



Clinical trial results:

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled Study of AG-120 in Previously-treated Subjects With Nonresectable or Metastatic Cholangiocarcinoma With an IDH1 Mutation

Summary

EudraCT number	2015-005117-72
Trial protocol	DE GB ES FR IT
Global end of trial date	17 May 2021

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	AG120-C-005
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02989857
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut de Recherches Internationales Servier (I.R.I.S.)
Sponsor organisation address	50, rue Carnot, Suresnes cedex, France, 92284
Public contact	Institut de Recherches Internationales Servier Clinical Studies Department , Institut de Recherches Internationales Servier , +33 155724366, scientificinformation@servier.com
Scientific contact	Medical Affairs Servier Pharmaceuticals LLC, Institut de Recherches Internationales Servier , +1 888-788-1735, scientificinformation@servier.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	17 May 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 May 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to demonstrate the efficacy of AG-120 based on Progression Free Survival (PFS) per Independent Radiology Center (IRC) assessment compared to placebo in subjects with nonresectable or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation.

Protection of trial subjects:

This study was conducted in accordance with Good Clinical Practice standards, ethical principles stated in the Declaration of Helsinki, and applicable regulatory requirements. All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 February 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 11
Country: Number of subjects enrolled	United States: 125
Worldwide total number of subjects	187
EEA total number of subjects	39

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)	115
From 65 to 84 years	72
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects took part in the study at 49 study sites in France, Italy, Spain, South Korea, the United States, and the United Kingdom from 20 February 2017 to 17 May 2021.

Pre-assignment

Screening details:

The final analysis of progression-free survival (PFS) occurred once 131 PFS events had been determined by Investigator assessment. Two subjects were randomised in the study after the data cutoff date (31 January 2019) for the final analysis of PFS.

Period 1

Period 1 title	Randomisation Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	AG-120

Arm description:

Subjects received AG-120 500 mg, tablet, orally, once daily (QD) in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study for up to approximately 45 months.

Arm type	Active comparator
Investigational medicinal product name	AG-120
Investigational medicinal product code	
Other name	Ivosidenib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally.

Arm title	Placebo
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Arm description:

Subjects received AG-120 matched placebo, orally, QD in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up or the sponsor ended the study for up to approximately 7 months. Subjects who experienced disease progression and received placebo were allowed to cross over and receive AG-120.

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

Dosage and administration details:

Tablet administered orally.

Number of subjects in period 1	AG-120	Placebo
Started	126	61
Completed	123	59
Not completed	3	2
Not Treated	3	2

Period 2

Period 2 title	Cross Over Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	After Crossover to AG-120
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Arm description:

Subjects who experienced disease progression and received placebo were allowed to cross over to receive AG-120 500 mg, tablet, orally, QD in each 28-day treatment cycle for up to approximately 32 months.

Arm type	Experimental
Investigational medicinal product name	AG-120
Investigational medicinal product code	
Other name	Ivosidenib
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablet administered orally.

Number of subjects in period 2 ^[1]	After Crossover to AG-120
Started	43
Completed	43

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Subjects who had experienced disease progression and received placebo were allowed to cross over to receive AG-120. Completed = Subjects who completed the protocol defined treatment.

Baseline characteristics

Reporting groups

Reporting group title	AG-120
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Reporting group description:

Subjects received AG-120 500 mg, tablet, orally, once daily (QD) in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study for up to approximately 45 months.

Reporting group title	Placebo
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Reporting group description:

Subjects received AG-120 matched placebo, orally, QD in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up or the sponsor ended the study for up to approximately 7 months. Subjects who experienced disease progression and received placebo were allowed to cross over and receive AG-120.

Reporting group values	AG-120	Placebo	Total
Number of subjects	126	61	187
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	60.3 ± 10.97	62.9 ± 10.38	-
Gender categorical Units: Subjects			
Female	82	37	119
Male	44	24	68
Ethnicity, Customized Units: Subjects			
Hispanic or Latino	7	2	9
Not Hispanic or Latino	84	40	124
Not Reported	0	2	2
Missing	35	17	52
Race, Customized Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	15	8	23
Black or African American	1	1	2
Native Hawaiian or Other Pacific Islander	1	0	1
White	71	35	106
Other	1	0	1
Not Reported	1	0	1
Missing	35	17	52

End points

End points reporting groups

Reporting group title	AG-120
Reporting group description: Subjects received AG-120 500 mg, tablet, orally, once daily (QD) in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study for up to approximately 45 months.	
Reporting group title	Placebo
Reporting group description: Subjects received AG-120 matched placebo, orally, QD in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up or the sponsor ended the study for up to approximately 7 months. Subjects who experienced disease progression and received placebo were allowed to cross over and receive AG-120.	
Reporting group title	After Crossover to AG-120
Reporting group description: Subjects who experienced disease progression and received placebo were allowed to cross over to receive AG-120 500 mg, tablet, orally, QD in each 28-day treatment cycle for up to approximately 32 months.	
Subject analysis set title	Randomisation phase AG-120 plus Cross over phase AG-120
Subject analysis set type	Sub-group analysis
Subject analysis set description: Participants received AG-120 500 mg, tablet, orally, QD in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study. Participants who experienced disease progression and received placebo were allowed to cross over to receive AG-120 500 mg, tablet, orally, QD in each 28-day treatment cycle.	

Primary: Progression Free Survival (PFS) as Determined by the Independent Radiology Committee (IRC)

End point title	Progression Free Survival (PFS) as Determined by the Independent Radiology Committee (IRC)
End point description: PFS is defined as the time from date of randomisation to the date of first documented disease progression as assessed by the IRC using Response Evaluation Criteria in Solid Tumors [RECIST] v1.1, or date of death due to any cause, whichever occurred first. Disease progression was defined as greater than or equal to (\geq)20 percent (%) increase in sum of the diameter of target lesions, taking as reference the smallest sum diameter recorded since the treatment started. In addition to relative increase of 20%, sum must also demonstrate an absolute increase of at least 5 millimetres (mm) or the appearance of 1 or more new lesions. ITT set=all subjects who were randomised, with the treatment group designated according to the randomisation. Number analysed=number of subjects with data available for analyses at the specified time point. Two subjects were excluded from analysis as they were randomised in the study after the data cutoff date (31 January 2019) for the analysis of PFS.	
End point type	Primary
End point timeframe: From the date of randomisation to the date of first documentation of disease progression or death due to any cause (Up to approximately 2 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	61		
Units: months				
median (confidence interval 95%)	2.7 (1.6 to 4.2)	1.4 (1.4 to 1.6)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS by the IRC
Statistical analysis description:	
Hazard ratio was calculated from stratified Cox regression model with placebo as the denominator, with two-sided 95% confidence interval.	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.54

Notes:

[1] - P-value was calculated from the one-sided stratified log-rank test.

Secondary: 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)
End point description:	
An AE is any untoward medical occurrence associated with the use of a drug in subjects, whether or not considered drug related. An AE or suspected adverse reaction is considered serious (an SAE) if it is fatal, life-threatening, causes in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, congenital anomaly/birth defect in a neonate/infant born to a mother or father exposed to study treatment or is an important medical event. Safety Analysis Set (SAS) included all subjects who had received at least one dose of study drug (AG-120 or Placebo). Treatment-emergent adverse events are reported.	
End point type	Secondary
End point timeframe:	
From first dose of study drug up to 28 days after last dose for each intervention (Up to approximately 4 Years)	

End point values	AG-120	After Crossover to AG-120	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	43	59	
Units: percentage of subjects				
number (not applicable)				
AEs	97.6	95.3	96.6	
SAEs	35.0	27.9	23.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Eastern Cooperative Oncology Group (ECOG) Performance Status

End point title	Percentage of Subjects With Eastern Cooperative Oncology Group (ECOG) Performance Status
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End point description:

The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score classified subjects according to their functional impairment, with scores ranging from 0 to 4. ECOG PS: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; 2 = ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours; 3 = capable of only limited self-care, confined to bed or chair more than 50% of waking hours; 4 = completely disabled, cannot carry on any self-care, totally confined to bed or chair. A higher score means a worse functional status. ITT population included all subjects who were randomised, with the treatment group designated according to the randomisation.

End point type	Secondary
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End point timeframe:

Baseline

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	61		
Units: percentage of subjects				
number (not applicable)				
Score 0	39.7	31.1		
Score 1	59.5	67.2		
Score 2	0.0	1.6		
Score 3	0.8	0.0		
Score 4	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Required At Least One Concomitant Medications During the Treatment

End point title	Percentage of Subjects Who Required At Least One Concomitant Medications During the Treatment
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End point description:

Concomitant medications were medications that were ongoing or initiated after the first dose of the study drug but before the last dose plus 28 days. Percentage of subjects who required at least one concomitant medications during the study along with their prescribed study drug (AG-120 or placebo) were reported. SAS included all subjects who had received at least one dose of study drug (AG-120 or Placebo).

End point type	Secondary
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End point timeframe:

From first dose of study drug up to 28 days after last dose (Up to approximately 4 Years)

End point values	AG-120	After Crossover to AG-120	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	43	59	
Units: percentage of subjects				
number (not applicable)	99.2	95.3	98.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Abnormal Electrocardiogram (ECG) Changes Reported as Adverse Events

End point title	Percentage of Subjects With Abnormal Electrocardiogram (ECG) Changes Reported as Adverse Events
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End point description:

SAS included all subjects who had received at least one dose of study drug (AG-120 or Placebo).

End point type	Secondary
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End point timeframe:

Pre-dose C1D1, C2D1; Post-dose C1D1, C1D15, C2D1 and Day 1 of C3D1 and all cycles thereafter up to last dose plus 28 days (Up to approximately 4 years)

End point values	AG-120	After Crossover to AG-120	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	43	59	
Units: percentage of subjects				
number (not applicable)				
Electrocardiogram QT Prolonged	9.8	2.3	3.4	
Electrocardiogram Abnormal	0.8	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
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End point description:

Overall survival was defined as the time in months from date of randomisation to the date of death due to any cause. Subjects without documentation of death at the time of the final collection were censored at the date the subject was last known to be alive, or the final collection date, whichever is earlier. ITT population included all subjects who were randomised, with the treatment group designated according to the randomisation.

End point type	Secondary
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End point timeframe:

From date of randomisation until the date of death due to any cause (Up to approximately 2 years)

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	61		
Units: months				
median (confidence interval 95%)	10.3 (7.8 to 12.4)	7.5 (4.8 to 11.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OS
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Statistical analysis description:

Hazard ratio was calculated from the stratified Cox regression model with placebo as the comparator, with two-sided 95% CI. Stratification factor was the number of prior line of therapies at randomisation.

Comparison groups	AG-120 v Placebo
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Number of subjects included in analysis	187
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	= 0.093 [2]
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Method	Logrank
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Parameter estimate	Hazard ratio (HR)
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Point estimate	0.79
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Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.12

Notes:

[2] - P-value was calculated from the one-sided stratified log-rank test. Stratification factor is the number of prior line of therapies at randomisation.

Secondary: Objective Response Rate (ORR) as Assessed by the Investigator RECIST Version 1.1

End point title	Objective Response Rate (ORR) as Assessed by the Investigator RECIST Version 1.1
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End point description:

ORR as assessed by the investigator was defined as the percentage of subjects with a best overall response (BOR) defined as complete response (CR) or partial response (PR) per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: ≥30% decrease in sum of diameters (SOD) from Baseline. ITT population included all subjects who were randomised, with the treatment group designated according to the randomisation. Two participants were excluded from the analysis as they were randomized in the study after the data cutoff date (31 January 2019) for the analysis of tumor response.

End point type	Secondary
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End point timeframe:

From the date of randomisation up to confirmed CR or PR (Up to approximately 2 years)

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	61		
Units: percentage of subjects				
number (confidence interval 95%)	3.2 (0.9 to 8.1)	1.6 (0.0 to 8.8)		

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR by the Investigator
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.466 ^[3]
Method	Fisher exact

Notes:

[3] - P-value was calculated from 1-sided Fisher exact test.

Secondary: ORR as Assessed by the IRC Per RECIST v1.1

End point title	ORR as Assessed by the IRC Per RECIST v1.1
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End point description:

ORR as assessed by the IRC was defined as the percentage of subjects with a BOR defined as CR or PR per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: ≥30% decrease in sum of diameters

(SOD) from Baseline. ITT population included all subjects who were randomised, with the treatment group designated according to the randomisation. Two participants were excluded from the analysis as they were randomized in the study after the data cutoff date (31 January 2019) for the analysis of tumor response.

End point type	Secondary
End point timeframe:	
From the date of randomisation up to confirmed CR or PR (Up to approximately 2 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	61		
Units: percentage of subjects				
number (confidence interval 95%)	2.4 (0.5 to 6.9)	0.0 (0.0 to 5.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis for ORR by the IRC
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.299 ^[4]
Method	Fisher exact

Notes:

[4] - P-value was calculated from 1-sided Fisher exact test.

Secondary: Duration of Response (DOR) as Assessed by the Investigator

End point title	Duration of Response (DOR) as Assessed by the Investigator
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End point description:

DOR was defined as the time in months from date of first documented CR or PR to date of first documented disease progression or death due to any cause, whichever is earlier, as assessed by the Investigator per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: ≥30% decrease in sum of diameters (SOD) from Baseline. Subjects with response and without progression were censored at the last observation. Subjects with CR or PR per investigator assessment by the data cutoff date (31 January 2019) for the analysis of tumor response. 9999=Median, upper and lower limit was not available due to the insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

From the date of first confirmed CR or PR to disease progression or death regardless of cause (Up to approximately 2 years)

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR) as Assessed by the Investigator

End point title	Time to Response (TTR) as Assessed by the Investigator
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End point description:

TTR was defined as the time from date of randomisation to date of first documented CR or PR for responders, as assessed by the Investigator per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: $\geq 30\%$ decrease in sum of diameters (SOD) from Baseline. Only responders were analysed for this outcome measure. Subjects with CR or PR per investigator assessment by the data cutoff date (31 January 2019) were analysed for tumor response. 9999=Median, upper and lower limit were not available due to the insufficient number of subjects with events.

End point type	Secondary
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End point timeframe:

From the date of randomisation up to the date of first documented CR or PR (Up to approximately 2 years)

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	1		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR as Assessed by the IRC Per RECIST v1.1

End point title	DOR as Assessed by the IRC Per RECIST v1.1
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End point description:

DOR was defined as the time in months from date of first documented CR or PR to date of first documented disease progression or death due to any cause, whichever is earlier, as assessed by the IRC per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: $\geq 30\%$ decrease in sum of diameters (SOD) from Baseline. Subjects with response and without progression were censored at the last observation. Subjects with CR or PR per investigator assessment by the data cutoff date (31 January 2019) for the analysis of tumor response. 9999=Median, upper and lower limit were not available due to the insufficient number of participants.

End point type	Secondary
End point timeframe:	
From the date of first confirmed CR or PR to disease progression or death regardless of cause (Up to approximately 2 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	0 ^[5]		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	(to)		

Notes:

[5] - There were no responders in placebo.

Statistical analyses

No statistical analyses for this end point

Secondary: TTR as Assessed by the IRC Per RECIST v1.1

End point title	TTR as Assessed by the IRC Per RECIST v1.1
End point description:	
TTR was defined as the time from date of randomisation to date of first documented CR or PR for responders, as assessed by the IRC per RECIST v1.1. CR: disappearance of all target and non-target lesions (TLs) and all pathological lymph nodes (LNs) (target and non target), with short axis <10mm. PR: ≥30% decrease in sum of diameters (SOD) from Baseline. Only responders were analysed for this outcome measure. Subjects with CR or PR per investigator assessment by the data cutoff date (31 January 2019) were analysed for tumor response. 9999= Median, lower limit, and upper limit were not available due to the insufficient number of subjects with events.	
End point type	Secondary
End point timeframe:	
From the date of randomisation up to the date of first documented CR or PR (Up to approximately 2 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	0 ^[6]		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	(to)		

Notes:

[6] - There were no responders in placebo.

Statistical analyses

No statistical analyses for this end point

Secondary: PFS as Determined by Investigator

End point title	PFS as Determined by Investigator
End point description:	
PFS was defined as the time from date of randomisation to the date of first documented disease progression as assessed by the investigator using RECIST v1.1, or date of death due to any cause, whichever occurred first. Disease progression was defined as $\geq 20\%$ increase in sum of the diameter of target lesions, taking as reference the smallest sum diameter recorded since the treatment started. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm or the appearance of 1 or more new lesions. No progression or death by data cutoff date was censored at the last adequate assessment date. ITT set included all subjects who were randomised, with the treatment group designated according to the randomisation. Two participants were excluded from the analysis as they were randomized in the study after the data cutoff date (31 January 2019) for the analysis of PFS.	
End point type	Secondary
End point timeframe:	
From the date of randomisation to the date of first documentation of disease progression or death due to any cause (Up to approximately 2 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	61		
Units: months				
median (confidence interval 95%)	2.7 (1.6 to 3.6)	1.4 (1.4 to 2.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS by Investigator
Statistical analysis description:	
Hazard ratio was calculated from the stratified Cox regression model with placebo as the denominator, with two-sided 95% CI. Stratification factor was the number of prior line of therapies at randomisation.	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	185
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[7]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	0.68

Notes:

[7] - P-value was calculated from one-sided stratified log-rank test. Stratification factor was the number of prior line of therapies at randomisation.

Secondary: Change From Baseline in Health-Related Quality of Life (HRQOL) Based on European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire- Core 30 Subscales Scores

End point title	Change From Baseline in Health-Related Quality of Life
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End point description:

EORTC-QLQ-C30 is the European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire – Core Questionnaire. For EORTC QLQ-C30, subscales of physical functioning, pain, and appetite loss were assessed. These had 4 response levels (not at all, a little, quite a bit, and very much). For functional scales, higher scores=better QOL (positive change from Baseline=improvement). For symptom scales, lower scores=better QOL (negative change from Baseline=improvement). ITT population included all randomised subjects, with treatment group designated according to the randomization. Number analysed is the number of subjects for a specific category with data available for analysis at the given timepoint.

End point type	Secondary
End point timeframe:	
Cycle 2 Day 1 and Cycle 3 Day 1	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	61		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1: Physical Functioning (n=67,21)	-2.4 (± 1.75)	-13.3 (± 2.95)		
Cycle 2 Day 1: Pain (n=67,21)	2.2 (± 2.48)	12.5 (± 4.35)		
Cycle 2 Day 1: Appetite Loss (n=67,21)	7.9 (± 2.60)	4.3 (± 4.55)		
Cycle 3 Day 1: Physical Functioning (n=50,9)	-0.2 (± 1.89)	-12.6 (± 3.88)		
Cycle 3 Day 1: Pain (n=50,9)	-1.2 (± 2.73)	-5.3 (± 5.96)		
Cycle 3 Day 1: Appetite Loss (n=50,9)	-0.5 (± 2.89)	3.2 (± 6.40)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cycle 2 Day 1: Physical Functioning	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	11
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.23
upper limit	17.73

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Cycle 2 Day 1: Pain	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	-10.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.18
upper limit	-0.52

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Cycle 2 Day 1: Appetite Loss	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.65
upper limit	13.91

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Cycle 3 Day 1: Physical Functioning	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	12.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.85
upper limit	20.78

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Cycle 3 Day 1: Pain	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.74
upper limit	17.04

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Cycle 3 Day 1: Appetite Loss	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	-3.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.46
upper limit	10.11

Secondary: Change From Baseline in HRQOL Based on: Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module (QLQ-BIL21)

End point title	Change From Baseline in HRQOL Based on: Quality of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module (QLQ-BIL21)
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End point description:

For HRQOL based on QLQ-BIL21, subscales of eating symptoms and pain symptoms were assessed. Each item is a 4-point Likert scale. There are 4 response levels (not at all, a little, quite a bit, and very much). For symptom scales, lower scores=better QOL (negative change from Baseline=improvement). ITT population included all randomised subjects, with treatment group designated according to the randomisation. Number analysed is the number of subjects for a specific category with data available for analysis at the given timepoint.

End point type	Secondary
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End point timeframe:

Cycle 2 Day 1 and Cycle 3 Day 1

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	61		
Units: score on a scale				
arithmetic mean (standard deviation)				
Cycle 2 Day 1: Pain (n=65,20)	5.1 (\pm 1.94)	10.1 (\pm 3.49)		
Cycle 2 Day 1: Appetite Loss (n=65,20)	4.3 (\pm 1.84)	3.6 (\pm 3.19)		
Cycle 3 Day 1: Pain (n=48,9)	2.3 (\pm 2.16)	-2.1 (\pm 4.70)		
Cycle 3 Day 1: Appetite Loss (n=48,9)	-2.0 (\pm 2.02)	4.1 (\pm 4.24)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Cycle 2 Day 1: Pain	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	-5.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.93
upper limit	2.8

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Cycle 2 Day 1: Appetite Loss	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.56
upper limit	7.88

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Cycle 3 Day 1: Pain	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	4.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.82
upper limit	14.55

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Cycle 3 Day 1: Appetite Loss	
Comparison groups	AG-120 v Placebo
Number of subjects included in analysis	187
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Least-squares mean difference
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.34
upper limit	3.12

Secondary: Percentage of Subjects With Change Based on HRQOL: Patient Global Impression of Change (PGI-C)

End point title	Percentage of Subjects With Change Based on HRQOL: Patient Global Impression of Change (PGI-C)
End point description:	
<p>The anchor-based questionnaire PGI-C contains the following 3 items (the overall change in the physical functioning since the start of taking the study medication, the overall change in the appetite since the start of taking the study medication, and the overall change in the pain since the start of taking the study medication). The PGI-C is measured using a 7-point Likert scale, with 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse. 9999: The data is not reported as the analyses were limited by small sample sizes available at post-baseline timepoints for PGI-C.</p>	
End point type	Secondary
End point timeframe:	
Baseline up to Survival follow-up (up to approximately 4 years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	0 ^[8]		
Units: percentage of subjects				
number (not applicable)	9999			

Notes:

[8] - Number analysed was 0 at safety follow up.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Severity Based on HRQOL: Patient Global Impression of Severity (PGI-S)

End point title	Percentage of Subjects With Severity Based on HRQOL: Patient Global Impression of Severity (PGI-S)
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End point description:

The anchor-based questionnaire PGI-S contains the following 3 items (the severity of the physical functioning decline over the past week, the severity of the appetite decrease over the past week, and the severity of the pain over the past week). The PGI-S is measured using a 7-point Likert scale, with 1 = very much better, 2 = much better, 3 = a little better, 4 = no change, 5 = a little worse, 6 = much worse, and 7 = very much worse. 9999: The data is not reported as the analyses were limited by small sample sizes available at post-baseline timepoints for PGI-S.

End point type	Secondary
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End point timeframe:

Baseline up to Survival follow up (up to approximately 4 years)

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	0 ^[9]		
Units: percentage of subjects				
number (not applicable)	9999			

Notes:

[9] - Number analysed was 0 at safety follow up.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Each EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) Dimension Response

End point title	Percentage of Subjects with Each EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) Dimension Response
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End point description:

The EQ-5D-5L assesses general health-related quality of life. Health is defined in 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no

problems, slight problems, moderate problems, severe problems, and extreme problems. 9999=The data is not reported as the analyses were limited by small sample sizes available at post-baseline timepoints for EQ-5D-5L.

End point type	Secondary
End point timeframe:	
From first dose of study drug up to EOT (Up to approximately 4 Years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	27		
Units: percentage of subjects				
number (not applicable)	9999	9999		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EQ-5D-5L Visual Analogue Scale (EQ-5D-5L VAS) Score

End point title	Change From Baseline in EQ-5D-5L Visual Analogue Scale (EQ-5D-5L VAS) Score
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End point description:

The EQ-5D-5L VAS records the participant's self-rated health on a vertical visual analogue scale numbered from 100 (best health imagined) to 0 (worst health imagined). 9999= The data is not reported as the analyses were limited by small sample sizes available at post-baseline timepoints for EQ-5D-5L VAS.

End point type	Secondary
End point timeframe:	
From first dose of study drug up to EOT (Up to approximately 4 Years)	

End point values	AG-120	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	22		
Units: score on a scale				
arithmetic mean (standard deviation)	9999 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of AG-120

End point title	Maximum Observed Plasma Concentration (Cmax) of AG-120
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End point description:

Pharmacokinetic (PK) Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=142)	4424.0 (\pm 1808.07)			
Cycle 2 Day 1 (n=107)	5050.5 (\pm 1666.07)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Maximal Plasma Concentration (Tmax) of AG-120

End point title	Time to Reach Maximal Plasma Concentration (Tmax) of AG-120
-----------------	---

End point description:

PK Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: hours (h)				
median (full range (min-max))				

Cycle 1 Day 1 (n=142)	2.63 (0.50 to 4.87)			
Cycle 2 Day 1 (n=107)	2.07 (0.50 to 4.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to 24 Hours (AUC0-24)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to 24 Hours (AUC0-24)
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End point description:

PK Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C2D1 visit was combined with C2D1 visit for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	107			
Units: h*ng/mL				
arithmetic mean (standard deviation)	91219.4 (± 31574.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-time Curve From Time Zero to 4 Hours (AUC0-4)

End point title	Area Under the Plasma Concentration-time Curve From Time Zero to 4 Hours (AUC0-4)
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End point description:

PK Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analyzed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose of Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=141)	10972.2 (± 5044.18)			
Cycle 2 Day 1 (n=106)	16651.7 (± 5269.96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Based on AUC0-4 (Racc AUC0-4)

End point title	Accumulation Ratio Based on AUC0-4 (Racc AUC0-4)
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End point description:

PK Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C2D1 visit was combined with C2D1 visit for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	98			
Units: ratio				
arithmetic mean (standard deviation)	1.6881 (± 0.83303)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation Ratio Based on Cmax (Racc Cmax)

End point title	Accumulation Ratio Based on Cmax (Racc Cmax)
End point description: PK Analysis Population consisted of all subjects who were enrolled and received at least one dose of study medication (AG-120) with sufficient plasma sample data to assess PK parameters. Crossover C2D1 visit was combined with C2D1 visit for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.	
End point type	Secondary
End point timeframe: Post-dose of Cycle 2 on Days 1 (each cycle = 28 days)	

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	100			
Units: ratio				
arithmetic mean (standard deviation)	1.2369 (\pm 0.50798)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: B (Baseline Effect Value)

End point title	Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: B (Baseline Effect Value)
End point description: B is the Baseline Effect Value. Pharmacodynamic (PD) Analysis Population consisted of all subjects who were enrolled and received any dose of study medication (AG-120) with sufficient plasma sample data to assess pharmacodynamic parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.	
End point type	Secondary
End point timeframe: Post-dose Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)	

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	142			
Units: ng/mL				
arithmetic mean (standard deviation)				

Cycle 1 Day 1	1107.70 (± 1709.919)			
Cycle 2 Day 1	795.09 (± 938.677)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Experienced Laboratory Abnormalities Reported as Grade 3 or Higher Adverse Events

End point title	Percentage of Subjects Who Experienced Laboratory Abnormalities Reported as Grade 3 or Higher Adverse Events
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End point description:

The laboratory parameters evaluated by the investigator included hematology and chemistry. Laboratory abnormalities reported in this endpoint are Grade 3 or higher adverse events. Grading categories were determined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. SAS included all subjects who received at least one dose of study drug (AG-120 or Placebo).

End point type	Secondary
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End point timeframe:

From first dose of the study drug up to end of treatment visit for each intervention (Up to approximately 4 Years)

End point values	AG-120	After Crossover to AG-120	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	43	59	
Units: percentage of subjects				
number (not applicable)				
Anaemia	7.3	9.3	0.0	
Platelet Count Decreased	2.4	2.3	0.0	
Neutrophil Count Decreased	1.6	0.0	0.0	
White Blood Cell Count decreased	1.6	0.0	0.0	
Lymphocyte Count Decreased	0.8	0.0	3.4	
Thrombocytopenia	0.8	0.0	0.0	
Blood Loss Anaemia	0.8	0.0	0.0	
Blood Bilirubin Increased	5.7	7.0	1.7	
Hyponatraemia	5.7	2.3	10.2	
Aspartate Aminotransferase Increased	4.9	4.7	1.7	
Hypophosphataemia	3.3	4.7	5.1	
Hyperbilirubinaemia	3.3	0.0	0.0	
Hyperkalaemia	2.4	2.3	3.4	
Blood Alkaline Phosphatase Increased	2.4	0.0	5.1	
Alanine Aminotransferase Increased	1.6	2.3	0.0	
Hypoalbuminaemia	1.6	0.0	1.7	
Gamma-glutamyltransferase Increased	0.8	0.0	1.7	
Hypercalcaemia	0.8	0.0	1.7	
Hyperuricaemia	0.8	0.0	0.0	

Hypokalaemia	0.8	2.3	1.7	
Transaminases Increased	0.8	0.0	0.0	
Blood Uric Acid Increased	0.0	0.0	1.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Significant Grade 3 or higher Vital Signs AEs

End point title	Percentage of Subjects With Clinically Significant Grade 3 or higher Vital Signs AEs
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End point description:

Clinically significant vital signs were recorded as adverse events; there were some vital signs reported as Grade 3 or higher adverse events. Grading categories were determined by NCI CTCAE, version 4.03.

End point type	Secondary
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End point timeframe:

From first dose of the study drug up to end of treatment visit for each intervention (Up to approximately 4 Years)

End point values	AG-120	After Crossover to AG-120	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	123	43	59	
Units: percentage of subjects				
number (not applicable)				
Pyrexia	0.8	2.3	0.0	
Weight Decreased	0.8	0.0	1.7	
Hypertension	1.6	7.0	1.7	
Hypotension	1.6	2.3	1.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: AUEC0-4

End point title	Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: AUEC0-4
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End point description:

AUEC0-4 is the area of the response curve from time point zero (predose) up to 4 hr postdose. PD Analysis Population consisted of all subjects who were enrolled and received any dose of study medication (AG-120) with sufficient plasma sample data to assess pharmacodynamic parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: h*ng/mL				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=141)	3334.3 (± 4785.48)			
Cycle 2 Day 1 (n=107)	368.4 (± 278.78)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: %BAUEC0-4

End point title	Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: %BAUEC0-4
End point description:	
%BAUEC0-4 is the percent inhibition for AUEC0-4. PD Analysis Population consisted of all subjects who were enrolled and received any dose of study medication (AG-120) with sufficient plasma sample data to assess pharmacodynamic parameters. Crossover C1D1 and crossover C2D1 visits were combined with C1D1 and C2D1 visits, respectively for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.	
End point type	Secondary
End point timeframe:	
Post-dose Cycle 1 Day 1 and Cycle 2 Day 1 (each cycle = 28 days)	

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	141			
Units: percent				
arithmetic mean (standard deviation)				
Cycle 1 Day 1 (n=141)	20.22090 (± 10.13659)			
Cycle 2 Day 1 (n=107)	74.9750 (± 22.53852)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: Rtrough

End point title	Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: Rtrough
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End point description:

Rtrough is the observed response value at the end of a dosing interval. PD Analysis Population consisted of all subjects who were enrolled and received any dose of study medication (AG-120) with sufficient plasma sample data to assess pharmacodynamic parameters. Crossover C2D1 visit was combined with C2D1 visit for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: ng/mL				
arithmetic mean (standard deviation)	97.66 (± 72.838)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: %BRtrough

End point title	Plasma 2-hydroxyglutarate (2-HG) Levels of AG-120: %BRtrough
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End point description:

%BRtrough is the percent inhibition for Rtrough. PD Analysis Population consisted of all subjects who were enrolled and received any dose of study medication (AG-120) with sufficient plasma sample data to assess pharmacodynamic parameters. Crossover C2D1 visit was combined with C2D1 visit for the analysis of this endpoint. Number analysed is the number of subjects with data available for analyses at the specified time point.

End point type	Secondary
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End point timeframe:

Post-dose Cycle 2 Day 1 (each cycle = 28 days)

End point values	Randomisation phase AG-120 plus Cross over phase AG-120			
Subject group type	Subject analysis set			
Number of subjects analysed	108			
Units: percent				
arithmetic mean (standard deviation)	73.726 (\pm 23.3113)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 28 days after last dose for each intervention (Up to approximately 4 years)

Adverse event reporting additional description:

Safety Analysis Set included all subjects who received at least one dose of study treatment.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	AG-120
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Reporting group description:

Subjects received AG-120 500 mg, tablet, orally, once daily (QD) in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up, or the sponsor ended the study for up to approximately 24 months.

Reporting group title	After Cross Over to AG-120
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Reporting group description:

Subjects who experienced disease progression and received placebo were allowed to cross over to receive AG-120 500 mg, tablet, orally, QD in each 28-day treatment cycle for up to approximately 24 months.

Reporting group title	Placebo
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Reporting group description:

Subjects received AG-120 matched placebo, orally, QD in each 28-day treatment cycle, until occurrence of disease progression, unacceptable toxicity, confirmed pregnancy, death, subject withdrawal, lost to follow-up or the sponsor ended the study for up to approximately 24 months. Subjects who experienced disease progression and received placebo were allowed to cross over and receive AG-120.

Serious adverse events	AG-120	After Cross Over to AG-120	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	43 / 123 (34.96%)	12 / 43 (27.91%)	14 / 59 (23.73%)
number of deaths (all causes)	99	34	14
number of deaths resulting from adverse events	6	2	0
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 123 (1.63%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 123 (1.63%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			

Mental status changes			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	2 / 123 (1.63%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial injury			

subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	2 / 123 (1.63%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Tachyarrhythmia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic encephalopathy			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			

subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thecal sac compression			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Abdominal pain lower			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	3 / 123 (2.44%)	1 / 43 (2.33%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal pseudo-obstruction			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 123 (1.63%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	2 / 123 (1.63%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 123 (0.81%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal varices haemorrhage			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis acute			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	3 / 123 (2.44%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary obstruction			
subjects affected / exposed	1 / 123 (0.81%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			

subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Hyperbilirubinaemia			
subjects affected / exposed	3 / 123 (2.44%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice cholestatic			
subjects affected / exposed	3 / 123 (2.44%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy toxic			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacteraemia			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary tract infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary sepsis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	0 / 123 (0.00%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastroenteritis			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia bacteraemia			
subjects affected / exposed	2 / 123 (1.63%)	1 / 43 (2.33%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 123 (3.25%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	4 / 123 (3.25%)	0 / 43 (0.00%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic candida			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound infection			

subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	0 / 59 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 123 (0.81%)	1 / 43 (2.33%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 123 (0.00%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	2 / 59 (3.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 123 (0.81%)	0 / 43 (0.00%)	1 / 59 (1.69%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	AG-120	After Cross Over to AG-120	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	118 / 123 (95.93%)	36 / 43 (83.72%)	56 / 59 (94.92%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 123 (8.94%)	3 / 43 (6.98%)	1 / 59 (1.69%)
occurrences (all)	16	5	1
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 123 (10.57%)	3 / 43 (6.98%)	3 / 59 (5.08%)
occurrences (all)	23	6	3
Blood creatinine increased			
subjects affected / exposed	7 / 123 (5.69%)	1 / 43 (2.33%)	3 / 59 (5.08%)
occurrences (all)	8	1	6
Blood bilirubin increased			
subjects affected / exposed	12 / 123 (9.76%)	2 / 43 (4.65%)	4 / 59 (6.78%)
occurrences (all)	16	4	4
Blood alkaline phosphatase increased			
subjects affected / exposed	11 / 123 (8.94%)	4 / 43 (9.30%)	6 / 59 (10.17%)
occurrences (all)	14	5	8
Electrocardiogram QT prolonged			
subjects affected / exposed	11 / 123 (8.94%)	1 / 43 (2.33%)	2 / 59 (3.39%)
occurrences (all)	27	3	2
Platelet count decreased			
subjects affected / exposed	7 / 123 (5.69%)	2 / 43 (4.65%)	3 / 59 (5.08%)
occurrences (all)	14	5	4
White blood cell count decreased			
subjects affected / exposed	9 / 123 (7.32%)	2 / 43 (4.65%)	1 / 59 (1.69%)
occurrences (all)	26	3	1
Weight decreased			
subjects affected / exposed	10 / 123 (8.13%)	6 / 43 (13.95%)	3 / 59 (5.08%)
occurrences (all)	17	8	7
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 123 (8.94%)	4 / 43 (9.30%)	2 / 59 (3.39%)
occurrences (all)	16	9	2
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 8	4 / 43 (9.30%) 6	1 / 59 (1.69%) 1
Headache subjects affected / exposed occurrences (all)	16 / 123 (13.01%) 24	2 / 43 (4.65%) 2	4 / 59 (6.78%) 5
Neuropathy peripheral subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 11	0 / 43 (0.00%) 0	0 / 59 (0.00%) 0
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	23 / 123 (18.70%) 47	7 / 43 (16.28%) 8	3 / 59 (5.08%) 3
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	17 / 123 (13.82%) 25	5 / 43 (11.63%) 8	7 / 59 (11.86%) 10
Chills subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 8	1 / 43 (2.33%) 1	3 / 59 (5.08%) 3
Fatigue subjects affected / exposed occurrences (all)	38 / 123 (30.89%) 42	10 / 43 (23.26%) 17	10 / 59 (16.95%) 13
Gait disturbance subjects affected / exposed occurrences (all)	0 / 123 (0.00%) 0	0 / 43 (0.00%) 0	3 / 59 (5.08%) 3
Oedema peripheral subjects affected / exposed occurrences (all)	17 / 123 (13.82%) 25	9 / 43 (20.93%) 12	6 / 59 (10.17%) 7
Pyrexia subjects affected / exposed occurrences (all)	16 / 123 (13.01%) 23	2 / 43 (4.65%) 4	6 / 59 (10.17%) 6
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all)	10 / 123 (8.13%) 16	4 / 43 (9.30%) 4	2 / 59 (3.39%) 2

Abdominal pain			
subjects affected / exposed	30 / 123 (24.39%)	7 / 43 (16.28%)	9 / 59 (15.25%)
occurrences (all)	46	9	12
Abdominal discomfort			
subjects affected / exposed	4 / 123 (3.25%)	3 / 43 (6.98%)	0 / 59 (0.00%)
occurrences (all)	5	4	0
Abdominal distension			
subjects affected / exposed	13 / 123 (10.57%)	2 / 43 (4.65%)	5 / 59 (8.47%)
occurrences (all)	13	4	6
Dyspepsia			
subjects affected / exposed	7 / 123 (5.69%)	1 / 43 (2.33%)	3 / 59 (5.08%)
occurrences (all)	7	1	3
Dry mouth			
subjects affected / exposed	3 / 123 (2.44%)	1 / 43 (2.33%)	4 / 59 (6.78%)
occurrences (all)	4	1	4
Diarrhoea			
subjects affected / exposed	43 / 123 (34.96%)	12 / 43 (27.91%)	10 / 59 (16.95%)
occurrences (all)	67	22	18
Constipation			
subjects affected / exposed	20 / 123 (16.26%)	5 / 43 (11.63%)	11 / 59 (18.64%)
occurrences (all)	26	5	11
Gastrooesophageal reflux disease			
subjects affected / exposed	9 / 123 (7.32%)	1 / 43 (2.33%)	2 / 59 (3.39%)
occurrences (all)	11	1	2
Ascites			
subjects affected / exposed	25 / 123 (20.33%)	5 / 43 (11.63%)	7 / 59 (11.86%)
occurrences (all)	59	9	10
Nausea			
subjects affected / exposed	52 / 123 (42.28%)	12 / 43 (27.91%)	17 / 59 (28.81%)
occurrences (all)	76	18	26
Vomiting			
subjects affected / exposed	28 / 123 (22.76%)	5 / 43 (11.63%)	11 / 59 (18.64%)
occurrences (all)	38	6	14
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	31 / 123 (25.20%) 38	5 / 43 (11.63%) 5	5 / 59 (8.47%) 6
Dyspnoea subjects affected / exposed occurrences (all)	12 / 123 (9.76%) 14	4 / 43 (9.30%) 5	10 / 59 (16.95%) 15
Skin and subcutaneous tissue disorders			
Rash maculo-papular subjects affected / exposed occurrences (all)	4 / 123 (3.25%) 6	1 / 43 (2.33%) 1	3 / 59 (5.08%) 3
Rash subjects affected / exposed occurrences (all)	10 / 123 (8.13%) 13	2 / 43 (4.65%) 2	0 / 59 (0.00%) 0
Pruritus subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 8	3 / 43 (6.98%) 4	3 / 59 (5.08%) 4
Psychiatric disorders			
Confusional state subjects affected / exposed occurrences (all)	4 / 123 (3.25%) 5	2 / 43 (4.65%) 2	3 / 59 (5.08%) 5
Insomnia subjects affected / exposed occurrences (all)	12 / 123 (9.76%) 13	3 / 43 (6.98%) 4	3 / 59 (5.08%) 3
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	14 / 123 (11.38%) 17	5 / 43 (11.63%) 7	6 / 59 (10.17%) 7
Back pain subjects affected / exposed occurrences (all)	16 / 123 (13.01%) 23	2 / 43 (4.65%) 2	7 / 59 (11.86%) 10
Muscular weakness subjects affected / exposed occurrences (all)	1 / 123 (0.81%) 1	4 / 43 (9.30%) 4	2 / 59 (3.39%) 2
Muscle spasms subjects affected / exposed occurrences (all)	6 / 123 (4.88%) 8	4 / 43 (9.30%) 6	1 / 59 (1.69%) 1

Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 123 (3.25%) 10	3 / 43 (6.98%) 3	0 / 59 (0.00%) 0
Urinary tract infection subjects affected / exposed occurrences (all)	7 / 123 (5.69%) 10	1 / 43 (2.33%) 1	1 / 59 (1.69%) 1
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all)	9 / 123 (7.32%) 10	2 / 43 (4.65%) 4	1 / 59 (1.69%) 2
Hypercalcaemia subjects affected / exposed occurrences (all)	2 / 123 (1.63%) 2	1 / 43 (2.33%) 1	7 / 59 (11.86%) 7
Decreased appetite subjects affected / exposed occurrences (all)	30 / 123 (24.39%) 41	6 / 43 (13.95%) 7	11 / 59 (18.64%) 13
Hyponatraemia subjects affected / exposed occurrences (all)	14 / 123 (11.38%) 25	1 / 43 (2.33%) 1	6 / 59 (10.17%) 9
Hypomagnesaemia subjects affected / exposed occurrences (all)	9 / 123 (7.32%) 9	1 / 43 (2.33%) 2	3 / 59 (5.08%) 3
Hypokalaemia subjects affected / exposed occurrences (all)	10 / 123 (8.13%) 15	2 / 43 (4.65%) 2	4 / 59 (6.78%) 4
Hypoalbuminaemia subjects affected / exposed occurrences (all)	8 / 123 (6.50%) 14	3 / 43 (6.98%) 5	4 / 59 (6.78%) 4
Hypophosphataemia subjects affected / exposed occurrences (all)	6 / 123 (4.88%) 7	3 / 43 (6.98%) 5	3 / 59 (5.08%) 6
Hyperkalaemia subjects affected / exposed occurrences (all)	6 / 123 (4.88%) 9	2 / 43 (4.65%) 2	3 / 59 (5.08%) 3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 August 2016	<p>The major changes included in Amendment 1 version 2.0:</p> <ul style="list-style-type: none">• The primary endpoint of PFS will be based on Independent Radiology center assessment instead of Investigator assessment.• The secondary endpoint of PFS was adjusted to be assessed by the Investigator versus the IRC, and the secondary response endpoints will be assessed by the Investigator and IRC.• The adjustment of statistical assumptions results in an increase in the number of subjects to be enrolled, and an increase in the statistical power to detect a significant difference. The number of study centers is slightly increased to account for the increase in the sample size.• The exact IDH mutation variants to be tested for eligibility were listed to account for assay specifications.• The screening window for baseline scans was shortened from within 28 days to within 21 days prior to C1D1.• After 54 weeks (approximately 1 year), scans will be performed every 8 weeks instead of every 9 weeks, which will be the schedule for PFS and QOL assessments in follow-up as well. <p>In addition to the above, minor formatting changes and clarifications were made that are not reflected in this document.</p>
05 October 2016	<p>The major changes included in Amendment 2 version 3.0:</p> <ul style="list-style-type: none">• Per FDA feedback, dose re-escalation will not be permitted in the event of life threatening Grade 4 AG-120 related toxicities.• Added clarification around qualifications for subjects who continue study treatment beyond disease progression, also per FDA feedback.• Other clarifications and corrections as outlined below were implemented for consistency. <p>In addition to the above, minor formatting changes and clarifications were made that are not reflected in this document.</p>
01 September 2017	<p>The substantial changes in Amendment 3 version 4.0 included :</p> <ul style="list-style-type: none">• Added the Patient Global Impression of Change (PGI-C) and the Patient Global Impression of Severity (PGI-S) as additional health related quality of life (HRQOL) measures throughout the protocol, per FDA's request to ask some anchor based questions in addition to the European Organisation for Research and Treatment of Cancer - Quality Of Life Questionnaire – Core Questionnaire (EORTC QLQ C30) and the European Organisation for Research and Treatment of Cancer - Quality Of Life Questionnaire - Cholangiocarcinoma and Gallbladder Cancer Module (EORTC QLQ BIL21).• Added the following caveat to exclusion criterion 17 per the Agios Clinical Science Department: "Subjects with chronic HBV that is adequately suppressed per institutional practice will be permitted."• Added exclusion criterion 20 per Germany's request: "The exclusion of persons who have been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities is missing, cf. § 40 par. 1 cl. 3 no. 4 of the AMG."• Added exclusion criterion 21 per Germany's request: "The exclusion of persons dependent on the sponsor, investigator, or study site is missing, cf. § 40 par. 1 cl. 3 no. 3 b) and c) of the AMG in conjunction with section 1.61 of the ICH/GCP guideline topic E6."• Updated text about taking the tablets with food per Agios's updated, approved food language.

04 April 2018	<p>The substantial changes included in Amendment 4 version 5.0:</p> <ul style="list-style-type: none"> • Palliative radiotherapy to treat symptomatic non target lesions that cannot otherwise be medically managed will be permitted after disease progression has been verified and unblinding has occurred, and in the setting of continuation of AG-120 beyond disease progression, with Medical Monitor approval. • Information on drug-drug interactions has been revised, consistent with the AG-120 Investigator's Brochure, Version 7.0. • As updated in the AG-120 Investigator's Brochure, Version 7.0, AG-120 does not inhibit P-gp at clinically relevant concentrations. Therefore, exclusion criterion 10, excluding subjects who are taking P-gp transporter-sensitive substrate medications with a narrow therapeutic window, unless they can be transferred to other medications within ≥ 5 half-lives prior to administration of study treatment, has been removed. • Hematology, serum chemistry, circulating tumor DNA, and exploratory biomarker assessments are required at both the end of treatment (EOT) visit and at the cross over Cycle 1 Day 1 (C1D1) visit. If the cross over C1D1 visit occurs within 3 days of the EOT visit, these laboratory assessments need not be repeated. • The list of medications known to prolong the QT interval was expanded and updated.
01 March 2019	<p>The substantial changes included in Amendment 5 version 6.0:</p> <ul style="list-style-type: none"> • Added language to outline the management of subjects following study unblinding. • Added an exclusion criterion to exclude subjects with a known medical history of PML. • Added new Section 11.3 (Other Potential Risks) describing leukoencephalopathy and sensorimotor neuropathy/polyneuropathy as other potential risks associated with AG 120.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported