Clinical trial results:
Single-Arm Study of Lorlatinib in Participants With Anaplastic Lymphoma Kinase (ALK)-Positive Non-Small Cell Lung Cancer (NSCLC) Whose Disease Progressed After one Prior Second-Generation ALK Tyrosine Kinase Inhibitor (TKI)

Summary

EudraCT number	2019-002504-41
Trial protocol	PL GB IT
Global end of trial date	23 October 2024

Results information

Result version number	v1 (current)
This version publication date	29 October 2025
First version publication date	29 October 2025

Trial information

Trial identification

Sponsor protocol code	B7461027

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04362072
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	66 Hudson Boulevard East, New York, United States, NY 10001-2192
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 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	25 February 2025
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess overall and intracranial response rate of single agent Lorlatinib in participants with advanced ALK positive NSCLC whose disease has progressed on alectinib or ceritinib as the first ALK tyrosine kinase inhibitor (TKI) therapy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trials participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 September 2020
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	Italy: 33
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	India: 11
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 2
Worldwide total number of subjects	71
EEA total number of subjects	54

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)	48
From 65 to 84 years	22
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

A total of 71 participants were enrolled in the study.

Pre-assignment

Screening details:

Participants were enrolled at multiple sites, where study started from 29 September 2020 and completed on 23 October 2024.

Period 1

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

Blinding implementation details:

There was no blinding.

Arms

Arm title	Lorlatinib

Arm description:

Participants received Lorlatinib 100 milligrams (mg) (25 mg*4 tablets) orally once daily (QD) in 21-day cycles. Participants continued to receive study treatment until objective disease progression, unacceptable toxicity, participant refusal, lost to follow up or death, whichever occurred first.

Arm type	Experimental
Investigational medicinal product name	Lorlatinib
Investigational medicinal product code	PF-06463922
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received Lorlatinib 100 mg orally once daily in 21-day cycle.

Number of subjects in period 1	Lorlatinib
Started	71
Completed	0
Not completed	71
Adverse event, serious fatal	9
Physician decision	2
Withdrawal by Participants	4
Global deterioration of health status	1
Adverse event, non-fatal	1
Entered Lorlatinib continuation Study	11
Switched to commercial Lorlatinib	13
Unspecified	3

Progressive disease	27

Baseline characteristics

Reporting groups	
Reporting group title	Overall study
Reporting group description:	
Participants received Lorlatinib 100 mg (25 mg*4 tablets) orally QD in 21-day cycles. Participants continued to receive study treatment until objective disease progression, unacceptable toxicity, participant refusal, lost to follow up or death, whichever occurred first.	

Reporting group values	Overall study	Total	
Number of subjects	71	71	
Age Categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 58.14 ± 12.93	 -	
Gender categorical Units: Subjects			
Male	41	41	
Female	30	30	
Race, Customized Units: Subjects			
Asian	15	15	
White	54	54	
Unknown or Not Reported	2	2	
Age categorical Units: Subjects			
18-44 years	13	13	
45-64 years	35	35	
>= 65 years	23	23	

End points

End points reporting groups

Reporting group title	Lorlatinib

Reporting group description:

Participants received Lorlatinib 100 milligrams (mg) (25 mg*4 tablets) orally once daily (QD) in 21-day cycles. Participants continued to receive study treatment until objective disease progression, unacceptable toxicity, participant refusal, lost to follow up or death, whichever occurred first.

Primary: Percentage of Participants With Confirmed Objective Response (OR) as per Independent Central Review (ICR) as Assessed by RECIST v1.1

End point title	Percentage of Participants With Confirmed Objective Response (OR) as per Independent Central Review (ICR) as Assessed by RECIST v1.1[1]

End point description:

Confirmed OR based on ICR assessment was defined as complete response (CR) or partial response (PR) according to response evaluation criteria in solid tumor (RECIST) version(v)1.1 from date of first dose until documented progressive disease(PD) or start of new anti-cancer therapy without regard to discontinuation from treatment. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after criteria for response are first met. CR: disappearance of all target and non-target(NT) lesions. PR: at least 30% decrease in sum of diameters of target, taking as reference baseline sum diameters. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. Intent to treat (ITT) analysis population included all enrolled participants who took at least 1 dose of Lorlatinib.

End point type	Primary

End point timeframe:

From date of first dose until documented PD or start of new anti-cancer therapy, whichever occurred earlier (maximum treatment exposure up to 42.78 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 this endpoint

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Percentage of participants				
number (confidence interval 95%)	42.3 (30.6 to 54.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed Intracranial (IC) Objective Response (IC-OR) as per ICR as Assessed by RECIST v 1.1

End point title	Percentage of Participants With Confirmed Intracranial (IC) Objective Response (IC-OR) as per ICR as Assessed by RECIST v 1.1

End point description:

IC-OR based on ICR assessment: IC-CR/PR according to RECISTv1.1 from date of first dose until documented IC-PD/start of new anti-cancer therapy without regard to discontinuation from treatment. Both IC-CR and IC-PR must be confirmed by repeat assessments performed no <4 weeks after criteria for response first met. IC-CR: disappearance of all target and non-target lesions. IC-PR:at least 30% decrease in sum of diameters of IC target lesions, taking reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one/more new IC lesions was also considered sign of progression. For non-target IC-PD: unequivocal progression of existing IC-non-target lesions. Per-protocol analysis population based on ICR(PPICR) included all enrolled participants who took at least 1 dose of Lorlatinib, had central nervous system(CNS)metastases at study entry(i.e. with lesions having disease site=brain)according to ICR.

End point type	Secondary

End point timeframe:

From date of first dose until documented PD or start of new anti-cancer therapy, whichever occurred earlier (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Percentage of participants				
number (confidence interval 95%)	46.7 (28.3 to 65.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed OR as per Investigator (INV) as Assessed by RECIST v 1.1

End point title	Percentage of Participants With Confirmed OR as per Investigator (INV) as Assessed by RECIST v 1.1

End point description:

Confirmed OR based on derived investigator assessment was defined as CR or PR according to RECIST v1.1 from date of first dose until PD or start of new anti-cancer therapy without regard to discontinuation from treatment. Both CR and PR must be confirmed by repeat assessments performed no less than 4 weeks after criteria for response are first met. CR: disappearance of all target and non-target lesions. PR: at least 30 % decrease in sum of diameters of target, taking as reference baseline sum diameters. PD: at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. ITT analysis population included all enrolled participants who took at least 1 dose of Lorlatinib.

End point type	Secondary

End point timeframe:

From date of first dose until documented PD or start of new anti-cancer therapy, whichever occurred earlier (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Percentage of participants				
number (confidence interval 95%)	36.6 (25.5 to 48.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) as per ICR as Assessed by RECIST v 1.1

End point title	Time to Response (TTR) as per ICR as Assessed by RECIST v 1.1

End point description:

TTR based on ICR assessments was defined, for participants with a confirmed OR, as the time from the date of first dose to the first documentation of OR (CR or PR) which was subsequently confirmed. For participants whose OR proceeded from PR to CR, the onset of PR was taken as the onset of response. CR: disappearance of all target and non-target lesions. PR: at least 30 % decrease in sum of diameters of target, taking as reference baseline sum diameters. Analysis population included all enrolled participants who took at least 1 dose of Lorlatinib and had confirmed CR or PR as per ICR.

End point type	Secondary

End point timeframe:

From date of first dose until first documented objective response, CR or PR (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
median (full range (min-max))	1.5 (1.2 to 8.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: TTR as per INV as Assessed by RECIST v 1.1

End point title	TTR as per INV as Assessed by RECIST v 1.1

End point description:

TTR based on derived investigator assessments was defined, for participants with a confirmed objective response, as the time from the date of first dose to the first documentation of objective response (CR or PR) which is subsequently confirmed. For participants whose OR proceeds from PR to CR, the onset of PR is taken as the onset of response. CR: disappearance of all target (T) and non-target lesions. PR: at least 30 % decrease in sum of diameters of target, taking as reference baseline sum diameters. Analysis population included all enrolled participants who took at least 1 dose of Lorlatinib and had confirmed CR or PR as per INV.

End point type	Secondary

End point timeframe:

From date of first dose until first documented objective response, CR or PR (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Months				
median (full range (min-max))	1.6 (1.2 to 8.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) as per ICR as Assessed by RECIST v 1.1

End point title	Duration of Response (DOR) as per ICR as Assessed by RECIST v 1.1

End point description:

DOR: as time from first documentation of OR per ICR(CR/PR whichever was earlier) to date of first documentation of PD/death due to any cause, whichever came first. CR: disappearance of all target and non-target lesions.PR:at least 30% decrease in sum of diameters of target,taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of >=1 new lesions:sign of progression.For non-target PD:unequivocal progression of existing non-target lesions.Participants who completed/discontinued study without PD/death, as well as who received alternate anti-cancer therapy prior to PD, were censored at last adequate response assessment date/last adequate assessment prior to start date of alternate anti-cancer therapy. Kaplan-Meier method used. Participants who took at least 1 dose of Lorlatinib with confirmed CR/ PR as per ICR. 99999:Median and 95%CI upper limit inestimable due to

End point type	Secondary

End point timeframe:

From first documented OR (CR or PR) to date of first documented PD or death due to any cause or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	30			
Units: Months				
median (confidence interval 95%)	99999 (8.6 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Confirmed IC-OR as per INV as Assessed by RECIST v 1.1

End point title	Percentage of Participants With Confirmed IC-OR as per INV as Assessed by RECIST v 1.1

End point description:

IC-OR based on derived investigator assessment:IC-CR/PR according to RECISTv1.1 from date of first dose until documented IC-PD/start of new anti-cancer therapy without regard to discontinuation from treatment.Both IC-CR and IC-PR must be confirmed by repeat assessments performed no <4 weeks after criteria for response first met. IC-CR: disappearance of all target and non-target lesions. IC-PR:at least 30% decrease in sum of diameters of IC target lesions, taking reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one/more new IC lesions was also considered sign of progression. For non-target IC-PD: unequivocal progression of existing IC-non-target lesions. Per-protocol analysis population based on INV(PPINV) included all enrolled participants who took at least 1 dose of Lorlatinib,had CNS metastases at study entry(i.e. with lesions having disease site=brain)according to investigator.

End point type	Secondary

End point timeframe:

From date of first dose until documented PD or start of new anti-cancer therapy, whichever occurred earlier (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Percentage of participants				
number (confidence interval 95%)	56.5 (34.5 to 76.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Intracranial Response (IC-DoR) as per ICR as Assessed by RECIST v 1.1

End point title	Duration of Intracranial Response (IC-DoR) as per ICR as Assessed by RECIST v 1.1

End point description:

IC-DoR:for participants with confirmed objective intra-cranial response per ICR,as time from first documentation of objective intra-cranial response to date of first documentation of PD in brain/death due to any cause,whichever occurs first. IC-CR:disappearance of all T & NT lesions. IC-PR: at least 30%decrease in sum of diameters of T,taking as reference baseline sum diameter. IC-PD:at least 20%increase in sum of diameters of T lesions, taking reference smallest sum on study/appearance of new IC lesions. IC-NT PD:unequivocal progression of existing IC-NT lesions.Participants who completed/discontinued study without PD/death,who received alternate anti-cancer therapy prior to IC-PD,were censored at last adequate response assessment date/last adequate assessment prior to start date of alternate anti-cancer therapy.Analysis:Kaplan-Meier. Subjects analyzed=no. of participants evaluable for endpoint.PPICR used.99999=Median,upper,lower limit of 95%CI not estimable due to insufficient data.

End point type	Secondary

End point timeframe:

From first documented IC-OR (CR or PR) to date of first documented PD or death due to any cause or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as per INV as Assessed by RECIST v 1.1

End point title	DOR as per INV as Assessed by RECIST v 1.1

End point description:

DOR: as time from first documentation of OR per INV (CR/PR whichever was earlier) to date of first documentation of PD/death due to any cause, whichever came first. CR: disappearance of all target and non-target lesions.PR:at least 30% decrease in sum of diameters of target,taking as reference baseline sum diameters. PD:at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of >=1 new lesions: sign of progression. For non-target PD:unequivocal progression of existing non-target lesions. Participants who completed/discontinued study without PD/death, as well as who received alternate anti-cancer therapy prior to PD, were censored at their last adequate response assessment date/last adequate assessment prior to start date of alternate anti-cancer therapy. Kaplan-Meier method used. Participants who took at least 1 dose of Lorlatinib with confirmed CR/PR as per INV. 99999: Upper limit of 95% inestimable due to insufficient

End point type	Secondary

End point timeframe:

From first documented OR (CR or PR) to date of first documented PD or death due to any cause or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	26			
Units: Months				
median (confidence interval 95%)	20.9 (9.9 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: IC-DoR as per INV as Assessed by RECIST v 1.1

End point title	IC-DoR as per INV as Assessed by RECIST v 1.1

End point description:

IC-DoR:for participants with confirmed objective intra-cranial response per INV,as time from first documentation of objective intra-cranial response to date of first documentation of PD in brain/death due to any cause,whichever occurs first. IC-CR:disappearance of all T & NT lesions. IC-PR:at least 30%decrease in sum of diameters of T,taking as reference baseline sum diameter. IC-PD:at least 20%increase in sum of diameters of T lesions, taking reference smallest sum on study/appearance of new IC lesions. IC-NT PD:unequivocal progression of existing IC-NT lesions.Participants who completed/discontinued study without PD/death,who received alternate anti-cancer therapy prior to IC-PD,were censored at last adequate response assessment date/last adequate assessment prior to start date of alternate anti-cancer therapy. Analysis:Kaplan-Meier. Subjects analyzed=no.of participants evaluable for endpoint.PPINV used.99999=Median,upper,lower limit of 95%CI not estimable due to insufficient data.

End point type	Secondary

End point timeframe:

From first documented IC-OR (CR or PR) to date of first documented PD or death due to any cause or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Progression (TTP) as per ICR as Assessed by RECIST v 1.1

End point title	Time to Tumor Progression (TTP) as per ICR as Assessed by RECIST v 1.1

End point description:

TTP according to RECIST v1.1 as time from date of first dose to the date of the first documentation of PD per IRC. PD was defined as at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. Participants who completed or discontinued study without PD or death, as well as participants who received alternate anti-cancer therapy prior to PD, were censored at their last adequate response assessment date or last adequate assessment prior to start date of alternate anti-cancer therapy. Analysis was performed using Kaplan-Meier method. ITT analysis population included all enrolled participants who took at least 1 dose of Lorlatinib. Here, 99999= Upper limit of 95% CI is not estimable due to insufficient data.

End point type	Secondary

End point timeframe:

From date of first dose until first documented PD or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Months				
median (confidence interval 95%)	18.0 (9.7 to 99999)			

Statistical analyses

No statistical analyses for this end point

Secondary: TTP as per INV as Assessed by RECIST v 1.1

End point title	TTP as per INV as Assessed by RECIST v 1.1

End point description:

TTP according to RECIST v1.1 as time from date of first dose to the date of the first documentation of PD per investigator. PD was defined as at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. Participants who completed or discontinued study without PD or death, as well as participants who received alternate anti-cancer therapy prior to PD, were censored at their last adequate response assessment date or last adequate assessment prior to start date of alternate anti-cancer therapy. Analysis was performed using Kaplan-Meier method. ITT analysis population included all enrolled participants who took at least 1 dose of Lorlatinib.

End point type	Secondary

End point timeframe:

From date of first dose until first documented PD or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Months				
median (confidence interval 95%)	12.2 (8.3 to 24.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-Free Survival (PFS) as per ICR as Assessed by RECIST v 1.1

End point title	Progression-Free Survival (PFS) as per ICR as Assessed by RECIST v 1.1

End point description:

PFS according to RECIST v1.1 was defined as the time from date of first dose to the date of the first documentation of PD per ICR or death due to any cause, whichever occurred first. PD was defined as at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. Participants who completed or discontinued study

without PD or death, as well as participants who received alternate anti-cancer therapy prior to PD, were censored at their last adequate response assessment date or last adequate assessment prior to start date of alternate anti-cancer therapy. Analysis was performed using Kaplan-Meier method. ITT analysis population included all enrolled participants who took at least 1 dose of Lorlatinib.

End point type	Secondary

End point timeframe:

From date of first dose until first documented PD or death or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Months				
median (confidence interval 95%)	12.2 (6.9 to 22.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as per INV as Assessed by RECIST v 1.1

End point title	PFS as per INV as Assessed by RECIST v 1.1

End point description:

PFS according to RECIST v1.1 was defined as the time from date of first dose to the date of the first documentation of PD per INV or death due to any cause, whichever occurred first. PD was defined as at least 20% increase in sum of diameters of target lesions, taking as reference smallest sum on study. Appearance of one or more new lesions was also considered sign of progression. For non-target PD: unequivocal progression of existing non-target lesions. Participants who completed or discontinued study without PD or death, as well as participants who received alternate anti-cancer therapy prior to PD, were censored at their last adequate response assessment date or last adequate assessment prior to start date of alternate anti-cancer therapy. Analysis was performed using Kaplan-Meier method. ITT analysis population included all enrolled participants who took at least 1 dose of Lorlatinib.

End point type	Secondary

End point timeframe:

From date of first dose until first documented PD or death or censoring date, whichever occurred first (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Months				
median (confidence interval 95%)	9.7 (6.9 to 18.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: IC-TTR as per INV as Assessed by RECIST v 1.1

End point title	IC-TTR as per INV as Assessed by RECIST v 1.1

End point description:

IC-TTR: for participants with a confirmed IC-OR per investigator, was defined as the time from the date of first dose to the first documentation of objective intra-cranial response (CR or PR) which is subsequently confirmed. For participants whose IC-OR proceeds from PR to CR, the onset of PR was taken as the onset of response. IC-CR: disappearance of all target and non-target lesions. IC-PR: at least 30 % decrease in sum of diameters of target, taking as reference baseline sum diameters. Here subjects analyzed signifies number of participants evaluable for this endpoint. PPINV included all enrolled participants who took at least 1 dose of Lorlatinib and had CNS metastases at study entry (i.e. with lesions having disease site = brain) according to investigator.

End point type	Secondary

End point timeframe:

From date of first dose to the first documented objective intra-cranial response (CR or PR) (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: Months				
median (full range (min-max))	2.8 (1.3 to 15.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Intra-Cranial Response (IC-TTR) as per ICR as Assessed by RECIST v 1.1

End point title	Time to Intra-Cranial Response (IC-TTR) as per ICR as Assessed by RECIST v 1.1

End point description:

IC-TTR: for participants with a confirmed IC-OR per ICR, was defined as the time from the date of first dose to the first documentation of objective intra-cranial response (CR or PR) which is subsequently confirmed. For participants whose IC-OR proceeds from PR to CR, the onset of PR was taken as the onset of response. IC-CR: disappearance of all target and non-target lesions. IC-PR: at least 30 % decrease in sum of diameters of target, taking as reference baseline sum diameters. Here subjects analyzed signifies number of participants evaluable for this endpoint. PPICR included all enrolled participants who took at least 1 dose of Lorlatinib and had CNS metastases at study entry (i.e. with lesions having disease site = brain) according to ICR.

End point type	Secondary

End point timeframe:

From date of first dose to the first documented objective intra-cranial response (CR or PR) (maximum treatment exposure up to 42.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	14			
Units: Months				
median (full range (min-max))	2.8 (1.3 to 12.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in participant or clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. A TEAE was defined as any event that occurs for first time during on-treatment period or AEs that were observed prior to start of study treatment but increased in severity during on-treatment period (defined as time from first dose of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after discontinuation of treatment, or start of new anti-cancer therapies [follow up systemic therapy, follow up radiation therapy or follow-up surgery], whichever occurs first). Adverse events occurring on same day as first dose of study treatment were also considered to have occurred during the on-treatment period. Safety analysis set included all enrolled participants who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants	69			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-Related TEAEs

End point title	Number of Participants With Treatment-Related TEAEs

End point description:

An AE was any untoward medical occurrence in participant or clinical study participant, temporally associated with use of study intervention, considered related to study intervention. A TEAE was defined as any event that occurs for first time during on-treatment period/ AEs that were observed prior to start of study treatment but increased in severity during on-treatment period (defined as time from first dose

of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after discontinuation of treatment, or start of new anti-cancer therapies [follow up systemic therapy, follow up radiation therapy or follow-up surgery], whichever occurs first). Adverse events occurring on same day as first dose of study treatment were also considered to have occurred during the on-treatment period. An AE was considered treatment related if investigator considered event related to study drugs/ information was unknown. Safety analysis set used.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants	64			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Maximum Grade 3 or 4 TEAEs by National Cancer Institute Common Terminology Criteria for AEs [NCI CTCAE] v.4.03

End point title	Number of Participants With Maximum Grade 3 or 4 TEAEs by National Cancer Institute Common Terminology Criteria for AEs [NCI CTCAE] v.4.03

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with use of study intervention, whether or not considered related to study intervention. A TEAE was defined as any event that occurs for first time during on-treatment period or AEs that were observed prior to start of study treatment but increased in severity during on-treatment period (defined as time from first dose of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after discontinuation of treatment, or start of new anti-cancer therapies, whichever occurs first). Adverse events occurring on same day as first dose of study treatment were also considered to have occurred during the on-treatment period. TEAEs were graded according to NCI CTCAE v4.03 as grade 3= severe AE and grade 4= life threatening consequences; urgent intervention indicated. Safety analysis set used.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants	28			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Maximum Grade 3 or 4 Treatment-Related AEs

End point title	Number of Participants With Maximum Grade 3 or 4 Treatment-Related AEs

End point description:

An AE was any untoward medical occurrence in a participant or clinical study participant, temporally associated with use of study intervention, considered related to study intervention. An AE was considered treatment related if investigator considered event related to study drugs or the information was unknown. TEAEs were graded according to CTCAE v4.03 as grade 3= severe AE and grade 4= life threatening consequences. Safety analysis set included all enrolled participants who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants	19			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Serious Adverse Events (TESAEs)

End point title	Number of Participants With Treatment Emergent Serious Adverse Events (TESAEs)

End point description:

A serious adverse event (SAE) was any untoward medical occurrence at any dose that: resulted in death; was life-threatening (immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions) or resulted in congenital anomaly/birth defect or was considered an important medical event. TESAEs were defined as any event that occurs for first time during on-treatment period or SAEs that were observed prior to start of study treatment but increased in severity during on-treatment period (defined as time from first dose of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after

discontinuation of treatment, or start of new anti-cancer therapies, whichever occurs first). Safety analysis set included all enrolled participants who took at least 1 dose of study intervention.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Participants	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants With Treatment-Related TESAEs

End point title	Number of participants With Treatment-Related TESAEs

End point description:

SAE was any untoward medical occurrence at any dose that: resulted in death; was life-threatening (immediate risk of death); required inpatient hospitalization or prolongation of existing hospitalization; resulted in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)/ resulted in congenital anomaly/birth defect/ was considered an important medical event. TESAEs: any event that occurs for first time during on-treatment period/ SAEs that were observed prior to start of study treatment but increased in severity during on-treatment period (defined as time from first dose of study treatment through end of safety follow-up period, ie at least 28 days, and no more than 35 days after discontinuation of treatment/ start of new anti-cancer therapies, whichever occurs first). SAE was considered treatment related if investigator considered event related to study drugs or information was unknown. Safety analysis set used.

End point type	Secondary

End point timeframe:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever is earlier (maximum treatment exposure up to 43.78 months)

End point values	Lorlatinib			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of the study treatment (Day 1) maximum up to 28-35 days after last dose of study drug or the new anti-cancer therapy date, whichever was earlier (maximum treatment exposure up to 43.78 months)

Adverse event reporting additional description:

Safety analysis set. Same event may appear as both non-SAE & SAE. Presented are distinct events. Event may be categorized: serious in 1 participant and non-serious in other/may have experienced both SAE & non-SAE.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	v27.1

Reporting groups

Reporting group title	Lorlatinib

Reporting group description:

Participants received Lorlatinib 100 mg (25 mg*4 tablets) orally QD in 21-day cycles. Participants continued to receive study treatment until objective disease progression, unacceptable toxicity, participant refusal, lost to follow up or death, whichever occurred first.

Serious adverse events	Lorlatinib		
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 71 (32.39%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events	10		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm progression			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Colon cancer			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Right ventricular dysfunction			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cranial nerve disorder			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Guillain-Barre syndrome			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Intracranial pressure increased			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
General physical health deterioration			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Dysphagia			

subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intestinal haemorrhage				
subjects affected / exposed	1 / 71 (1.41%)			
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	3 / 71 (4.23%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Acute respiratory failure				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bronchial haemorrhage				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	3 / 71 (4.23%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 1			
Haemoptysis				
subjects affected / exposed	1 / 71 (1.41%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				

subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hydronephrosis			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Infections and infestations			
Pneumonia viral			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 71 (2.82%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 1		
Infectious pleural effusion			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
COVID-19 pneumonia			
subjects affected / exposed	1 / 71 (1.41%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Lorlatinib		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	66 / 71 (92.96%)		
Investigations			
Blood creatinine increased			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	7		
Blood cholesterol increased			
subjects affected / exposed	19 / 71 (26.76%)		
occurrences (all)	40		
Alanine aminotransferase increased			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	7		
Blood glucose increased			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Blood triglycerides increased			
subjects affected / exposed	16 / 71 (22.54%)		
occurrences (all)	42		
Weight increased			
subjects affected / exposed	7 / 71 (9.86%)		
occurrences (all)	11		
SARS-CoV-2 test positive			
subjects affected / exposed	5 / 71 (7.04%)		
occurrences (all)	5		
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	7		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	4		
Headache			

subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	5 / 71 (7.04%) 6 7 / 71 (9.86%) 13		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	 12 / 71 (16.90%) 18		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all) Oedema subjects affected / exposed occurrences (all) Oedema peripheral subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all)	 5 / 71 (7.04%) 5 14 / 71 (19.72%) 18 6 / 71 (8.45%) 7 26 / 71 (36.62%) 42 12 / 71 (16.90%) 15		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 13 / 71 (18.31%) 17 6 / 71 (8.45%) 8 6 / 71 (8.45%) 6		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all) Dyspnoea exertional subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	8 / 71 (11.27%) 13 4 / 71 (5.63%) 5 12 / 71 (16.90%) 16		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	6 / 71 (8.45%) 7		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	9 / 71 (12.68%) 9 4 / 71 (5.63%) 4 9 / 71 (12.68%) 11		
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	8 / 71 (11.27%) 8		
Metabolism and nutrition disorders Hypercholesterolaemia subjects affected / exposed occurrences (all) Hyperlipidaemia subjects affected / exposed occurrences (all) Hypertriglyceridaemia	24 / 71 (33.80%) 48 12 / 71 (16.90%) 33		

subjects affected / exposed	27 / 71 (38.03%)		
occurrences (all)	76		
Hyperuricaemia			
subjects affected / exposed	4 / 71 (5.63%)		
occurrences (all)	6		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 September 2022	Permitted participants meeting criteria who continued to experience clinical benefit from the study intervention to continue therapy after disease progression and to provide clarity around reasons for discontinuation of study intervention.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported