Clinical trial results:
A Phase 1/2, Open-Label, Multi-Arm Trial to Investigate the Safety, Tolerability, Pharmacokinetics, Biological, and Clinical Activity of AGEN1884 in Combination with AGEN2034 in Subjects with Metastatic or Locally Advanced Solid Tumors, and Expansion into Select Solid Tumors

Summary

EudraCT number	2018-000120-33
Trial protocol	HU PL ES
Global end of trial date	15 July 2022

Results information

Result version number	v1
This version publication date	29 July 2023
First version publication date	29 July 2023

Trial information

Trial identification

Sponsor protocol code	C-550-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03495882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Agenus, Inc.
Sponsor organisation address	3 Forbes Road, Lexington, MA, United States, 02421
Public contact	Agenus, Inc. Clinical Trial Information, Agenus, Inc., 1 781-674-4265, clinicaltrialinfo@agenusbio.com
Scientific contact	Agenus, Inc. Clinical Trial Information, Agenus, Inc., 1 781-674-4265, clinicaltrialinfo@agenusbio.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	15 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of Phase 1 of this study was to assess safety and tolerability of zalifrelimab (AGEN1884) in combination with balstilimab (AGEN2034) in participants with locally advanced, recurrent and/or metastatic solid tumors. The main objective of Phase 2 was to assess ORR (objective response rate) according to Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as determined by the Independent Endpoint Review Committee (IERC).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2018
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	Poland: 7
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	United States: 19
Country: Number of subjects enrolled	Ukraine: 48
Country: Number of subjects enrolled	Australia: 40
Country: Number of subjects enrolled	Georgia: 11
Country: Number of subjects enrolled	Moldova, Republic of: 9
Country: Number of subjects enrolled	Brazil: 5
Worldwide total number of subjects	175
EEA total number of subjects	43

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)	155
From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Comprehensive Phase 1 study data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

Pre-assignment

Screening details:

The trial was conducted at 46 trial centres.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1 – Dose 1: Zalifrelimab + Balstilimab

Arm description:

Participants received zalifrelimab in combination with balstilimab.

Arm type	Experimental
Investigational medicinal product name	Zalifrelimab
Investigational medicinal product code	
Other name	AGEN1884
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zalifrelimab was administered over 30 minutes and following the infusion of balstilimab.

Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusion was administered over 30 minutes.

Arm title	Phase 1 – Dose 2: Zalifrelimab + Balstilimab

Arm description:

Participants received zalifrelimab in combination with balstilimab.

Arm type	Experimental
Investigational medicinal product name	Zalifrelimab
Investigational medicinal product code	
Other name	AGEN1884
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zalifrelimab was administered over 30 minutes and following the infusion of balstilimab.

Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion

Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusion was administered over 30 minutes.

Arm title	Phase 2: Zalifrelimab + Balstilimab

Arm description:

Participants received zalifrelimab in combination with balstilimab.

Arm type	Experimental
Investigational medicinal product name	Zalifrelimab
Investigational medicinal product code	
Other name	AGEN1884
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Zalifrelimab was administered over 30 minutes and following the infusion of balstilimab.

Investigational medicinal product name	Balstilimab
Investigational medicinal product code	
Other name	AGEN2034, Anti-PD-1
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Balstilimab infusion was administered over 30 minutes.

Number of subjects in period 1	Phase 1 – Dose 1: Zalifrelimab + Balstilimab	Phase 1 – Dose 2: Zalifrelimab + Balstilimab	Phase 2: Zalifrelimab + Balstilimab
Started	10	10	155
Received at Least 1 Dose of Study Drug	10	10	155
Completed	2	0	36
Not completed	8	10	119
Consent withdrawn by subject	-	-	15
Adverse event, non-fatal	2	-	2
Death	-	-	88
Progressive Disease	6	10	2
Study Terminated by Sponsor	-	-	5
Lost to follow-up	-	-	7

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study
Reporting group description:	
Safety Analysis Set: all participants who received ≥1 dose of any study treatment.	

Reporting group values	Overall Study	Total	
Number of subjects	175	175	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	155	155	
From 65-84 years	20	20	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	170	170	
Male	5	5	
Race Units: Subjects			
American Indian or Alaska Native	1	1	
Asian (Chinese)	1	1	
Black or African American	1	1	
White	168	168	
South African	1	1	
Indigenous And Torres Strait Islander	1	1	
Australian Aboriginal	1	1	
Unknown	1	1	
Ethnicity Units: Subjects			
Hispanic or Latino	9	9	
Not Hispanic or Latino	163	163	
Unknown	3	3	

End points

End points reporting groups

Reporting group title	Phase 1 – Dose 1: Zalifrelimab + Balstilimab
Reporting group description: Participants received zalifrelimab in combination with balstilimab.	
Reporting group title	Phase 1 – Dose 2: Zalifrelimab + Balstilimab
Reporting group description: Participants received zalifrelimab in combination with balstilimab.	
Reporting group title	Phase 2: Zalifrelimab + Balstilimab
Reporting group description: Participants received zalifrelimab in combination with balstilimab.	
Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description: All participants who received ≥1 dose of any study treatment.	
Subject analysis set title	Intent-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description: All participants who received ≥1 dose of any study treatment, with measurable disease at baseline (per IERC).	
Subject analysis set title	Pharmacokinetic Set
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants who received ≥1 dose of any study drug and who had sufficient evaluable drug concentrations measurements prior to and after treatment.	

Primary: Objective Response Rate (ORR): IERC

End point title	Objective Response Rate (ORR): IERC[1][2]
End point description: The ORR was defined as the proportion of participants with a confirmed best overall response (BOR) of partial response (PR) or complete response (CR), as determined by an IERC per RECIST 1.1.	
End point type	Primary
End point timeframe: Up to 2 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: Only the geometric mean and the geometric coefficient of variation are reported for this primary end point.
[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[3]			
Units: Percentage of participants				
number (confidence interval 95%)	26.2 (19.7 to 33.9)			

Notes:

[3] - Intent-to-treat

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Drug Concentration Observed Postdose at Steady-state (Cmax-ss)

End point title	Maximum Drug Concentration Observed Postdose at Steady-state (Cmax-ss)[4]

End point description:

Blood samples were collected for serum balstilimab and zalifrelimab concentration determinations. Results are reported as micrograms/millilitre (ug/mL).

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Comprehensive Phase 1 study data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[5]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Zalifrelimab	16.45 (± 120.2)			
Balstilimab	62.40 (± 26.7)			

Notes:

[5] - Zalifrelimab PK Analysis Set: N=42;
Balstilimab PK Analysis Set: N=7

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Drug Concentration-time Curve From Day 0 to Day 14 at Steady-state (AUC0-14d-ss)

End point title	Area Under the Drug Concentration-time Curve From Day 0 to Day 14 at Steady-state (AUC0-14d-ss)[6]

End point description:

Blood samples were collected for serum balstilimab and zalifrelimab concentration determinations. Results are reported as day times ug/mL (day*ug/mL).

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comprehensive Phase 1 study data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[7]			
Units: day*ug/mL				
geometric mean (geometric coefficient of variation)				
Zalifrelimab	131.1 (± 119.5)			
Balstilimab	250.9 (± 119.5)			

Notes:

[7] - Zalifrelimab PK Analysis Set: N=41;
Balstilimab PK Analysis Set: N=6

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Serum Anti-drug Antibodies (ADAs) for Balstilimab and Zalifrelimab

End point title	Number of Participants with Serum Anti-drug Antibodies (ADAs) for Balstilimab and Zalifrelimab[8]

End point description:

Blood samples were collected for serum balstilimab and zalifrelimab ADA determination.

End point type	Secondary

End point timeframe:

Pre-dose through 3 months after last dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Comprehensive Phase 1 study data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	155[9]			
Units: Participant				
Zalifrelimab	3			
Balstilimab	6			

Notes:

[9] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: ORR: Investigator

End point title	ORR: Investigator[10]

End point description:

The ORR was defined as the proportion of participants with a confirmed BOR of PR or CR, as determined by the investigator per RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[11]			
Units: Percentage of participants				
number (confidence interval 95%)	23.4 (17.3 to 31.0)			

Notes:

[11] - Intent-to-treat

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)[12]

End point description:

DOR was defined as time from first observation of response to first observation of documented disease progression (or death within 12 weeks after last tumor assessment), as determined by an IERC and investigator, per RECIST 1.1. Participants without an event at the analysis cutoff date were censored on date of last tumor assessment.

End point type	Secondary

End point timeframe:

Up to 3 years

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[13]			
Units: month				
number (confidence interval 95%)				
IERC	9.7 (5.6 to 9999)			

Investigator	8.5 (6.9 to 18.1)			

Notes:

[13] - IERC Intent-to-treat: N=38; 9999=Not available;
Investigator Intent-to-treat: N=34

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)[14]

End point description:

DCR was defined as proportion of participants with CR, PR, or stable disease (SD) without progressive disease (PD) within 81 days of study start, or durable SD following PD, as determined by the investigator per RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to 3 years

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[15]			
Units: Percentage of participants				
number (confidence interval 95%)	58.6 (50.5 to 66.3)			

Notes:

[15] - Intent-to-treat

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Response (TTR)

End point title	Time to Response (TTR)[16]

End point description:

TTR was defined as the time interval between the date of treatment initiation and the earliest date of first documented confirmed complete response or partial response based on independent radiologic review, as determined by an IERC and investigator, per RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[17]			
Units: day				
median (confidence interval 95%)	79.5 (66.5 to 123.5)			

Notes:

[17] - Intent-to-treat: N=38

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free Survival (PFS)

End point title	Progression-free Survival (PFS)[18]

End point description:

PFS was defined as the interval from the date of first dose of investigational agent until the earliest date of PD, as determined by IERC and investigator assessment of objective radiographic disease assessments per RECIST 1.1, or death due to any cause if occurring sooner than progression.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[19]			
Units: month				
median (confidence interval 95%)				
IERC	2.7 (1.5 to 3.7)			
Investigator	3.0 (2.7 to 5.4)			

Notes:

[19] - IERC Intent-to-treat: N=110;
Investigator Intent-to-treat: N=118

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)[20]

End point description:

OS was defined as the interval from the date of first dose of investigational agent until the date of death.

End point type	Secondary

End point timeframe:

Up to 2 years

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This end point applies only to Phase 2 of the study.

End point values	Phase 2: Zalifrelimab + Balstilimab			
Subject group type	Reporting group			
Number of subjects analysed	145[21]			
Units: month				
median (confidence interval 95%)	13.0 (9.7 to 18.5)			

Notes:

[21] - Intent-to-treat

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

36 months

Adverse event reporting additional description:

Comprehensive Phase 1 safety data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	Phase 2: Zalifrelimab + Balstilimab

Reporting group description:

Participants received zalifrelimab in combination with balstilimab.

Serious adverse events	Phase 2: Zalifrelimab + Balstilimab		
Total subjects affected by serious adverse events			
subjects affected / exposed	68 / 155 (43.87%)		
number of deaths (all causes)	88		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour haemorrhage			
subjects affected / exposed	2 / 155 (1.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Metastases to bone			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to the respiratory system			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tumour associated fever			

subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tumour pain				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Shock haemorrhagic				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Superior vena cava syndrome				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Nephrostomy				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	2 / 155 (1.29%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Disease progression				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			

Fatigue			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sudden death			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Reproductive system and breast disorders			
Cervix haemorrhage uterine			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Female genital tract fistula			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal discharge			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vaginal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	3 / 155 (1.94%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	1 / 1		
Acute respiratory failure			

subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bronchial obstruction			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory arrest			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Product issues			
Device occlusion			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cardiac disorders			
Immune-mediated myocarditis			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pericardial effusion			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Thrombotic cerebral infarction			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Brain oedema			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Headache			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemiparesis			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Neurological decompensation			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	6 / 155 (3.87%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			
Febrile neutropenia				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Diarrhoea				
subjects affected / exposed	3 / 155 (1.94%)			
occurrences causally related to treatment / all	2 / 3			
deaths causally related to treatment / all	0 / 0			
Immune-mediated enterocolitis				
subjects affected / exposed	3 / 155 (1.94%)			
occurrences causally related to treatment / all	3 / 3			
deaths causally related to treatment / all	0 / 0			
Anal fistula				
subjects affected / exposed	2 / 155 (1.29%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Abdominal distension				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Colonic fistula				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dysphagia				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				

subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestinal haemorrhage			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated hepatitis			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 155 (1.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ureteric obstruction			
subjects affected / exposed	2 / 155 (1.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Postrenal failure			

subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune-mediated nephritis				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Renal failure				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Endocrine disorders				
Adrenal insufficiency				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia of malignancy				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypophysitis				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Hypopituitarism				

subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Immune-mediated hypothyroidism			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 155 (1.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 155 (2.58%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	4 / 155 (2.58%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 155 (1.94%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	2 / 155 (1.29%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Device related infection				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterocolitis infectious				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Escherichia urinary tract infection				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Kidney infection				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lower respiratory tract infection viral				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pelvic infection				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory tract infection viral				
subjects affected / exposed	1 / 155 (0.65%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urosepsis				

subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 155 (0.65%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		

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

Non-serious adverse events	Phase 2: Zalifrelimab + Balstilimab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	145 / 155 (93.55%)		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	29 / 155 (18.71%)		
occurrences (all)	42		
Pyrexia			
subjects affected / exposed	25 / 155 (16.13%)		
occurrences (all)	36		
Asthenia			
subjects affected / exposed	18 / 155 (11.61%)		
occurrences (all)	23		
Oedema peripheral			
subjects affected / exposed	10 / 155 (6.45%)		
occurrences (all)	11		
Reproductive system and breast disorders			
Vaginal haemorrhage			

subjects affected / exposed	8 / 155 (5.16%)		
occurrences (all)	10		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	15 / 155 (9.68%)		
occurrences (all)	20		
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	19 / 155 (12.26%)		
occurrences (all)	31		
Blood creatinine increased			
subjects affected / exposed	18 / 155 (11.61%)		
occurrences (all)	43		
Alanine aminotransferase increased			
subjects affected / exposed	16 / 155 (10.32%)		
occurrences (all)	35		
Blood alkaline phosphatase increased			
subjects affected / exposed	8 / 155 (5.16%)		
occurrences (all)	16		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	8 / 155 (5.16%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 155 (9.03%)		
occurrences (all)	19		
Dizziness			
subjects affected / exposed	11 / 155 (7.10%)		
occurrences (all)	12		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	43 / 155 (27.74%)		
occurrences (all)	122		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	38 / 155 (24.52%) 66		
Nausea subjects affected / exposed occurrences (all)	32 / 155 (20.65%) 45		
Vomiting subjects affected / exposed occurrences (all)	30 / 155 (19.35%) 36		
Constipation subjects affected / exposed occurrences (all)	18 / 155 (11.61%) 24		
Abdominal pain subjects affected / exposed occurrences (all)	18 / 155 (11.61%) 19		
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	12 / 155 (7.74%) 15		
Rash subjects affected / exposed occurrences (all)	11 / 155 (7.10%) 14		
Rash maculo-papular subjects affected / exposed occurrences (all)	10 / 155 (6.45%) 10		
Endocrine disorders Hypothyroidism subjects affected / exposed occurrences (all)	23 / 155 (14.84%) 28		
Hyperthyroidism subjects affected / exposed occurrences (all)	17 / 155 (10.97%) 19		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	16 / 155 (10.32%) 24		

Arthralgia subjects affected / exposed occurrences (all)	11 / 155 (7.10%) 17		
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all)	 26 / 155 (16.77%) 39 9 / 155 (5.81%) 11		
Metabolism and nutrition disorders Hypomagnesaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all) Hyponatraemia subjects affected / exposed occurrences (all)	 14 / 155 (9.03%) 22 11 / 155 (7.10%) 13 8 / 155 (5.16%) 12		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 November 2017	- Added the following language in the 5.4 Dosage and Administration "Relevant clinical laboratory results essential for subject management decisions (hematology, biochemistry, liver function tests) must be available and reviewed before administration of AGEN1884 and/or AGEN2034."
09 March 2018	- Addition of best overall response, duration of response, and progression-free survival per immune-RECIST as secondary end points, including the requirement for a repeat scan to be performed 4-8 weeks after initial diagnosis of progressive disease - Screening period shortened from 42 days to 28 days
22 August 2018	- A 2-week washout was permitted for palliative radiation to non-central nervous system disease with sponsor approval - Infusion times and waiting period were shortened in dosage and administration of zalifrelimab and balstilimab
15 April 2019	- Reorganized and refined the trial objectives and endpoints for Phase 1 versus Phase 2 - Added information from Phase 1 part of the trial that was not available at the time of the previous amendment to support Phase 2 part - Increased sample size to 100 participants in Phase 2 - Changed tumor assessments to continue at 6-week intervals rather than 9-week intervals after Week 18 in order to collect more comprehensive data and consistent tumor response data - Modified the schedule of assessments to align with Study C-700-01 and to increase and enhance data collected to support registration - Updated the planned trial duration from 60 months to 73 months - Updated that administration of balstilimab and zalifrelimab was over 30 minutes - Updated duration of the Follow-up Phase and overall trial duration - Added that response assessment was to be done according to RECIST 1.1 in both phases - The primary end point changed from BOR to ORR to align with change in objectives
29 September 2019	- The Phase 2 sample size was increased from approximately 100 to 150 participants to allow for a more robust analysis of safety and PK data - Eligible patients required to have measurable disease per RECIST 1.1 confirmed by an independent central review prior to trial entry; the prior version of the protocol did not specify central review of measurable disease - Statistical assumptions were updated to accommodate the change in sample size - The planned interim analyses were updated, with a second interim analysis added for 3 months after 100 participants have been treated - New information (per RECIST 1.1) on what constitutes clinical disease progression in the absence of radiologic progression was added

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.

Comprehensive Phase 1 study data are currently unavailable. The posting will be updated accordingly as soon as the data become available.

Notes: