Clinical trial results:
An Extension Protocol for Subjects Who Were Previously Enrolled in Other Tivantinib (ARQ 197) Protocols

Summary

EudraCT number	2010-020151-31
Trial protocol	DE LV IT
Global end of trial date	14 January 2019

Results information

Result version number	v1 (current)
This version publication date	05 June 2021
First version publication date	05 June 2021

Trial information

Trial identification

Sponsor protocol code	ARQ197-299

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01178411
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck Sharp & Dohme Corp.
Sponsor organisation address	2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033
Public contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.com
Scientific contact	Clinical Trials Disclosure, Merck Sharp & Dohme Corp., ClinicalTrialsDisclosure@merck.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	14 January 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2019
Global end of trial reached?	Yes
Global end of trial date	14 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This is an open label extension study that will allow participants to continue to receive study therapy when the original studies into which they were enrolled have reached their designated end-dates. This extension study is designed to further evaluate the safety and tolerability of tivantinib (ARQ 197) monotherapy or in combination with other drug(s) when given to participants who tolerated previous treatment well and may benefit from the continuing treatment.

This study enrolls participants from previous phase 1 (NCT01149720, NCT01517399, NCT01699061, NCT00612703, NCT00827177, and NCT00874042) and phase 2 (NCT00777309, NCT00557609, NCT00988741, NCT01395758, and NCT01055067) tivantinib studies that reached their designated end-dates. Participants in this extension protocol will provide further safety and tolerability information about tivantinib monotherapy or in combination with other drug(s) at the same dose(s), and same schedule(s) in which they were originally enrolled.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 August 2010
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: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	United States: 56
Worldwide total number of subjects	60
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	29
From 65 to 84 years	28
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Adult male and female participants previously enrolled in phase 1 or phase 2 studies of tivantinib (ARQ 197) were eligible for enrollment.

Period 1

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

Arms

Arm title	Tivantinib (Monotherapy or Combination)

Arm description:

Participants received tivantinib 360 mg twice daily by mouth as monotherapy or combination therapy.

Arm type	Experimental
Investigational medicinal product name	Tivantinib
Investigational medicinal product code	
Other name	ARQ 197
Pharmaceutical forms	Tablet, Capsule
Routes of administration	Oral use

Dosage and administration details:

Tivantinib 360 mg (3 x 120 mg tablets or capsules) twice daily by mouth.

Investigational medicinal product name	Anti-cancer Combination Therapy
Investigational medicinal product code	
Other name	erlotinib, sorafenib, pemetrexed, docataxel, gemcitabine, irinotecan, cetuximab
Pharmaceutical forms	Solution for infusion, Tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Tivantinib 360 mg twice daily in combination with other anti-cancer therapy (eg, erlotinib, sorafenib, pemetrexed, docataxel, gemcitabine, irinotecan, and/or cetuximab) at the same dose and schedule in which they were administered in the original (previous) study.

Number of subjects in period 1	Tivantinib (Monotherapy or Combination)
Started	60
Completed	0
Not completed	60
Adverse event, serious fatal	1
Consent withdrawn by subject	4
Progressive disease per clinician	9
Physician decision	6

Adverse event, non-fatal	5
Drug manufacturing ended	1
Protocol deviation	1
Progressive disease per RECIST	32
No reason provided	1

Baseline characteristics

Reporting groups	
Reporting group title	Tivantinib (Monotherapy or Combination)
Reporting group description:	
Participants received tivantinib 360 mg twice daily by mouth as monotherapy or combination therapy.	

Reporting group values	Tivantinib (Monotherapy or Combination)	Total	
Number of subjects	60	60	
Age categorical Units: Participants			
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	29	29	
From 65-84 years	28	28	
85 years and over	1	1	
Age Continuous Units: Years			
arithmetic mean	61.6		
standard deviation	± 14.79	-	
Sex: Female, Male Units: Participants			
Female	31	31	
Male	29	29	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	4	4	
White	54	54	
More than one race	0	0	
Unknown or Not Reported	2	2	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	12	12	
Not Hispanic or Latino	48	48	
Unknown or Not Reported	0	0	

End points

End points reporting groups

Reporting group title	Tivantinib (Monotherapy or Combination)

Reporting group description:

Participants received tivantinib 360 mg twice daily by mouth as monotherapy or combination therapy.

Primary: Extent of Exposure to ARQ 197 in Participants Benefiting from Prior ARQ 197 Therapy

End point title	Extent of Exposure to ARQ 197 in Participants Benefiting from Prior ARQ 197 Therapy[1]

End point description:

The duration of ARQ 197 exposure in this study was calculated as [(date of last dose of study drug - date of first dose of study drug) + 1]. Results refer to duration of ARQ 197 treatment in the present study only (i.e., does not include treatment received during participation in "feeder" studies). All participants who received ≥1 dose of study drug are included.

End point type	Primary

End point timeframe:

Up to 3,021 days (up to 14-Jan-2019)

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: Per protocol, only descriptive statistics are presented.

End point values	Tivantinib (Monotherapy or Combination)			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Days				
median (full range (min-max))	125 (5 to 3021)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with ≥1 Treatment-emergent Adverse Event (TEAE)

End point title	Number of Participants with ≥1 Treatment-emergent Adverse Event (TEAE)

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All participants who received ≥1 dose of study drug are included.

End point type	Secondary

End point timeframe:

Up to 3021 days

End point values	Tivantinib (Monotherapy or Combination)			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Participants	56			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Discontinuing Treatment Due to an AE

End point title	Number of Participants Discontinuing Treatment Due to an AE

End point description:

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All participants who received ≥1 dose of study drug are included.

End point type	Secondary

End point timeframe:

Up to 3,021 days

End point values	Tivantinib (Monotherapy or Combination)			
Subject group type	Reporting group			
Number of subjects analysed	60			
Units: Participants	6			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 3021 days	
Adverse event reporting additional description: All participants who received ≥1 dose of study drug are included.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Tivantinib (Monotherapy or Combination)
Reporting group description: Participants received tivantinib 360 mg twice daily by mouth as monotherapy or combination therapy.	

Serious adverse events	Tivantinib (Monotherapy or Combination)		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 60 (31.67%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Superior vena caval occlusion			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Radical neck dissection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombectomy			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 60 (3.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary mass			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Injury, poisoning and procedural complications			
Fractured Sacrum			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary failure			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			

subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal mass			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Jaundice cholestatic				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bile duct obstruction				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pathological fracture				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Bronchitis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 60 (1.67%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Urinary tract infection			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	1 / 60 (1.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Tivantinib (Monotherapy or Combination)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	55 / 60 (91.67%)		
Investigations			
Weight decreased			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	11		
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	7		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	9		
Anaemia			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	11		
Thrombocytopenia			

subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	10		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	17 / 60 (28.33%)		
occurrences (all)	28		
Mucosal inflammation			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Oedema peripheral			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	10		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	6		
Abdominal pain			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Diarrhoea			
subjects affected / exposed	16 / 60 (26.67%)		
occurrences (all)	25		
Dyspepsia			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	5		
Nausea			

subjects affected / exposed	14 / 60 (23.33%)		
occurrences (all)	23		
Vomiting			
subjects affected / exposed	20 / 60 (33.33%)		
occurrences (all)	33		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	14		
Dyspnoea			
subjects affected / exposed	11 / 60 (18.33%)		
occurrences (all)	16		
Rhinitis allergic			
subjects affected / exposed	5 / 60 (8.33%)		
occurrences (all)	5		
Oropharyngeal pain			
subjects affected / exposed	4 / 60 (6.67%)		
occurrences (all)	4		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	8		
Dry skin			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	10		
Rash			
subjects affected / exposed	7 / 60 (11.67%)		
occurrences (all)	12		
Psychiatric disorders			
Depression			
subjects affected / exposed	8 / 60 (13.33%)		
occurrences (all)	9		
Insomnia			
subjects affected / exposed	6 / 60 (10.00%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			

Back pain subjects affected / exposed occurrences (all) Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 8 / 60 (13.33%) 8 4 / 60 (6.67%) 6		
Infections and infestations Sinusitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 5 / 60 (8.33%) 8 7 / 60 (11.67%) 9		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 12 / 60 (20.00%) 14		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2010	The primary purposes of amendment (AM) 1 were to allow participants who previously received tivantinib monotherapy to receive combination therapy if that could benefit the participant in the opinion of the Investigator, and to modify laboratory test inclusion criteria.
18 February 2014	The primary purposes of AM 2 were to clarify that combination dose therapy regimen would be determined with sponsor approval, to allow for participants who had not yet started tivantinib therapy to initiate treatment for the first time, and to modify laboratory test inclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported