Clinical trial results:
An international, randomized, open-label Phase I/II study of vismodegib in combination with temozolomide versus temozolomide alone in adult patients with recurrent or refractory medulloblastoma presenting an activation of the Sonic Hedgehog pathway

Summary

EudraCT number	2011-003372-37
Trial protocol	FR
Global end of trial date	04 March 2019

Results information

Result version number	v1 (current)
This version publication date	25 March 2021
First version publication date	25 March 2021

Trial information

Trial identification

Sponsor protocol code	ET11-072

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01601184
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Centre Léon Bérard
Sponsor organisation address	28 rue Laennec, LYON, France, 69008
Public contact	Dr Didier FRAPPAZ, Centre Léon Bérard, 33 4 78 78 28 28, DRCIreglementaire@lyon.unicancer.fr
Scientific contact	Dr Didier FRAPPAZ, Centre Léon Bérard, 33 4 78 78 28 28, DRCIreglementaire@lyon.unicancer.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	06 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 March 2019
Global end of trial reached?	Yes
Global end of trial date	04 March 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase I: to evaluate the safety of a fixed dose of vismodegib in combination with temozolomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma

Phase II: to estimate the efficacy of vismodegib in combination with concomitant temozolomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma

Protection of trial subjects:

At pre-registration visit, the investigator or its designee will inform the patient of the study, check the eligibility criteria using medical records of the patient and ask him/her to sign the Inform Consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 October 2012
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: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	24
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

At pre-registration visit, the investigator or its designee will inform the patient of the study, check the eligibility criteria using medical records of the patient and ask him/her to sign the Inform Consent form.

Pre-assignment

Screening details:

Before randomisation, FFPE archival tumor samples will be collected for pathological review and assessment of SHH pathway activation by imunohistochemistry (SFRP1, Gab1, Filamin A, YAP1, b-catenin). Only patients with confirmed medulloblastoma presenting an activation of the SHH pathway validated by IHC will be randomized.

Period 1

Period 1 title	Phase I
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

The combination of vismodegib (150 mg/day continuously) with temozolomide (150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles, n= 6 patients)

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

Dose: 150mg/day continuously

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles

Arm title	Arm B

Arm description:

Temozolomide alone (150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles

Number of subjects in period 1[1]	Arm A	Arm B
Started	10	5
Completed	10	5

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of successes expected to go further was not reached.

Period 2

Period 2 title	Phase II
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

The combination of vismodegib (150 mg/day continuously) with temozolomide (150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles, n= 6 patients)

Arm type	Experimental
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

Dose: 150mg/day continuously

Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles

Arm title	Arm B

Arm description:

Temozolomide alone (150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles

Number of subjects in period 2	Arm A	Arm B
Started	10	5
Completed	10	5

Period 3

Period 3 title	Compassionate period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Compassionate arm

Arm description: -

Arm type	compassionate arm
Investigational medicinal product name	Vismodegib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Buccal use

Dosage and administration details:

150 mg/day continuously

Number of subjects in period 3[2]	Compassionate arm
Started	9
Completed	9

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The number of successes expected to go further was not reached.

Baseline characteristics

End points

End points reporting groups

Reporting group title	Arm A
Reporting group description:	
The combination of vismodegib (150 mg/day continuously) with temozolomide (150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles, n= 6 patients)	
Reporting group title	Arm B
Reporting group description:	
Temozolomide alone (150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles	
Reporting group title	Arm A
Reporting group description:	
The combination of vismodegib (150 mg/day continuously) with temozolomide (150 mg/m2 from day 1 to day 5 over a 28 day-cycle period during Cycle 1 and 200mg/m2 from day 1 to day 5 over a 28 day-cycle period during subsequent cycles, n= 6 patients)	
Reporting group title	Arm B
Reporting group description:	
Temozolomide alone (150 mg/m2 day 1 to day 5 / 28 day-cycle during Cycle 1 and 200mg/m2 day 1 to day 5/ 28 day-cycle during subsequent cycles	
Reporting group title	Compassionate arm
Reporting group description: -	

Primary: Primary end point

End point title	Primary end point[1]
End point description:	
PHASE I: To evaluate the safety of a fixed dose of vismodegib in combination with temozolomide (TMZ) in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma measured by the incidence of adverse events graded using CTC AE v4.03 PHASE II: To estimate the efficacy of vismodegib in combination with concomitant temozolomide in adult patients with recurrent, progressive, or refractory to standard therapy medulloblastoma measured by the 6-month progression-free rate (Complete response + Partial Response + Stable disease according to WHO criteria	
End point type	Primary
End point timeframe:	
PHASE II: 6 month	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Phase I: The safety profile of will be summarized with descriptive statistics (appropriate proportions with their 95% confidence interval). Phase II: The non progression rate at 6 months will be analyzed using central read tumor assessments. It will be summarized by a proportion together with its 95% confidence interval.	

End point values	Arm A	Arm B	Arm A	Arm B
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	10	5	10	5
Units: number of AE	10	5	10	5

End point values	Compassionate arm			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: number of AE	9			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The investigator collects (spontaneous patient report or questionning) and immediately notifies the sponsor of all SAEs, in a written report, wether or not theay are deemed to be attributable to research and wich occur during the study.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: At least one AE related to TMZ: 15
At least one AE related to vismodegib: 15
At least one AE related to TMZ and vismodegib: 9
At least one grade >=3 AE: 10
At least one SAE: 6
At least SAE related to TMZ: 1
At least one SAE related to vismodegib: 1
At least one SAE related to TMZ and vismodegib: 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 June 2012	Addition of a compassionate program for patients randomized to the "standard treatment" arm
17 May 2013	Authorize the inclusion of patients previously treated with temozolomide in a new treatment arm: Arm C = vismodegib alone (150 mg / d continuously) Update of clinical data implemented in the attached documents following the publication by Roche laboratories of a new BI for vismodegib
04 August 2014	Alignment of study documents with the SPC of vismodegib Modification of criterion I12 relating to the duration of contraception Update of the potential risks associated with ME in the benefit / risk balance Modification of the contraceptive methods accepted by the protocol Update of clinical data following the BI update
22 March 2016	Extend the duration of the inclusion period by 24 months and therefore the duration of the study
27 April 2017	New edition of the vismodegib BI (Version 10 of January 2016) Update of definitions and vigilance rules

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
04 March 2019	The number of successes expected to go further was not reached.	-

Notes:

Limitations and caveats

None reported