Clinical trial results:
0A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations

Summary

EudraCT number	2015-003614-24
Trial protocol	DE NL IT
Global end of trial date	21 November 2018

Results information

Result version number	v1 (current)
This version publication date	06 June 2019
First version publication date	06 June 2019

Trial information

Trial identification

Sponsor protocol code	CLTT462X2101

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02711345
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, +41 613241111,

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	21 November 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 November 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult and adolescent patients with advanced solid tumors harboring MAPK pathway alterations.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 April 2016
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	Japan: 7
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Germany: 13
Worldwide total number of subjects	65
EEA total number of subjects	24

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)	1
Adults (18-64 years)	44
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

65 subjects were enrolled into 10 treatment groups in the escalation part.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LTT462 45 mg QD

Arm description:

Subjects received LTT462 45 milligram (mg) once daily (QD)

Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received LTT462 QD as oral capsules.

Arm title	LTT462 100 mg QD

Arm description:

Subjects received 100 mg LTT462 QD as oral capsules.

Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received LTT462 QD as oral capsules.

Arm title	LTT462 150 mg QD

Arm description:

Subjects received 150 mg LTT462 QD as oral capsules.

Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received LTT462 QD as oral capsules.

Arm title	LTT462 200 mg QD

Arm description:	
Subjects received 200 mg LTT462 QD as oral capsules.	
Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received LTT462 QD as oral capsules.	
Arm title	LTT462 300 mg QD
Arm description:	
Subjects received 300 mg LTT462 QD as oral capsules.	
Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received LTT462 QD as oral capsules.	
Arm title	LTT462 400 mg QD
Arm description:	
Subjects received 400 mg LTT462 QD as oral capsules.	
Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received LTT462 QD as oral capsules.	
Arm title	LTT462 450 mg QD
Arm description:	
Subjects received 450 mg LTT462 QD as oral capsules.	
Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Subjects received LTT462 QD as oral capsules.	
Arm title	LTT462 600 mg QD
Arm description:	
Subjects received 600 mg LTT462 QD as oral capsules.	
Arm type	Experimental

Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects received LTT462 QD as oral capsules.

Arm title	LTT462 150 mg BID

Arm description:
Subjects received 150 mg LTT462 twice daily (BID) as oral capsules.

Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects received LTT462 BID as oral capsules.

Arm title	LTT462 200 mg BID

Arm description:
Subjects received 200 mg LTT462 BID as oral capsules.

Arm type	Experimental
Investigational medicinal product name	LTT462
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
Subjects received LTT462 BID as oral capsules.

Number of subjects in period 1	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD
Started	2	3	6
Entered post-treatment follow-up	0	0	1
Completed	0	0	0
Not completed	2	3	6
Physician decision	-	-	1
Adverse event, non-fatal	-	-	-
Death	1	-	-
Progressive disease	1	3	5
Subject/guardian decision	-	-	-

Number of subjects in period 1	LTT462 200 mg QD	LTT462 300 mg QD	LTT462 400 mg QD
Started	4	8	6
Entered post-treatment follow-up	1	1	2

Completed	0	0	0
Not completed	4	8	6
Physician decision	-	-	-
Adverse event, non-fatal	1	1	2
Death	-	-	-
Progressive disease	3	7	2
Subject/guardian decision	-	-	2

Number of subjects in period 1	LTT462 450 mg QD	LTT462 600 mg QD	LTT462 150 mg BID
Started	12	6	6
Entered post-treatment follow-up	3	0	1
Completed	0	0	0
Not completed	12	6	6
Physician decision	-	-	1
Adverse event, non-fatal	1	-	-
Death	-	1	-
Progressive disease	8	4	5
Subject/guardian decision	3	1	-

Number of subjects in period 1	LTT462 200 mg BID
Started	12
Entered post-treatment follow-up	1
Completed	0
Not completed	12
Physician decision	-
Adverse event, non-fatal	2
Death	-
Progressive disease	6
Subject/guardian decision	4

Baseline characteristics

Reporting groups	
Reporting group title	LTT462 45 mg QD
Reporting group description:	
Subjects received LTT462 45 milligram (mg) once daily (QD)	
Reporting group title	LTT462 100 mg QD
Reporting group description:	
Subjects received 100 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 150 mg QD
Reporting group description:	
Subjects received 150 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 200 mg QD
Reporting group description:	
Subjects received 200 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 300 mg QD
Reporting group description:	
Subjects received 300 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 400 mg QD
Reporting group description:	
Subjects received 400 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 450 mg QD
Reporting group description:	
Subjects received 450 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 600 mg QD
Reporting group description:	
Subjects received 600 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 150 mg BID
Reporting group description:	
Subjects received 150 mg LTT462 twice daily (BID) as oral capsules.	
Reporting group title	LTT462 200 mg BID
Reporting group description:	
Subjects received 200 mg LTT462 BID as oral capsules.	

Reporting group values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD
Number of subjects	2	3	6
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	2	5
From 65-84 years	1	1	1
Gender categorical Units: Subjects			
Female	1	3	4
Male	1	0	2

Reporting group values	LTT462 200 mg QD	LTT462 300 mg QD	LTT462 400 mg QD
Number of subjects	4	8	6

Age categorical Units: Subjects			
Adolescents (12-17 years)	0	1	0
Adults (18-64 years)	3	5	5
From 65-84 years	1	2	1
Gender categorical Units: Subjects			
Female	2	6	4
Male	2	2	2

Reporting group values	LTT462 450 mg QD	LTT462 600 mg QD	LTT462 150 mg BID
Number of subjects	12	6	6
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	5	5
From 65-84 years	5	1	1
Gender categorical Units: Subjects			
Female	5	4	4
Male	7	2	2

Reporting group values	LTT462 200 mg BID	Total	
Number of subjects	12	65	
Age categorical Units: Subjects			
Adolescents (12-17 years)	0	1	
Adults (18-64 years)	6	44	
From 65-84 years	6	20	
Gender categorical Units: Subjects			
Female	7	40	
Male	5	25	

Subject analysis sets

Subject analysis set title	All LTT462 QD
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received 45 to 600 mg LTT462 QD as oral capsules

Subject analysis set title	All LTT462 BID
Subject analysis set type	Full analysis

Subject analysis set description:

All subjects who received 150 and 200 mg LTT462 BID as oral capsules.

Reporting group values	All LTT462 QD	All LTT462 BID	
Number of subjects	47	18	
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	
Adults (18-64 years)	33	11	

From 65-84 years	13	7	

Gender categorical Units: Subjects			
Female	29	11	
Male	18	7	

End points

End points reporting groups

Reporting group title	LTT462 45 mg QD
Reporting group description: Subjects received LTT462 45 milligram (mg) once daily (QD)	
Reporting group title	LTT462 100 mg QD
Reporting group description: Subjects received 100 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 150 mg QD
Reporting group description: Subjects received 150 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 200 mg QD
Reporting group description: Subjects received 200 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 300 mg QD
Reporting group description: Subjects received 300 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 400 mg QD
Reporting group description: Subjects received 400 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 450 mg QD
Reporting group description: Subjects received 450 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 600 mg QD
Reporting group description: Subjects received 600 mg LTT462 QD as oral capsules.	
Reporting group title	LTT462 150 mg BID
Reporting group description: Subjects received 150 mg LTT462 twice daily (BID) as oral capsules.	
Reporting group title	LTT462 200 mg BID
Reporting group description: Subjects received 200 mg LTT462 BID as oral capsules.	
Subject analysis set title	All LTT462 QD
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received 45 to 600 mg LTT462 QD as oral capsules	
Subject analysis set title	All LTT462 BID
Subject analysis set type	Full analysis
Subject analysis set description: All subjects who received 150 and 200 mg LTT462 BID as oral capsules.	

Primary: Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Percentage of Subjects With Adverse Events (AEs) and Serious Adverse Events (SAEs)[1]
End point description: An adverse events is defined as the appearance of (or worsening of any pre-existing) undesirable signs, symptoms, or medical conditions that occur after subject's signed informed consent has been obtained. Analysis was performed in safety set population defined as all subjects who had received at least one dose of LTT462.	
End point type	Primary

End point timeframe:

Up to 2.8 years

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: The statistical analyses was not planned for this outcome measure.

End point values	All LTT462 QD	All LTT462 BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	18		
Units: Percentage of subjects				
number (not applicable)				
AEs	100	100		
SAEs	48.9	44.4		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With Dose Limiting Toxicities (DLTs)

End point title	Percentage of Subjects With Dose Limiting Toxicities (DLTs)[2]

End point description:

Percentage of subjects with dose limiting toxicity were reported. The dose determining set included all subjects from the safety set enrolled in the escalation part of the study who, during the first 28 days of dosing, had received at least 75 percent of the planned daily doses of LTT462 and had had sufficient safety evaluations, or had experienced a DLT.

End point type	Primary

End point timeframe:

Up to 2.8 years

Notes:

[2] - 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: The statistical analyses was not planned for this outcome measure.

End point values	All LTT462 QD	All LTT462 BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	36	13		
Units: Percentage of subjects				
number (not applicable)	19.4	30.8		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With at Least One Dose Reduction

End point title	Percentage of Subjects With at Least One Dose Reduction[3]

End point description:

Percentage of subjects with at least one dose reduction were reported. The safety set included all subjects who had received at least one dose of LTT462.

End point type	Primary

End point timeframe:

Up to 2.8 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses was not planned for this outcome measure.

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Percentage of subjects				
number (not applicable)	0	0	16.7	0

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6
Units: Percentage of subjects				
number (not applicable)	0	0	16.7	33.3

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Percentage of subjects				
number (not applicable)	16.7	33.3		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects With at Least One Dose Interruptions

End point title	Percentage of Subjects With at Least One Dose Interruptions[4]

End point description:

Percentage of subjects with at least dose interruptions were reported. The safety set included all subjects who had received at least one dose of LTT462.

End point type	Primary

End point timeframe:

Up to 2.8 years

Notes:

[4] - 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: The statistical analyses was not planned for this outcome measure.

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Percentage of subjects				
number (not applicable)	100	100	100	100

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6
Units: Percentage of subjects				
number (not applicable)	100	100	100	100

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Percentage of subjects				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Primary: Dose Intensity Received by Subjects

End point title	Dose Intensity Received by Subjects[5]

End point description:

Dose intensity of LTT462 received by treatment group was reported. The safety set included all subjects who had received at least one dose of LTT462.

End point type	Primary

End point timeframe:

Up to 2.8 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analyses was not planned for this outcome measure.

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: milligram per day (mg/day)				
arithmetic mean (standard deviation)	65.3 (± 28.74)	98.1 (± 3.21)	133.9 (± 21.84)	200 (± 0)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6
Units: milligram per day (mg/day)				
arithmetic mean (standard deviation)	272.7 (± 30.9)	326.7 (± 81.54)	409.2 (± 64.88)	468.2 (± 171.48)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: milligram per day (mg/day)				
arithmetic mean (standard deviation)	131.6 (± 22.08)	178.0 (± 35.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Overall Response Rate (ORR)

End point title	Percentage of Subjects With Overall Response Rate (ORR)

End point description:

Percentage of subjects with ORR were reported. The full analysis set included all Subjects who had received at least one dose of LTT462.

End point type	Secondary

End point timeframe:

Every 2 cycles after starting LTT462 treatment until end of treatment (Up to 2.8 years)

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Percentage of Subjects				
number (confidence interval 95%)	0 (0 to 84.2)	0 (0 to 70.8)	0 (0 to 45.9)	0 (0 to 60.2)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6
Units: Percentage of Subjects				
number (confidence interval 95%)	0 (0 to 36.9)	0 (0 to 45.9)	0 (0 to 26.5)	0 (0 to 45.9)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Percentage of Subjects				
number (confidence interval 95%)	0 (0 to 45.9)	0 (0 to 26.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Disease Control Rate (DCR)

End point title	Percentage of Subjects With Disease Control Rate (DCR)

End point description:

Percentage of subjects with DCR were reported. The full analysis set included all Subjects who had received at least one dose of LTT462.

End point type	Secondary

End point timeframe:

Every 2 cycles after starting LTT462 treatment until end of treatment (Up to 2.8 years)

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Percentage of subjects				
number (confidence interval 95%)	50 (1.3 to 98.7)	0 (0 to 70.8)	0 (0 to 45.9)	0 (0 to 60.2)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6

Units: Percentage of subjects				
number (confidence interval 95%)	37.5 (8.5 to 75.5)	16.7 (0.4 to 64.1)	8.3 (0.2 to 38.5)	16.7 (0.4 to 64.1)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Percentage of subjects				
number (confidence interval 95%)	16.7 (0.4 to 64.1)	0 (0 to 26.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Percentage of subjects with DOR were reported. The study was stopped due to limited clinical activity at the end of the dose escalation phase. The dose expansion part was not opened.

End point type	Secondary

End point timeframe:

Every 2 cycles after starting LTT462 treatment until end of treatment (Up to 2.8 years)

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[6]	0[7]	0[8]	0[9]
Units: Months				
number (not applicable)				

Notes:

[6] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[7] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[8] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[9] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[10]	0[11]	0[12]	0[13]
Units: Months				
number (not applicable)				

Notes:

[10] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[11] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[12] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[13] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: Months				
number (not applicable)				

Notes:

[14] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

[15] - The study was stopped due to limited clinical activity at the end of the dose escalation phase.

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Median time for progression free survival was reported. The full analysis set included all Subjects who had received at least one dose of LTT462.

End point type	Secondary

End point timeframe:

Every 2 cycles after starting LTT462 treatment until end of treatment (Up to 2.8 years)

End point values	All LTT462 QD	All LTT462 BID		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	18		
Units: Months				
median (confidence interval 95%)	1.7 (1.3 to 1.8)	1.6 (1.2 to 1.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) - Only for Dose Expansion Phase

End point title	Overall Survival (OS) - Only for Dose Expansion Phase

End point description:

Median time for overall survival, only for dose expansion phase was reported. Overall survival was not evaluated because the study ended before enrolling into the dose-expansion part.

End point type	Secondary

End point timeframe:

Every 2 cycles after starting LTT462 treatment until end of treatment (Up to 2.8 years)

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[16]	0[17]	0[18]	0[19]
Units: Months				
number (not applicable)				

Notes:

[16] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[17] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[18] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[19] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	0[20]	0[21]	0[22]	0[23]
Units: Months				
number (not applicable)				

Notes:

[20] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[21] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[22] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[23] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: Months				
number (not applicable)				

Notes:

[24] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion
[25] - Overall survival was not evaluated because the study ended before enrolling into the dose-expansion

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum (Peak) Observed Plasma, Blood, Serum, or Other Body Fluid Drug Concentration (Cmax) After Single Dose Administration of LTT462

End point title	Maximum (Peak) Observed Plasma, Blood, Serum, or Other Body Fluid Drug Concentration (Cmax) After Single Dose Administration of LTT462

End point description:

Cmax is the maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration

after single dose administration expressed in mass x volume-1. Pharmacokinetic (PK) analysis set (PAS) included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn't vomit within 4 hours post-dose, had at least 1 primary PK parameter. Here 'n' number analyzed signifies number of Subjects who were evaluable at each time point.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	61.3 (± 55.9)	134 (± 38.8)	218 (± 230.9)	494 (± 126.8)
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	139 (± 29.9)	938 (± 82.5)	707 (± 69)	972 (± 92.4)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	11	4
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	717 (± 127.4)	1580 (± 60.8)	1420 (± 83.5)	1280 (± 47.7)
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	1330 (± 131.9)	2370 (± 83.3)	3470 (± 49.7)	1030 (± 248.8)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	598 (± 83)	575 (± 73.8)		
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	1390 (± 58.5)	1510 (± 108)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve From Time Zero to the Last Measurable

Concentration Sampling Time (AUClast) of LTT462

End point title	Area Under the Curve From Time Zero to the Last Measurable Concentration Sampling Time (AUClast) of LTT462

End point description:

AUClast is the area under the curve from time zero to the last measurable concentration sampling time calculated by mass * time *volume^-1. PAS included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn't vomit within 4 hours postdose, had at least 1 primary PK parameter. Here 'N' number of Subjects analyzed signifies number of Subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	2	6	4
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	851 (± 106)	2260 (± 30)	3880 (± 133.6)	10400 (± 95.4)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	10	3
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	12800 (± 157.4)	23300 (± 55.5)	23800 (± 115.3)	11800 (± 64.2)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	12		
Units: hour*nanogram per milliliter (h*ng/mL)				
geometric mean (geometric coefficient of variation)	9240 (± 78.3)	7630 (± 98.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximum (Peak) Plasma, Blood, Serum, or Other Body

Fluid Drug Concentration (Tmax) After Single Dose Administration of LTT462

End point title	Time to Reach Maximum (Peak) Plasma, Blood, Serum, or Other Body Fluid Drug Concentration (Tmax) After Single Dose Administration of LTT462

End point description:

Tmax is the time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration. PAS included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn't vomit within 4 hours post-dose, had at least 1 primary PK parameter. Here 'n' number analyzed signifies number of Subjects who were evaluable at each time point.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Hours				
median (full range (min-max))				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	2.45 (0.967 to 3.93)	1.98 (0.867 to 24)	3.49 (2 to 24.3)	5.48 (3 to 46.4)
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	5.93 (4 to 7.85)	4.02 (1 to 4.83)	4.05 (2.13 to 8)	3 (2.17 to 3.02)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	11	4
Units: Hours				
median (full range (min-max))				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	3.08 (2.08 to 48.8)	3.04 (1.12 to 4)	3.98 (2.42 to 7.77)	3.95 (2 to 4.2)
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	2.59 (1.58 to 4.03)	2.55 (1.87 to 3.15)	2.98 (1 to 7.62)	5.25 (3 to 7.5)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Hours				
median (full range (min-max))				
Day 1 (n=2,3,6,4,7,6,10,3,5,12)	2.25 (2 to 49.8)	3.03 (0.467 to 7.78)		
Day 15 (n=2,3,5,3,6,4,8,2,5,6)	2.17 (2.05 to 3.15)	2.18 (2 to 4.15)		

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (T1/2) of LTT462

End point title	Elimination Half-life (T1/2) of LTT462

End point description:

T1/2 is the Elimination half-life. PAS included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn't vomit within 4 hours postdose, had at least 1 primary PK parameter. Here 'N' number of Subjects analyzed signifies number of Subjects who were evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	2	4	2
Units: Hours				
median (full range (min-max))	27.9 (27.9 to 27.9)	39.2 (28.8 to 49.5)	20.8 (13.4 to 24.5)	16.8 (16.7 to 16.8)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3	6	7	2
Units: Hours				
median (full range (min-max))	15.2 (14.9 to 19.6)	14.0 (12.0 to 18.7)	17.6 (16.1 to 18.9)	13.2 (11.8 to 14.5)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	9		
Units: Hours				
median (full range (min-max))	16.2 (13.3 to 19.1)	17.1 (11.6 to 41.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Curve Calculated to the End of a Dosing Interval (Tau) at Steady-state (AUCtau) of LTT462

End point title	Area Under the Curve Calculated to the End of a Dosing Interval (Tau) at Steady-state (AUCtau) of LTT462

End point description:

AUCtau is the area under the curve calculated to the end of a dosing interval (tau) at steady-state calculated by formula amount *time * volume^-1. PAS included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn't vomit within 4 hours post-dose, had at least 1 primary PK parameter. Here 'N' number of Subjects analyzed signifies number of Subjects who were evaluable for this outcome measure. Here, '99999' signifies data was not calculated due to single subject in the arm.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	4	3
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	3010 (± 99999)	6370 (± 99999)	8660 (± 50.0)	14600 (± 96.5)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	5	4	4	1
Units: h*ng/mL				
geometric mean (geometric coefficient of variation)	13100 (± 81.6)	25400 (± 74.3)	35400 (± 94.8)	6760 (± 99999)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	4		
Units: h*ng/mL				
geometric mean (geometric coefficient	11100 (± 59.5)	18600 (± 85.2)		

of variation)

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio (Racc) of LTT462

End point title	Accumulation Ratio (Racc) of LTT462

End point description:

Racc is the accumulation ratio calculated by AUCtau ratio Day 15 versus Day 1. PAS included of all Subjects who have at least 1 PK blood sample providing measurable LTT462 and received at least 1 dose of study drug, didn’t vomit within 4 hours post-dose, had at least 1 primary PK parameter. Here ‘N’ number of Subjects analyzed signifies number of Subjects who were evaluable for this outcome measure. Here, '99999' signifies data was not calculated due to single subject in the arm. Here, '99999' signifies data was not calculated due to single subject in the arm.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 8, 15 and 16; Cycle 2 day 1 and 15; Cycle 3 Day 1; Cycle 5 Day 1

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	1	4	3
Units: Ratio				
geometric mean (geometric coefficient of variation)	3.01 (± 99999)	3.35 (± 99999)	5.09 (± 72.7)	2.74 (± 46.9)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4	4	3	0[26]
Units: Ratio				
geometric mean (geometric coefficient of variation)	1.49 (± 25.1)	1.73 (± 62.4)	1.44 (± 73.4)	()

Notes:

[26] - No subject was evaluable in this arm

End point values	LTT462 150 mg BID	LTT462 200 mg BID		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	4		
Units: Ratio				
geometric mean (geometric coefficient of variation)	3.19 (± 50.2)	6.89 (± 84.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Changes From Baseline in Relative Quantity (RQ) of Dual Specificity Phosphatase 6 (DUSP6) in Blood sample

End point title	Changes From Baseline in Relative Quantity (RQ) of Dual Specificity Phosphatase 6 (DUSP6) in Blood sample

End point description:

Assessment of Pharmacodynamic (PD) effects of LTT462 in tumor, pre- and post- treatment tumor biopsies were examined for expression of DUSP6. For assessment of PD effects in blood, levels of DUSP6 were measured in blood samples. The full analysis set included all subjects who had received at least one dose of LTT462. Here, '99999' signifies data was not calculated due to single subject in the arm.

End point type	Secondary

End point timeframe:

Cycle 1 Days 1, 2, 3, 15 and 16

End point values	LTT462 45 mg QD	LTT462 100 mg QD	LTT462 150 mg QD	LTT462 200 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2	3	6	4
Units: Ratio				
arithmetic mean (standard deviation)				
Tumor Sample (n=1,2,4,1,4,1,4,1,2,3)	-0.2 (± 99999)	0.8 (± 1.11)	-1.1 (± 29.46)	-28.8 (± 99999)
Blood Sample (n=2,3,6,3,8,6,12,6,6,11)	-50.8 (± 6.14)	-66.1 (± 40.22)	-35.2 (± 27.33)	-34.7 (± 22.02)

End point values	LTT462 300 mg QD	LTT462 400 mg QD	LTT462 450 mg QD	LTT462 600 mg QD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	8	6	12	6
Units: Ratio				
arithmetic mean (standard deviation)				
Tumor Sample (n=1,2,4,1,4,1,4,1,2,3)	-31.0 (± 31.06)	-56.5 (± 99999)	-22.2 (± 28.67)	-79.9 (± 99999)
Blood Sample (n=2,3,6,3,8,6,12,6,6,11)	-42.5 (± 16.56)	-43 (± 13.67)	-40.1 (± 9.92)	-40.4 (± 21.04)

End point values	LTT462 150 mg BID	LTT462 200 mg BID		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	12		
Units: Ratio				
arithmetic mean (standard deviation)				
Tumor Sample (n=1,2,4,1,4,1,4,1,2,3)	-61.8 (± 4.16)	-14.4 (± 22.27)		
Blood Sample (n=2,3,6,3,8,6,12,6,6,11)	-39.2 (± 12.98)	-32.9 (± 18.71)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were evaluated from screening until at least 30 days after the discontinuation of study treatment (Up to 2.8 years)	
Adverse event reporting additional description:	
The Safety Set included all subjects who had received at least one dose of LTT462.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	All LTT462 QD
Reporting group description:	
All subjects who received 45 to 600 mg LTT462 QD as oral capsules	
Reporting group title	All LTT462 BID
Reporting group description:	
Subjects received 150 and 200 mg LTT462 BID as oral capsules.	

Serious adverse events	All LTT462 QD	All LTT462 BID	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 47 (48.94%)	8 / 18 (44.44%)	
number of deaths (all causes)	6	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 47 (6.38%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 47 (4.26%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	3 / 47 (6.38%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonitis			

subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinopathy			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 47 (10.64%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Colitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 47 (2.13%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			

subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal injury			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Biliary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 47 (2.13%)	2 / 18 (11.11%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyponatraemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 18 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	All LTT462 QD	All LTT462 BID	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 47 (97.87%)	18 / 18 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	6	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 47 (10.64%)	2 / 18 (11.11%)	
occurrences (all)	8	2	
Fatigue			
subjects affected / exposed	8 / 47 (17.02%)	6 / 18 (33.33%)	
occurrences (all)	9	7	
Mucosal haemorrhage			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Oedema peripheral			
subjects affected / exposed	6 / 47 (12.77%)	2 / 18 (11.11%)	
occurrences (all)	7	2	
Pyrexia			
subjects affected / exposed	4 / 47 (8.51%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Swelling			

subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 47 (8.51%)	1 / 18 (5.56%)	
occurrences (all)	4	1	
Dyspnoea			
subjects affected / exposed	2 / 47 (4.26%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Psychiatric disorders			
Delirium			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 47 (19.15%)	1 / 18 (5.56%)	
occurrences (all)	9	1	
Amylase increased			
subjects affected / exposed	2 / 47 (4.26%)	3 / 18 (16.67%)	
occurrences (all)	2	3	
Aspartate aminotransferase increased			
subjects affected / exposed	10 / 47 (21.28%)	5 / 18 (27.78%)	
occurrences (all)	11	6	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	7 / 47 (14.89%)	1 / 18 (5.56%)	
occurrences (all)	8	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 47 (2.13%)	2 / 18 (11.11%)	
occurrences (all)	1	4	
Blood creatine phosphokinase increased			
subjects affected / exposed	7 / 47 (14.89%)	3 / 18 (16.67%)	
occurrences (all)	9	4	

Blood creatinine increased			
subjects affected / exposed	9 / 47 (19.15%)	2 / 18 (11.11%)	
occurrences (all)	10	3	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
C-reactive protein increased			
subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Gamma-glutamyltransferase			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Gamma-glutamyltransferase increased			
subjects affected / exposed	7 / 47 (14.89%)	2 / 18 (11.11%)	
occurrences (all)	8	2	
Lipase			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	2 / 47 (4.26%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Liver function test			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 47 (6.38%)	1 / 18 (5.56%)	
occurrences (all)	7	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 47 (38.30%)	4 / 18 (22.22%)	
occurrences (all)	22	6	
Leukocytosis			

subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Leukopenia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Neutropenia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 18 (5.56%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	1	2	
Chorioretinopathy			
subjects affected / exposed	7 / 47 (14.89%)	2 / 18 (11.11%)	
occurrences (all)	11	3	
Cystoid macular oedema			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Macular oedema			
subjects affected / exposed	1 / 47 (2.13%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Retinal detachment			
subjects affected / exposed	3 / 47 (6.38%)	3 / 18 (16.67%)	
occurrences (all)	6	3	
Retinal pigment epitheliopathy			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Retinopathy			
subjects affected / exposed	4 / 47 (8.51%)	3 / 18 (16.67%)	
occurrences (all)	5	3	
Vision blurred			
subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	5	0	

Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 47 (6.38%)	1 / 18 (5.56%)	
occurrences (all)	3	1	
Abdominal pain			
subjects affected / exposed	6 / 47 (12.77%)	0 / 18 (0.00%)	
occurrences (all)	7	0	
Abdominal pain upper			
subjects affected / exposed	1 / 47 (2.13%)	2 / 18 (11.11%)	
occurrences (all)	1	2	
Ascites			
subjects affected / exposed	2 / 47 (4.26%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Constipation			
subjects affected / exposed	6 / 47 (12.77%)	1 / 18 (5.56%)	
occurrences (all)	6	1	
Diarrhoea			
subjects affected / exposed	22 / 47 (46.81%)	6 / 18 (33.33%)	
occurrences (all)	30	7	
Gingival bleeding			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	21 / 47 (44.68%)	7 / 18 (38.89%)	
occurrences (all)	26	10	
Vomiting			
subjects affected / exposed	19 / 47 (40.43%)	7 / 18 (38.89%)	
occurrences (all)	25	10	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Jaundice			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Portal vein thrombosis			

subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 47 (4.26%)	2 / 18 (11.11%)	
occurrences (all)	2	2	
Alopecia			
subjects affected / exposed	0 / 47 (0.00%)	2 / 18 (11.11%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dermatitis acneiform			
subjects affected / exposed	6 / 47 (12.77%)	2 / 18 (11.11%)	
occurrences (all)	6	2	
Dermatitis exfoliative generalised			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Dry skin			
subjects affected / exposed	3 / 47 (6.38%)	2 / 18 (11.11%)	
occurrences (all)	3	2	
Hyperkeratosis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Pain of skin			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	8 / 47 (17.02%)	4 / 18 (22.22%)	
occurrences (all)	9	4	
Rash			
subjects affected / exposed	14 / 47 (29.79%)	7 / 18 (38.89%)	
occurrences (all)	20	7	
Rash maculo-papular			
subjects affected / exposed	3 / 47 (6.38%)	2 / 18 (11.11%)	
occurrences (all)	3	2	

Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Myalgia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Cystitis			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Rash pustular			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	14 / 47 (29.79%)	3 / 18 (16.67%)	
occurrences (all)	14	4	
Hypercalcaemia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 18 (5.56%)	
occurrences (all)	0	1	
Hyperkalaemia			
subjects affected / exposed	2 / 47 (4.26%)	1 / 18 (5.56%)	
occurrences (all)	2	1	
Hyperphosphataemia			

subjects affected / exposed	3 / 47 (6.38%)	0 / 18 (0.00%)	
occurrences (all)	4	0	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 47 (2.13%)	1 / 18 (5.56%)	
occurrences (all)	1	1	
Hypoalbuminaemia			
subjects affected / exposed	8 / 47 (17.02%)	1 / 18 (5.56%)	
occurrences (all)	11	1	
Hypocalcaemia			
subjects affected / exposed	4 / 47 (8.51%)	0 / 18 (0.00%)	
occurrences (all)	5	0	
Hypomagnesaemia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 18 (0.00%)	
occurrences (all)	3	0	
Hyponatraemia			
subjects affected / exposed	5 / 47 (10.64%)	4 / 18 (22.22%)	
occurrences (all)	5	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 July 2016	- Added laboratory evaluation for inorganic phosphorus to blood chemistry panel
14 August 2017	- Changed description of LTT462 from having mild phototoxic potential to no phototoxic potential and removed requirement for sun protection precautions
13 March 2018	- Reduced the minimum age of prospective subjects from ≥18 years to ≥12 years. - Amended biopsy inclusion criterion to allow adolescent subjects to participate without having to provide the required new biopsy at screening or on treatment if not feasible.

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.

The study was stopped due to limited clinical activity at the end of the dose escalation phase. The dose expansion part was not opened.

Notes: