Clinical trial results:
A Randomized Discontinuation, Blinded, Placebo-Controlled, Phase II Study of Sorafenib in Patients with Chemonaïve Metastatic Uveal Melanoma
(Sorafenib Treatment of Metastatic Uveal Melanoma)

Summary

EudraCT number	2010-022687-12
Trial protocol	DE
Global end of trial date	16 December 2016
Results information	
Result version number	v1 (current)
This version publication date	13 December 2021
First version publication date	13 December 2021

Trial information

Trial identification	
Sponsor protocol code	STREAM
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany
Sponsor organisation address	Hufelandstrasse 55, Essen, Germany, 45147
Public contact	ClinAssesss GmbH , Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany, +49 2171363360, info@clinassess.de
Scientific contact	Monitoring was performed by: ClinAssess GmbH Dr med. Burkhard Deuß 51379 Leverkusen, Department of Medical Oncology, West German Cancer Center, University Medicine Essen, Germany, +49 20172384140, WTZI-Studie@uk-essen.de
Sponsor organisation name	Bayer Vital GmbH
Sponsor organisation address	Kaiser-Wilhelm-Allee 70, Leverkusen, Germany, 51368
Public contact	Bayer Vital GmbH, Bayer Vital GmbH, 0049 021430 51 348, uwephillip.strauss@bayer.com
Scientific contact	Dr. med. Uwe Philipp Strauss, Bayer Vital GmbH supported us financially and with sorafenib- was not direct sponsor, 0049 0214 30-51952, uwephillip.strauss@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	04 November 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 November 2016
Global end of trial reached?	Yes
Global end of trial date	16 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine progression free survival (PFS) of sorafenib versus placebo after random assignment (randomized subset only).

Protection of trial subjects:

cleary planned management of side effects e.g. treatment-associated skin toxicity, prophylactic supportive measures to prevent the development of HFSR
clearly defined management of treatment-associated hypertension, of treatment-associated diarrhea, of hematological toxicities and non-hematologic toxicities

Background therapy:

prophylactic and therapeutic supportive measures before/after development of HFSR
all medication which was considered necessary for the patient's welfare and which were not expected to interfere with the evaluation of the study drug were allowed

Evidence for comparator:

all patient received sorafenib within the first 56 days- no comparators in that initial time given
There are no approved systemic treatment options for patients with metastatic uveal melanoma. Patients achieving stable disease after a 56-days run-in phase of sorafenib 400 mg bid were randomly assigned, in a 1:1 ratio, to blinded sorafenib (S) or placebo (P).

Actual start date of recruitment	16 June 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 147

Worldwide total number of subjects	147
EEA total number of subjects	147

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)	86
From 65 to 84 years	59
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

randomized placebo-controlled discontinuation study was conducted at three centers from June 2011 until December, 2016 in accordance with the standards of each site's independent ethics committees, the Declaration of Helsinki, and GCP guidelines. In total 147 consecutive patients were enrolled in the run-in period, which was completed by 117 pat.

Pre-assignment

Screening details:

Chemonaïve, patients (aged ≥18 years) with metastatic uveal melanoma with at least one measurable metastasis were eligible. Additional inclusion criteria included an ECOG performance status of 0, 1 or 2, a life expectancy of at least 12 weeks, and adequate hematologic, hepatic, and renal function.

Period 1

Period 1 title	first 56 days = run-in
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	run-in phase
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

400mg BID every day

Number of subjects in period 1	run-in phase
Started	147
patients without staging at day 56	30 [1]
evaluable patients on day 56	117
Completed	117
Not completed	30
Consent withdrawn by subject	4
Physician decision	3
death	5
Adverse event, non-fatal	4
missing compliance	1
early PD	13

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: that is correct:
147 patients fulfilled inclusion criteria and entered the run-in phase
30 of them dropped out during this run in phase and could not receive a restaging on day 56
evaluable patients at the end of this run-in phase at day 56: 117

Period 2

Period 2 title	randomization phase
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

for patients who experience progression (either clinical progression according to RECIST) at any timr during the randomization phase, the blind should be broken- patients having received placebo should be offered continuing treatment with sorafenib

Arms

Are arms mutually exclusive?	No
Arm title	Sorafenib Arm

Arm description:

In patients who completed the run-in period, tumor response was classified according to RECIST. Patients with partial response (PR) were continued on sorafenib, patients with progression (PD) were taken off study and patients with stable disease (SD) were randomly assigned to sorafenib (2 x 200 mg bid) or matching placebo in a double-blind fashion without stratification.

Arm type	Experimental
Investigational medicinal product name	sorafenib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

sorafenib (2 x 200 mg bid) daily use

Arm title	Placebo

Arm description:

control arm with placebo

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

Dosage and administration details:

BID

Number of subjects in period 2	Sorafenib Arm	Placebo
Started	39	39
blinded placebo	39	39
blinded sorafenib	39	39
Completed	39	39

Baseline characteristics

Reporting groups	
Reporting group title	first 56 days = run-in

Reporting group description: -

Reporting group values	first 56 days = run-in	Total	
Number of subjects	147	147	
Age categorical Units: Subjects			
Adults (18-64 years)	86	86	
From 65-84 years	59	59	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	60	60	
Male	87	87	
patients enrolled			
patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase			
Units: Subjects			
patients enrolled	147	147	
not recorded	0	0	
Age			
age of patients			
Units: years			
median	62		
full range (min-max)	23 to 88	-	

Subject analysis sets	
Subject analysis set title	treated in run-in phase
Subject analysis set type	Full analysis

Subject analysis set description:
patients entering run in phase and receiving study medication in not blinded phase

Subject analysis set title	not evaluable at day 56
Subject analysis set type	Full analysis

Subject analysis set description:
patient that entered run-in phase but not beiing evaluable at the end of this phase

Subject analysis set title	evaluable on day 56
Subject analysis set type	Full analysis

Subject analysis set description:
patients of run in phase who were evaluable on day 56

Subject analysis set title	SD patients entering randomized phase
Subject analysis set type	Full analysis

Subject analysis set description:
patients with SD at the end of run-in phase entering randomized phase

Subject analysis set title	blinded placebo
Subject analysis set type	Full analysis

Subject analysis set description:
patients in blinded phase ranzomized to placebo

Subject analysis set title	blinded sorafenib
Subject analysis set type	Full analysis

Subject analysis set description:
patients in blinded phase ranzomized to sorafenib

Reporting group values	treated in run-in phase	not evaluable at day 56	evaluable on day 56
Number of subjects	147	30	117
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female Male			
patients enrolled			
patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase			
Units: Subjects			
patients enrolled not recorded	147 0	147 30	117 30
Age			
age of patients			
Units: years median full range (min-max)	 62 23 to 88		

Reporting group values	SD patients entering randomized phase	blinded placebo	blinded sorafenib
Number of subjects	78	39	39
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female Male			
patients enrolled			
patients fulfilling the inclusion criteria versus patients who could not enter the run-in phase			
Units: Subjects			
patients enrolled not recorded			
Age			
age of patients			
Units: years median full range (min-max)		 66 47 to 88	 58 23 to 79

End points

End points reporting groups

Reporting group title	run-in phase
Reporting group description: -	
Reporting group title	Sorafenib Arm
Reporting group description:	
In patients who completed the run-in period, tumor response was classified according to RECIST. Patients with partial response (PR) were continued on sorafenib, patients with progression (PD) were taken off study and patients with stable disease (SD) were randomly assigned to sorafenib (2 x 200 mg bid) or matching placebo in a double-blind fashion without stratification.	
Reporting group title	Placebo
Reporting group description:	
control arm with placebo	
Subject analysis set title	treated in run-in phase
Subject analysis set type	Full analysis
Subject analysis set description:	
patients entering run in phase and receiving study medication in not blinded phase	
Subject analysis set title	not evaluable at day 56
Subject analysis set type	Full analysis
Subject analysis set description:	
patient that entered run-in phase but not beiing evaluable at the end of this phase	
Subject analysis set title	evaluable on day 56
Subject analysis set type	Full analysis
Subject analysis set description:	
patients of run in phase who were evaluable on day 56	
Subject analysis set title	SD patients entering randomized phase
Subject analysis set type	Full analysis
Subject analysis set description:	
patients with SD at the end of run-in phase entering randomized phase	
Subject analysis set title	blinded placebo
Subject analysis set type	Full analysis
Subject analysis set description:	
patients in blinded phase ranzomized to placebo	
Subject analysis set title	blinded sorafenib
Subject analysis set type	Full analysis
Subject analysis set description:	
patients in blinded phase ranzomized to sorafenib	

Primary: PFS

End point title	PFS
End point description:	
PFS measured by ct-scan: after 56days run in, then every 8 weeks within randomized phase	
End point type	Primary
End point timeframe:	
PFS measured by ct-scan: after 56days run in, then every 8 weeks within randomized phase	

End point values	Sorafenib Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: months	6	2		

Statistical analyses

Statistical analysis title	PFS of Sorafenib versus Placebo

Statistical analysis description:

According to the Study Protocol, the primary objective of the study was to determine progression-free survival (PFS) of Sorafenib versus Placebo after random assignment to blinded study medication in the randomised subset (tumour assessment according to RECIST 1.1 criteria)

Comparison groups	Sorafenib Arm v Placebo
Number of subjects included in analysis	78
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0079 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)

Notes:

[1] - A statistical significant difference between the treatment arms was found with a p-value of the log-rank test of 0.0079. The hazard ratio was 0.527

Secondary: OS

End point title	OS

End point description:

measured by ct-scan after 56days after run-in phase and every 8 weeks thereafter within randomization phase

End point type	Secondary

End point timeframe:

measured by ct-scan after 56days after run-in phase and every 8 weeks thereafter within randomization phase

End point values	Sorafenib Arm	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	39		
Units: months	15	14		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: One year after LPLV: December 2016	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	17
Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Sorafenib
Reporting group description: -	

Serious adverse events	Placebo	Sorafenib	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 39 (20.51%)	8 / 39 (20.51%)	
number of deaths (all causes)	39	39	
number of deaths resulting from adverse events	0	1	
General disorders and administration site conditions			
general disorders and administration site conditions			
subjects affected / exposed	2 / 39 (5.13%)	2 / 39 (5.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Gastrointestinal disorders			
gastrointestinal disorders			
subjects affected / exposed	2 / 39 (5.13%)	4 / 39 (10.26%)	
occurrences causally related to treatment / all	0 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Sorafenib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	38 / 39 (97.44%)	36 / 39 (92.31%)	

Investigations Investigations subjects affected / exposed occurrences (all)	 12 / 39 (30.77%) 31	 8 / 39 (20.51%) 21	
Vascular disorders Vascular disorders subjects affected / exposed occurrences (all)	 6 / 39 (15.38%) 6	 7 / 39 (17.95%) 7	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 3	 6 / 39 (15.38%) 6	
General disorders and administration site conditions General disorders and administration site conditions subjects affected / exposed occurrences (all)	 14 / 39 (35.90%) 36	 14 / 39 (35.90%) 36	
Gastrointestinal disorders gastrointestinal disorder subjects affected / exposed occurrences (all)	 18 / 39 (46.15%) 46	 23 / 39 (58.97%) 59	
Hepatobiliary disorders Hepatobiliary disorder subjects affected / exposed occurrences (all)	 10 / 39 (25.64%) 26	 6 / 39 (15.38%) 15	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	 10 / 39 (25.64%) 26	 26 / 39 (66.67%) 67	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	 6 / 39 (15.38%) 15	 8 / 39 (20.51%) 21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	the treatment allocation of patients will be unblinded if they experience progression during the randomized phase. Until 19th July 2013 31 patients have been unblinded as they experienced progression during the randomized phase. 19 of these patients had received placebo and only 12 patients had received sorafenib. As patients are randomized equally to both treatment arms (sorafenib or placebo), the suspicion arises that with regard to the primary endpoint progression-free survival after random assignment to blinded study medication treatment with sorafenib is more effective. Therefore, in order to prevent patient's unnecessary exposure to placebo an interims analysis will be performed to verify or exclude this suspicion. Further on, due to the retirement of Prof. Dr. Max Scheulen on 1st September 2013, the coordinating investigator will change to Frau Dr. Heike Richly.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported