Clinical trial results:
A Phase 2 Study of TAK-659 in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL) After at Least 2 Prior Lines of Chemotherapy

Summary

EudraCT number	2016-003716-12
Trial protocol	GB ES DE IT
Global end of trial date	17 December 2019

Results information

Result version number	v1 (current)
This version publication date	22 August 2020
First version publication date	22 August 2020

Trial information

Trial identification

Sponsor protocol code	C34004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03123393
WHO universal trial number (UTN)	U1111-1187-6208
Other trial identifiers	NRES: 17/YH/0181

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge,MA, United States,
Public contact	Medical Director, Takeda, +1 866835-2233, GlobalOncologyMedinfo@takeda.com
Scientific contact	Medical Director, Takeda, +1 8778253327, trialdisclosures@takeda.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 December 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 December 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to assess the efficacy of TAK-659 measured by the independent radiologic review committee (IRC)-assessed overall response rate (ORR) in participants with relapsed or refractory DLBCL.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 8
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	49
EEA total number of subjects	34

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)	23
From 65 to 84 years	26
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 26 investigative sites in France, Great Britain, Italy, Spain, Canada, United States from 10 October 2017 to 17 December 2019. The study was terminated by the sponsor before the initiation of the stage 2 efficacy evaluation.

Pre-assignment

Screening details:

Participants with a diagnosis of relapsed or refractory diffuse large B-cell lymphoma who had at least 2 prior lines of chemotherapy were enrolled in Cohorts A and B. Cohort A received a single dose and Cohort B received ramp-up doses of TAK-659 in Stage 1 of the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort A: TAK-659 100 mg

Arm description:

TAK-659 100 mg tablet, orally, once daily (QD), during each 28-days cycle (median exposure was 41 days).

Arm type	Experimental
Investigational medicinal product name	TAK-659
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-659 tablets

Arm title	Cohort B: TAK-659 Ramp-up Dosing

Arm description:

TAK-659 60-100 mg tablet, orally, QD, dose based on safety and tolerability during each 28-days cycle (median exposure was 28 days).

Arm type	Experimental
Investigational medicinal product name	TAK-659
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

TAK-659 tablets

Number of subjects in period 1	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing
Started	24	25
Completed	3	2
Not completed	21	23
Consent withdrawn by subject	2	1
Study Terminated by Sponsor	6	9
Reason not Specified	13	13

Baseline characteristics

Reporting groups	
Reporting group title	Cohort A: TAK-659 100 mg
Reporting group description:	
TAK-659 100 mg tablet, orally, once daily (QD), during each 28-days cycle (median exposure was 41 days).	
Reporting group title	Cohort B: TAK-659 Ramp-up Dosing
Reporting group description:	
TAK-659 60-100 mg tablet, orally, QD, dose based on safety and tolerability during each 28-days cycle (median exposure was 28 days).	

Reporting group values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing	Total
Number of subjects	24	25	49
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	13	10	23
From 65-84 years	11	15	26
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	64.2	64.6	
standard deviation	± 9.01	± 11.37	-
Sex: Female, Male Units: participants			
Female	6	14	20
Male	18	11	29
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	21	19	40
More than one race	0	0	0
Unknown or Not Reported	2	6	8
Race/Ethnicity, Customized Units: Subjects			
Hispanic or Latino	1	4	5
Non-Hispanic and Latino	21	13	34
Not Reported	2	7	9

Unknown	0	1	1
Region of Enrollment Units: Subjects			
France	3	11	14
United Kingdom	3	3	6
Italy	4	4	8
Spain	3	3	6
Canada	1	0	1
United States	10	4	14
Height Units: cm			
arithmetic mean	172.8	167.5	
standard deviation	± 9.55	± 9.52	-
Weight Units: kg			
arithmetic mean	92.88	72.81	
standard deviation	± 21.132	± 18.388	-

End points

End points reporting groups

Reporting group title	Cohort A: TAK-659 100 mg
Reporting group description: TAK-659 100 mg tablet, orally, once daily (QD), during each 28-days cycle (median exposure was 41 days).	
Reporting group title	Cohort B: TAK-659 Ramp-up Dosing
Reporting group description: TAK-659 60-100 mg tablet, orally, QD, dose based on safety and tolerability during each 28-days cycle (median exposure was 28 days).	

Primary: Stage 2: ORR as Assessed by Independent Radiologic Review Committee (IRRC) Based on Modified 2007 International Working Group (IWG) Criteria

End point title	Stage 2: ORR as Assessed by Independent Radiologic Review Committee (IRRC) Based on Modified 2007 International Working Group (IWG) Criteria[1]
End point description: ORR was defined as the percentage of participants with complete response (CR), or partial response (PR) as assessed by IRRC according to the modified 2007 IWG criteria for malignant lymphoma. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.	
End point type	Primary
End point timeframe: Up to 12 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Not Applicable.

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: percentage of participants				

Notes:

[2] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[3] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: CR Rate as Assessed by IRC Based on Modified 2007 IWG Criteria

End point title	Stage 2: CR Rate as Assessed by IRC Based on Modified 2007 IWG Criteria
End point description: CR rate was defined as percentage of participants with complete response as assessed by IRC according to the modified 2007 IWG. CR was defined as disappearance of all evidence of disease.	
End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[4]	0[5]		
Units: percentage of participants				

Notes:

[4] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[5] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: ORR as Assessed by IRRC Based on 2014 IWG-Lugano Criteria

End point title	Stage 2: ORR as Assessed by IRRC Based on 2014 IWG-Lugano Criteria

End point description:

ORR was defined as the percentage of participants with CR or PR as assessed by IRRC according to the 2014 Lugano classification, IWG criteria for malignant lymphoma. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[6]	0[7]		
Units: percentage of participants				

Notes:

[6] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[7] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: CR Rate as Assessed by IRRC Based on 2014 IWG-Lugano Criteria

End point title	Stage 2: CR Rate as Assessed by IRRC Based on 2014 IWG-Lugano Criteria

End point description:

CR rate was defined as percentage of participants with complete response as assessed by IRC according to the 2014 Lugano classification, IWG criteria. CR was defined as disappearance of all evidence of disease.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[8]	0[9]		
Units: percentage of participants				

Notes:

[8] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[9] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Duration of Response (DOR)

End point title	Stage 2: Duration of Response (DOR)

End point description:

DOR was defined as the time from the date of first documentation of a CR/PR to the date of first documentation of tumor progression or progressive disease (PD) per IRRC assessment according to IWG criteria. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites. PD was defined as presence of any new lesion or increase by >=50% of previously involved sites from nadir.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[10] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[11] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Duration of CR

End point title	Stage 2: Duration of CR

End point description:

Duration of CR was defined as the time from the date of first documentation of a CR/PR to the date of

first documentation of tumor progression or PD per IRRC assessment according to IWG criteria. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites. PD was defined as presence of any new lesion or increase by >=50% of previously involved sites from nadir.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[12]	0[13]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[12] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[13] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: ORR as Assessed by IRRC in Participants with Germinal Center B-cell (GCB) DLBCL

End point title	Stage 2: ORR as Assessed by IRRC in Participants with Germinal Center B-cell (GCB) DLBCL

End point description:

ORR was defined as the percentage of participants with CR or PR as assessed by IRRC according to the modified 2007 IWG criteria for malignant lymphoma. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[14]	0[15]		
Units: percentage of participants				

Notes:

[14] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[15] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: ORR as Assessed by IRC in Participants with DLBCL Transformed from Indolent Non-Hodgkin's Lymphoma (NHL)

End point title	Stage 2: ORR as Assessed by IRC in Participants with DLBCL Transformed from Indolent Non-Hodgkin's Lymphoma (NHL)

End point description:

ORR was defined as the percentage of participants with CR or PR as assessed by IRC according to the modified 2007 IWG criteria for malignant lymphoma. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[16]	0[17]		
Units: percentage of participants				

Notes:

[16] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[17] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Progression Free Survival (PFS) as Assessed by IRC

End point title	Stage 2: Progression Free Survival (PFS) as Assessed by IRC

End point description:

PFS was defined as time from start of study treatment to first documentation of PD per IRC assessment or up to death due to any cause, whichever occurs first based on IWG criteria. PD was defined as presence of any new lesion or increase by >=50% of previously involved sites from nadir.

End point type	Secondary

End point timeframe:

Up to 18 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[18]	0[19]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[18] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[19] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: Overall Survival (OS)

End point title	Stage 2: Overall Survival (OS)

End point description:

OS was defined as the time from start of study treatment to date of death due to any cause.

End point type	Secondary

End point timeframe:

Up to 24 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[20]	0[21]		
Units: months				
median (full range (min-max))	(to)	(to)		

Notes:

[20] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[21] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 1: ORR as Assessed by IRRC to Select Stage 2 Dose Regimen of TAK-659 from the Lead-in Dose Exploration Phase

End point title	Stage 1: ORR as Assessed by IRRC to Select Stage 2 Dose Regimen of TAK-659 from the Lead-in Dose Exploration Phase

End point description:

ORR was defined as the percentage of participants with CR or PR as assessed by IRC. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.

End point type	Secondary

End point timeframe:

Up to 12 months

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[22]	0[23]		
Units: percentage of participants				

Notes:

[22] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[23] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Stage 2: ORR as Assessed by IRC at 3, 6, and 9 cycles in Participants with DLBCL

End point title	Stage 2: ORR as Assessed by IRC at 3, 6, and 9 cycles in Participants with DLBCL

End point description:

ORR was defined as the percentage of participants with CR or PR as assessed by IRC according to the modified 2007 IWG criteria for malignant lymphoma. CR was defined as disappearance of all evidence of disease. PR was defined as regression of measurable disease and no new sites.

End point type	Secondary

End point timeframe:

At Cycles 3, 6 and 9 (Up to 12 months) (Each cycle of 28 days)

End point values	Cohort A: TAK-659 100 mg	Cohort B: TAK-659 Ramp-up Dosing		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[24]	0[25]		
Units: percentage of participants				

Notes:

[24] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

[25] - Study was terminated before the initiation of Stage 2, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the signing of the informed consent form (ICF) through 28 days after administration of the last dose of study drug or until the start of subsequent anticancer therapy, whichever occurs first (Up to approximately 14 months).

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Cohort B: TAK-659 Ramp-up Dosing

Reporting group description:

TAK-659 60-100 mg tablet, orally, QD, dose based on safety and tolerability during each 28-days cycle (median exposure was 28 days).

Reporting group title	Cohort A: TAK-659 100 mg

Reporting group description:

TAK-659 100 mg tablet, orally, once daily (QD), during each 28-days cycle (median exposure was 41 days).

Serious adverse events	Cohort B: TAK-659 Ramp-up Dosing	Cohort A: TAK-659 100 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 25 (52.00%)	14 / 24 (58.33%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	1	0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			

subjects affected / exposed	3 / 25 (12.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal adenocarcinoma			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural fever			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bone marrow failure			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphocytic infiltration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 25 (8.00%)	3 / 24 (12.50%)	
occurrences causally related to treatment / all	1 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Rectal haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			

subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 25 (4.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida sepsis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal bacteraemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			

subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary nocardiosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 25 (4.00%)	0 / 24 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cohort B: TAK-659 Ramp-up Dosing	Cohort A: TAK-659 100 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 25 (80.00%)	24 / 24 (100.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	8 / 25 (32.00%)	6 / 24 (25.00%)	
occurrences (all)	9	8	
Oedema peripheral			
subjects affected / exposed	2 / 25 (8.00%)	7 / 24 (29.17%)	
occurrences (all)	2	9	
Asthenia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Oedema			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Pyrexia			
subjects affected / exposed	10 / 25 (40.00%)	9 / 24 (37.50%)	
occurrences (all)	12	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 25 (12.00%)	9 / 24 (37.50%)	
occurrences (all)	3	9	
Dyspnoea			
subjects affected / exposed	3 / 25 (12.00%)	4 / 24 (16.67%)	
occurrences (all)	3	4	
Pleural effusion			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Oropharyngeal pain			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	

Sputum discoloured			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 25 (20.00%)	9 / 24 (37.50%)	
occurrences (all)	6	14	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 25 (16.00%)	7 / 24 (29.17%)	
occurrences (all)	5	10	
Amylase increased			
subjects affected / exposed	4 / 25 (16.00%)	6 / 24 (25.00%)	
occurrences (all)	4	7	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 25 (8.00%)	6 / 24 (25.00%)	
occurrences (all)	5	15	
Lipase increased			
subjects affected / exposed	3 / 25 (12.00%)	4 / 24 (16.67%)	
occurrences (all)	4	6	
Gamma-glutamyltransferase increased			
subjects affected / exposed	4 / 25 (16.00%)	1 / 24 (4.17%)	
occurrences (all)	5	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 25 (0.00%)	4 / 24 (16.67%)	
occurrences (all)	0	5	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 25 (8.00%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
C-reactive protein increased			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	2	
Neutrophil count decreased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	

Platelet count decreased			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 25 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences (all)	2	0	
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 25 (8.00%)	3 / 24 (12.50%)	
occurrences (all)	2	3	
Dizziness			
subjects affected / exposed	0 / 25 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	4	
Neuropathy peripheral			
subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Hypoaesthesia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 25 (20.00%)	7 / 24 (29.17%)	
occurrences (all)	9	11	
Neutropenia			
subjects affected / exposed	4 / 25 (16.00%)	2 / 24 (8.33%)	
occurrences (all)	6	4	
Thrombocytopenia			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Increased tendency to bruise			

subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Eye disorders			
Periorbital oedema			
subjects affected / exposed	3 / 25 (12.00%)	5 / 24 (20.83%)	
occurrences (all)	3	9	
Vision blurred			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 25 (8.00%)	4 / 24 (16.67%)	
occurrences (all)	2	4	
Abdominal pain			
subjects affected / exposed	1 / 25 (4.00%)	4 / 24 (16.67%)	
occurrences (all)	1	6	
Constipation			
subjects affected / exposed	1 / 25 (4.00%)	3 / 24 (12.50%)	
occurrences (all)	1	3	
Nausea			
subjects affected / exposed	2 / 25 (8.00%)	2 / 24 (8.33%)	
occurrences (all)	2	2	
Dry mouth			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Vomiting			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Abdominal distension			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 25 (4.00%)	5 / 24 (20.83%)	
occurrences (all)	1	8	
Pruritus			

subjects affected / exposed	1 / 25 (4.00%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 25 (4.00%)	4 / 24 (16.67%)	
occurrences (all)	1	4	
Arthralgia			
subjects affected / exposed	0 / 25 (0.00%)	3 / 24 (12.50%)	
occurrences (all)	0	3	
Myalgia			
subjects affected / exposed	0 / 25 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	4 / 25 (16.00%)	2 / 24 (8.33%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Hypophosphataemia			
subjects affected / exposed	1 / 25 (4.00%)	7 / 24 (29.17%)	
occurrences (all)	2	8	
Decreased appetite			
subjects affected / exposed	2 / 25 (8.00%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	2 / 25 (8.00%)	0 / 24 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 November 2017	• The study design was revised to add a dose exploration phase (Stage 1) to select the dosing regimen for use in the efficacy evaluation phase of the study (Stage 2), and statistical methods were revised accordingly. • Clinical experience with TAK-659 was revised to include updated safety and efficacy data from Studies C34001 and C34002, and the rationale for dose and schedule selection was revised with updated safety and efficacy data from Study C34001. • The objectives and endpoints were revised to reflect new 2-phase study design: dose exploration phase, (Stage 1) and efficacy evaluation phase (Stage 2). Secondary objectives and endpoints were revised, as were PK measurements. • The expected numbers of participants and study centers and the expected duration of the study were increased.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported