
subjects affected / exposed	2 / 30 (6.67%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	1 / 30 (3.33%)	1 / 30 (3.33%)	
occurrences (all)	4	1	
Myalgia			
subjects affected / exposed	1 / 30 (3.33%)	0 / 30 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2020	- Addition of clarifications of 2 non-inclusion criteria concerning the history of gastrointestinal ulcers and thrombosis - Collection of medication intake in epistaxis grids - Modification of the SAE reporting circuit to the sponsor (via eCRF) - Modification of the definition of the per protocol population - New version of the OFEV® BI - Addition of a user notice
02 June 2022	- Extension of the recruitment period by 6 months. - New version of the OFEV® BI

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported