Clinical trial results:
A single arm, open-label, multicenter Phase 2 study of regorafenib in participants who have been treated in a previous Bayer-sponsored regorafenib study (monotherapy or combination treatment) that has reached the primary completion endpoint, or main data analysis, or has been stopped prematurely

Summary

EudraCT number	2018-003650-24
Trial protocol	GB DE IT
Global end of trial date	28 February 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	BAY73-4506/20328

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03890731
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, +49 30 300139003, clinical-trials-contact@bayer.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	13 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- The primary purpose of the program was to enable participants, currently receiving regorafenib in a Bayer sponsored clinical trial and assessed by the principal investigator to be benefitting, to continue regorafenib treatment after their respective study has met its primary completion date, or main data analysis, or has been stopped prematurely. - And the documentation of safety

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 April 2019
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	Germany: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 1
Country: Number of subjects enrolled	Japan: 1
Worldwide total number of subjects	6
EEA total number of subjects	3

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)	4
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted in multiple centers located in 5 countries (including Germany, Japan, Italy, United Kingdom, United States), first subject first visit of the study was on 02 APR 2019 and last subject last visit was on 28 FEB 2023.

Pre-assignment

Screening details:

This was a rollover study designed to enroll participants from ongoing or future feeder studies. Overall, 6 subjects were enrolled and treated in this study.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Regorafenib

Arm description:

Adult patients from completed Bayer-sponsored regorafenib trials who were benefitting from regorafenib treatment.

Arm type	Experimental
Investigational medicinal product name	BAY73-4506 (Regorafenib, Stivarga)
Investigational medicinal product code	
Other name	Tyrosine-kinase inhibitor
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Either 60, 80, 120 or 160 mg once daily for 3 weeks of every 4-week cycle (3 weeks on, 1 week off)

Number of subjects in period 1	Regorafenib
Started	6
Completed	0
Not completed	6
Adverse event, non-fatal	4
Patient's decision	1
Progressive disease	1

Baseline characteristics

Reporting groups	
Reporting group title	Regorafenib
Reporting group description:	
Adult patients from completed Bayer-sponsored regorafenib trials who were benefitting from regorafenib treatment.	

Reporting group values	Regorafenib	Total	
Number of subjects	6	6	
Age Categorical Units: Subjects			
Adults (18-64 years)	4	4	
From 65-84 years	2	2	
Age Continuous Units: years			
median	61		
full range (min-max)	44 to 71	-	
Gender Categorical Units: Subjects			
Female	3	3	
Male	3	3	
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	6	6	
Race (NIH/OMB) Units: Subjects			
Asian	2	2	
White	4	4	

End points

End points reporting groups

Reporting group title	Regorafenib

Reporting group description:

Adult patients from completed Bayer-sponsored regorafenib trials who were benefitting from regorafenib treatment.

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

All subjects who took at least one dose of regorafenib within this rollover study.

Primary: Number and severity of subjects with adverse events (AEs) and serious AEs (SAEs)

End point title	Number and severity of subjects with adverse events (AEs) and serious AEs (SAEs)[1]

End point description:

An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. An SAE is defined as any untoward medical occurrence that, at any dose: 1. results in death 2. is life-threatening 3. requires inpatient hospitalization or prolongation of existing hospitalization, etc.,

End point type	Primary

End point timeframe:

Up to 57 months

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: No statistical analysis was planned for AEs, more information please refer to AE section.

End point values	Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	6[2]			
Units: Subjects				
Any AE	6			
- Non-serious	6			
- Serious	3			

Notes:

[2] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Severity (by worst grade) of subjects with adverse events (AEs) and serious AEs (SAEs)

End point title	Severity (by worst grade) of subjects with adverse events (AEs) and serious AEs (SAEs)[3]

End point description:

AEs were categorized by Common Terminology Criteria for Adverse Events (CTCAE) v5.0

End point type	Primary

End point timeframe:

Up to 57 months

Notes:

[3] - 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: No statistical analysis was planned for AEs, more information please refer to AE section.

End point values	Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	6[4]			
Units: Subjects				
Worst grade - Grade 1	0			
Worst grade - Grade 2	2			
Worst grade - Grade 3	1			
Worst grade - Grade 4	3			
Worst grade - Grade 5 (death)	0			

Notes:

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Number and severity of subjects with drug-related adverse events (AEs) and serious AEs (SAEs)

End point title	Number and severity of subjects with drug-related adverse events (AEs) and serious AEs (SAEs)[5]

End point description:

A drug-related adverse event was any AE judged by investigator as having a reasonable suspected causal relationship to study drug.

End point type	Primary

End point timeframe:

Up to 57 months

Notes:

[5] - 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: No statistical analysis was planned for AEs, more information please refer to AE section.

End point values	Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	6[6]			
Units: Subjects				
Any drug-related AE	5			
- Non-serious	5			
- Serious	1			

Notes:

[6] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Severity (by worst grade) of subjects with drug-related adverse events (AEs) and serious AEs (SAEs)

End point title	Severity (by worst grade) of subjects with drug-related adverse events (AEs) and serious AEs (SAEs)[7]

End point description:

A drug-related adverse event was any AE judged by investigator as having a reasonable suspected causal relationship to study drug. AEs were categorized by Common Terminology Criteria for Adverse Events (CTCAE) v5.0

End point type	Primary

End point timeframe:

Up to 57 months

Notes:

[7] - 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: No statistical analysis was planned for AEs, more information please refer to AE section.

End point values	Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	6[8]			
Units: Subjects				
Worst grade - Grade 1	1			
Worst grade - Grade 2	3			
Worst grade - Grade 3	0			
Worst grade - Grade 4	1			
Worst grade - Grade 5 (death)	0			

Notes:

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with dose modifications

End point title	Number of subjects with dose modifications

End point description:

End point type	Secondary

End point timeframe:

Up to 57 months

End point values	Regorafenib			
Subject group type	Reporting group			
Number of subjects analysed	6[9]			
Units: Subjects				
Any dose modification	6			
Interruption/Delay	2			
Drug Withdrawn	5			

Notes:
[9] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the signing of the ICF until the safety follow up- visit (up to 35 days after the last study treatment)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Regorafenib

Reporting group description:

Adult patients from completed Bayer-sponsored regorafenib trials who are benefitting from regorafenib treatment.

Serious adverse events	Regorafenib		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 6 (50.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Electrocardiogram change			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Peritonitis			

subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypocalcaemia			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Regorafenib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Haemoglobin decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	11		
International normalised ratio increased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	5		
Nervous system disorders			
Cerebral venous sinus thrombosis			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 3		
Eye disorders Retinal vein occlusion subjects affected / exposed occurrences (all)	 1 / 6 (16.67%) 2		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 2 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 1 1 / 6 (16.67%) 3 1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) Hyperkeratosis subjects affected / exposed occurrences (all)	 2 / 6 (33.33%) 4 1 / 6 (16.67%) 6		

Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Flank pain			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	2		
Osteonecrosis of jaw			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Infections and infestations			
Lower respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 6 (33.33%)		
occurrences (all)	3		
Hyperglycaemia			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 November 2018	Protocol Amendment 1, date 20 NOV 2018 introduced the following important changes: Safety was upgraded to a second primary objective and a respective endpoint was added to the protocol. A respective endpoint was also added for the secondary objective tolerability.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported