Clinical trial results:
A phase 2, randomized, open label study to evaluate the efficacy, safety, pharmacodynamics, pharmacokinetics of the anti-ALK-1 MAB PF-03446962 in combination with best supportive care vs. best supportive care alone in adult patients with advanced hepatocellular carcinoma.

Summary

EudraCT number	2013-001426-26
Trial protocol	IT ES
Global end of trial date	09 July 2014

Results information

Result version number	v1 (current)
This version publication date	25 May 2016
First version publication date	21 June 2015

Trial information

Trial identification

Sponsor protocol code	A8471005

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01911273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	ClinicalTrials.gov Call Centre, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	ClinicalTrials.gov Call Centre, Pfizer Inc, +1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.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	09 July 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 July 2014
Global end of trial reached?	Yes
Global end of trial date	09 July 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To determine whether overall survival (OS) of PF-03446962 plus best supportive care (BSC) is superior to OS of BSC in subjects with advanced HCC following sorafenib failure.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonization [ICH] 1996), and the Declaration of Helsinki (World Medical Association, 1996 & 2008 versions).
In addition, the study was conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Japan: 3
Worldwide total number of subjects	3
EEA total number of subjects	0

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)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Only 3 subjects were randomized under the open-lable study design: 1 subject in Arm A (PF-03446962 plus BSC) and 2 in Arm B (BSC alone). The 2 subjects randomized to Arm B (BSC alone) withdrew the consent after being aware of the assigned arm.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	PF-03446962 plus BSC

Arm description:

PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.

Arm type	Active comparator
Investigational medicinal product name	PF-03446962
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

PF-03446962 7 mg/kg was administered IV as 1-hour infusion q2w plus BSC.

Arm title	BSC alone

Arm description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

Arm type	best supportive care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	PF-03446962 plus BSC	BSC alone
Started	1	2
Premature termination of the study	0	0
Completed	0	0
Not completed	1	2
Premature termination of the study	1	-
Consent withdrawn by subject	-	2

Baseline characteristics

Reporting groups	
Reporting group title	PF-03446962 plus BSC
Reporting group description:	
PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.	
Reporting group title	BSC alone
Reporting group description:	
BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.	

Reporting group values	PF-03446962 plus BSC	BSC alone	Total
Number of subjects	1	2	3
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)	1	2	3
From 65-84 years	0	0	0
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	1	0	1
Male	0	2	2

End points

End points reporting groups

Reporting group title	PF-03446962 plus BSC

Reporting group description:

PF-03446962 7 milligram per kilogram (mg/kg) was administered intravenously (IV) as 1-hour infusion every two weeks (q2w) plus BSC.

Reporting group title	BSC alone

Reporting group description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

Primary: Overall Survival (OS)

End point title	Overall Survival (OS)[1]

End point description:

OS was the duration from date of randomization to date of death due to any cause. For subjects who are alive, overall survival was censored at the last contact. Death was determined from adverse event (AE) data where outcome was death or from follow-up contact data where the subject current status was death.
Analysis population description: Full analysis set (FAS) included all randomized subjects regardless of what treatment, if any, was received.

End point type	Primary

End point timeframe:

From first randomization to date of death from any cause, whichever came first, assessed up to 24 months after last subject randomization.

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: Insufficient data available to conduct adequate analysis due to premature termination of the study.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[2]	2[3]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[2] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[3] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Progression (TTP)

End point title	Time to Tumor Progression (TTP)

End point description:

TTP was defined as the time from first randomization to date of first documentation of objective tumor progression. If tumor progession data included more than (>) 1 date, the first date was to be used. TTP (in months) was calculated as first event date or last known progression-free date minus the first

randomization date plus 1 divided by 30.4. Tumor progression was determined from oncologic assessment data (where data meet the criteria for progressive disease per Respones Evaluation Criteria in Solid Tumors [RECIST]).
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[4]	2[5]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[4] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[5] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS)

End point title	Progression-Free Survival (PFS)

End point description:

PFS was defined as the time from randomization to first documentation of objective tumor progression or to death due to any cause, whichever occured first. If tumor progression data included >1 date, the first date was to be used. PFS (in months) was calculated as first event date minus first randomization date plus 1 divided by 30.4.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[6]	2[7]		
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[6] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[7] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate (ORR) - Percentage of Participants With Objective Response

End point title	Objective Response Rate (ORR) - Percentage of Participants With Objective Response

End point description:

ORR was defined as the proportion of participants with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST version 1.1, relative to all randomized participants. CR were those that persisted on repeat imaging study more than or equal to (>=) 4 weeks after initial documentation of response. PR was defined as >=30% decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions. Participants who did not have on study radiographic tumor re-evaluation or who died, progressed or dropped out for any reason prior to reaching a CR or PR were to be counted as non-responders in the assessment of ORR. A participant who initially met the criteria for a PR and then subsequently became a confirmed CR, was to be assigned a best response of CR.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Screening and every 8 weeks by calendar thereafter, up to 24 months after last subject randomization.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[8]	2[9]		
Units: Percentage of Subjects				
number (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[8] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[9] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR was defined as the time from the first documentation of objective tumor response to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. If tumor progression data included >1 date, the first date was to be used. DR (in months) was calculated as the end date for DR minus date of first CR or PR that was subsequently confirmed plus 1 divided by 30.4. CR was defined as disapperance of all target lesions and non-target, if any. PR was defined as >=30% decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions.
Analysis population description: Subgroup of subjects with objective response. Since objective response was not assessed in any of the subjects, ideally the number of subjects analyzed field should be 0 and the reason was insufficient data available to conduct adequate analysis due to premature termination of the study.

End point type	Secondary

End point timeframe:

From first randomization to date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months after last subject randomization

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Months				
median (confidence interval 95%)	(to)	(to)		

Notes:

[10] - No data displayed because Outcome Measure has zero total subjects analyzed.

[11] - No data displayed because Outcome Measure has zero total subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disease Control Rate (DCR) at 16 Weeks

End point title	Percentage of Subjects with Disease Control Rate (DCR) at 16 Weeks

End point description:

DCR was defined as the proportion of subjects with confirmed CR or confirmed PR or a best response of stable disease (SD) >=16 weeks according to RECIST, relative to all randomized subjects. CR was defined as disapperance of all target lesions. PR was defined as >=30% decrease in the sum of diameters of target lesions and non CR/non PD to non-target lesions. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (PD), taking as reference the smallest sum diameters while on study.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

From first randomization to date of first documented progression or date of death from any cause, whichever came first, assessed up to 24 months after last participant randomization.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[12]	2[13]		
Units: Percentage of Participants				
number (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[12] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

[13] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep)

End point title	Change From Baseline in Functional Assessment of Cancer Therapy-Hepatobiliary Questionnaire (FACT-Hep)

End point description:

Patient reported outcomes (PROs) were assessed using the FACT-Hep. The FACT-Hep included the FACT-general (FACT-G) and a hepatobiliary module, it consisted of the 27-item FACT-G, which assessed generic health-related quality of life (HRQoL) concerns, and the 18-item hepatobiliary subscale (HS), which assessed disease-specific issues. The questionnaire used a 5 point Likert scale from '0' "not at all" to '4' "very much" regarding how much each item was present in the last 7 days; lower score indicated severer symptom. Eight of the items (lack of energy, pain, weight loss, back pain, fatigue, stomach pain/discomfort, nausea, and jaundice) made up the Fact Hepatobiliary Symptom Index (FHSI 8) were considered to be symptoms specific to hepatobiliary cancer.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Screening, Cycle 1 Day1,8; Cycle >=2 Day 1; End of treatment, survival follow-up up to 24 months after last subject randomization.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[14]	2[15]		
Units: Unites on Scale				
log mean (standard deviation)	99999 (± 99999)	99999 (± 99999)		

Notes:

[14] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[15] - Insufficient data available to conduct adequate analysis due to premature termination of the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum PF-03446962 Serum Concentration (Cmax)

End point title	Maximum PF-03446962 Serum Concentration (Cmax)

End point description:

Analysis population description: The pharmacokinetic (PK) concentration set consisted of all subjects who were treated and had at least one concentration on at least 1 day of PK assessment.

End point type	Secondary

End point timeframe:

1 hour (after start of infusion) on Day1 of Cycles 1, 2, 4, 6, and 8

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[16]	0[17]		
Units: microgram per milliliter (mcg/mL)				
geometric mean (standard deviation)	99999 (± 99999)	()		

Notes:

[16] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[17] - No specimen were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Serum Concentration of PF-03446962 (Ctrough)

End point title	Trough Serum Concentration of PF-03446962 (Ctrough)

End point description:

Analysis population description: The PK concentration set consisted of all subjects who were treated and had at least one concentration on at least 1 day of PK assessment.

End point type	Secondary

End point timeframe:

0 hour (predose) on Day 1 of Cycles 1, 2, 4, 6, and 8

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[18]	0[19]		
Units: mcg/mL				
geometric mean (standard deviation)	99999 (± 99999)	()		

Notes:

[18] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[19] - No specimen were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Human Anti-Human Antibodies (HAHA)

End point title	Number of Subjects with Human Anti-Human Antibodies (HAHA)

End point description:

Analysis population description: The immunogenicity assessment consisted of all subjects who had at least 1 sample on at least 1 day of immunogenicity assessment.

End point type	Secondary

End point timeframe:

Cycle 1, 2, 4, 6, 8 Day 1 at 0 hour (pre-dose)

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[20]	0[21]		
Units: Subjects				
number (not applicable)	99999			

Notes:

[20] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[21] - No specimen were analyzed

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of Sensitivity Signature

End point title	Presence of Sensitivity Signature

End point description:

Tumor molecular characteristics including but not limited to transcriptomic (RNA) signatures of sensitivity.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawl.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: Percentage				
number (not applicable)				

Notes:

[22] - No data displayed because Outcome Measure has zero total subjects analyzed.

[23] - No data displayed because Outcome Measure has zero total subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio to Baseline of Serum Circulating Protein Concentration

End point title	Ratio to Baseline of Serum Circulating Protein Concentration

End point description:

Protein involved TGFB1, VEGF-A, VEGF-C, PIGF, Endoglin, BMP-9, VEGFR1, VEGFR2, VEGFr3, Ang-2, VEGF-D, CD54, CD106, and CCL2. Tumor molecular characteristics including but not limited to transcriptomic (ribonucleic acid) signatures of efficacy.
Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawl.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[24]	0[25]		
Units: Percentage				
number (not applicable)	99999			

Notes:

[24] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[25] - No data displayed because Outcome Measure has zero total subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Serum Concentration of Circulating Protein

End point title	Observed Serum Concentration of Circulating Protein

End point description:

Analysis population description: FAS included all randomized subjects regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (before infusion), Cycle 4 Day 1 (before infusion), at disease progression/subject withdrawl.

End point values	PF-03446962 plus BSC	BSC alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[26]	0[27]		
Units: mcg/mL				
number (not applicable)	99999			

Notes:

[26] - Insufficient data available to conduct adequate analysis due to premature termination of the study.
[27] - No data displayed because Outcome Measure has zero total subjects analyzed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 1 up to 28 days after the last administration of study medication.

Adverse event reporting additional description:

Three subjects were assigned to receive study treatment, as of study termination date. One subject was assigned to receive PF-03446962 plus BSC treatment and discontinued due to progression of disease; 2 were assigned to receive BSC only treatment and discontinued due to withdrawal of consent.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	PF-03446962 plus BSC

Reporting group description:

PF-03446962 7 mg/kg was administered IV as 1-hour infusion q2w plus BSC.

Reporting group title	BSC alone

Reporting group description:

BSC might vary depending on the subject's signs and symptoms, site current practice, and country practice and might include medications and supportive measures deemed necessary to palliate disease-related symptoms and improve quality of life.

Serious adverse events	PF-03446962 plus BSC	BSC alone	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 2 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	PF-03446962 plus BSC	BSC alone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 2 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			

Gastroenteritis subjects affected / exposed occurrences (all)	1 / 1 (100.00%) 1	0 / 2 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 August 2013	1) Section 5.2.5, Dose Reductions: Table 2, "PF 03446962 Dose Modification at Start of Subsequent Cycle" updated to reflect the most common type of toxicities associated with the administration of PF 03446962. 2) In agreement with updated Table 2, amylase and lipase have been added to Appendix 2, List of Laboratory Tests. 3) Schedule of Activities: time of collection of Banked Biospecimens, Blood Sample for Soluble Proteins and HAHA corrected.
04 November 2013	1) The description of the safety profile of PF 0344962 has been expanded and updated in agreement with the current IB. 2) Some study secondary objectives have been expanded in order to clarify the translational research component of the study. The relevant study endpoints have also been clarified. 3) In order to limit patient burden and to support the identification of mechanism of resistance to PF 0344962, mandatory tumor biopsy collection at the time of disease progression has been limited to those patients randomized to PF 0344962 (Arm A) who progress after showing objective response or stable disease for at least 16 weeks after randomization. 4) The duration of treatment/active observation periods have been clarified in the study design section. 5) Some patient selection criteria have been clarified. Patients with known portal hypertension and untreated high risk esophageal varices have been excluded. Patients with history of any other malignancy in the previous 3 years have also been excluded. 6) Dose Modification Criteria for PF 03446962 have been clarified. 7) Schedule of Activities: inconsistencies between table and footnotes and some protocol sections have been fixed. Some footnotes have been reworded to improve clarity.IRC description has been added. 8) PRO testing on Day 8 of Cycle 1 has been added to Arm B. 9) EoT in non Member States has been defined. 10) Appendix 2 List of Laboratory Tests has been clarified. 11) Appendix 4 List of abbreviations and definitions of terms has been added. 12) Typos and minor inconsistencies have been fixed across the protocol.
08 April 2014	1) The study design has been changed from open label to double blind in order to minimize the risk of premature dropout from the comparator arm and preserve the integrity of the study. 2) Schedule of Activities and assessment types and frequencies have been made identical in both treatment arms. 3) A statement relevant to failure of targeted agents to show clinical benefit in the 2nd line treatment of HCC has been included upon IRB/health authority request. 4) Timing of adverse events and laboratory abnormalities occurrence has been removed from relevant secondary endpoints since it is not part of the standard safety analysis. 5) Reference to the pathology report and statement has been removed from the protocol with details included in the Study Manual. 6) The description of the Internal Review Committee role has been elaborated. 7) Editorial changes to address typos and align protocol language with updated protocol template have been made.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was prematurely terminated due to a Sponsor decision not to pursure the clinical development of PF-03446962 as monotherapy in second-line HCC. Primary and secondary objectives were not achived in this study due to the premature termination

Notes: