Clinical trial results:
A Phase II, open label, dose escalation study to investigate the pharmacokinetics, pharmacodynamics, safety and clinical activity of begelomab as an initial treatment of acute Graft-versus-Host Disease in combination with standard steroid therapy

Summary

EudraCT number	2017-002715-34
Trial protocol	IT
Global end of trial date	29 July 2022

Results information

Result version number	v1 (current)
This version publication date	14 April 2023
First version publication date	14 April 2023

Trial information

Trial identification

Sponsor protocol code	ADN014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	ADIENNE SA
Sponsor organisation address	Via Zurigo, 46, Lugano, Switzerland, 6900
Public contact	Clinical Development Director, Renata Palmieri, +41 912104726, renata.palmieri@adienne.com
Scientific contact	Clinical Development Director, Renata Palmieri, +41 912104726, renata.palmieri@adienne.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001744-PIP01-14
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 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	08 July 2022
Global end of trial reached?	Yes
Global end of trial date	29 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objectives of the trial will be:
•to establish the optimal biological dose (OBD) of intravenously infused begelomab in terms of modulation of CD26/CD3 lymphocyte activity;
•to investigate efficacy endpoints;
•to investigate the pharmacokinetics and pharmacodynamics of begelomab following escalating multiple doses of begelomab;
•to investigate the safety and tolerability of multiple doses of begelomab in patients with acute Graft-versus-Host Disease.

Protection of trial subjects:

The study was planned to comprise up to four dose levels in the dose escalation phase; only two additional dose levels were necessary to reach the Optimal Biiological Dose (OBD). The starting dose level was 4 mg/m^2, the second dose level 8 mg/m^2 and the third dove level was 16 mg/m^2. At the end of the dose escalation phase, the data from all cohorts was analysed to determine the optimal biologically active dose for further evaluation in the extended cohort.
Prior to each dose escalation, the Trial Steering Committee (TSC) has met to review all available safety, tolerability, Pharmacokinetic (PK) and Pharmacodynamic (PD) data. A decision to escalate the dose could only be made when none of the dose escalation stopping criteria are expected to be met at the next higher dose level.
A minimum of four evaluable subjects from each cohort were needed to reach a dose escalation decision.

Background therapy:

Alongside the study treatments, methylprednisolone intravenous (IV) at the dose of ≤2 mg/kg/day (or other steroid and dose equivalent) was administered to subjects as baseline therapy.

Evidence for comparator: -

Actual start date of recruitment	05 September 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	Italy: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

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)	3
Adults (18-64 years)	38
From 65 to 84 years	9
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was divided in two phases. At initial stage, up to 6 patients per cohort were enrolled into sequential cohorts receiving increasing multiple doses of begelomab. Only two additional dose levels were necessary in order to reach the OBD. At the second stage, 25 additional patients were enrolled and treated at the OBD.

Pre-assignment

Screening details:

Patient who underwent allogeneic HSCT who developed clinical manifestations compatible with aGvHD were considered for enrolment, provided they have not been treated with Corticosteroids or other aGvHD therapies and had aGvHD grade greater than 2.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	begelomab 4 mg/m^2 FAS

Arm description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The first dose level was 4mg/m^2.

Arm type	Experimental
Investigational medicinal product name	begelomab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses. First day of treatment is defined as Day 1.

Arm title	begelomab 8 mg/m^2 FAS

Arm description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The second dose level was 8mg/m^2.

Arm type	Experimental
Investigational medicinal product name	begelomab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses. First day of treatment is defined as Day 1.

Arm title	begelomab 16 mg/m^2 FAS

Arm description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The third dose level was 16mg/m^2. OBD has been reached at this dose level, therefore the second stage of the study (dose expansion phase) has been performed at the same dose level.

Arm type	Experimental
Investigational medicinal product name	begelomab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Infusion

Dosage and administration details:

The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses. First day of treatment is defined as Day 1.

Number of subjects in period 1	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS
Started	8	11	31
Completed	5	7	13
Not completed	3	4	18
Adverse event, serious fatal	-	-	10
Physician decision	1	-	1
Adverse event, non-fatal	1	-	1
Lost to follow-up	-	3	2
Lack of efficacy	1	1	4

Baseline characteristics

Reporting groups	
Reporting group title	begelomab 4 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The first dose level was 4mg/m^2.	
Reporting group title	begelomab 8 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The second dose level was 8mg/m^2.	
Reporting group title	begelomab 16 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The third dose level was 16mg/m^2. OBD has been reached at this dose level, therefore the second stage of the study (dose expansion phase) has been performed at the same dose level.	

Reporting group values	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS
Number of subjects	8	11	31
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	2
Adults (>18)	7	11	29
Age continuous Units: years			
median	57.5	62.0	52.0
full range (min-max)	12 to 66	22 to 70	14 to 69
Gender categorical Units: Subjects			
Female	4	5	18
Male	4	6	13

Reporting group values	Total		
Number of subjects	50		
Age categorical Units: Subjects			
Adolescents (12-17 years)	3		
Adults (>18)	47		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	27		
Male	23		

Subject analysis sets	
Subject analysis set title	4mg/m^2 Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects registered in the 4.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.

Subject analysis set title	8mg/m^2 Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects registered in the 8.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.

Subject analysis set title	16mg/m^2 Per Protocol
Subject analysis set type	Per protocol

Subject analysis set description:

All subjects registered in the 16.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.

Subject analysis set title	4mg/m^2 Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who provided informed consent receiving at least one dose of study medication in the 4.0 mg/m^2 cohort were included in the analysis.

Subject analysis set title	8mg/m^2 Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who provided informed consent receiving at least one dose of study medication in the 8.0 mg/m^2 cohort were included in the analysis.

Subject analysis set title	16mg/m^2 Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients who provided informed consent receiving at least one dose of study medication in the 16.0 mg/m^2 cohort were included in the analysis.

Subject analysis set title	4mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients enrolled in the 4.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.

Subject analysis set title	8mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients enrolled in the 8.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.

Subject analysis set title	16mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients enrolled in the 16.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.

Reporting group values	4mg/m^2 Per Protocol	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol
Number of subjects	5	7	23

Age categorical Units: Subjects			
Adolescents (12-17 years) Adults (>18)			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

Reporting group values	4mg/m^2 Safety Set	8mg/m^2 Safety Set	16mg/m^2 Safety Set
Number of subjects	8	11	31
Age categorical Units: Subjects			
Adolescents (12-17 years)	1	0	2
Adults (>18)	7	11	29
Age continuous Units: years			
median	57.5	62.0	52.0
full range (min-max)	12 to 66	22 to 70	14 to 69
Gender categorical Units: Subjects			
Female	4	5	18
Male	4	6	13

Reporting group values	4mg/m^2 LOCF FAS	8mg/m^2 LOCF FAS	16mg/m^2 LOCF FAS
Number of subjects	8	11	31
Age categorical Units: Subjects			
Adolescents (12-17 years) Adults (>18)			
Age continuous Units: years median full range (min-max)			
Gender categorical Units: Subjects			
Female Male			

End points

End points reporting groups

Reporting group title	begelomab 4 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The first dose level was 4mg/m^2.	
Reporting group title	begelomab 8 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The second dose level was 8mg/m^2.	
Reporting group title	begelomab 16 mg/m^2 FAS
Reporting group description:	
In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The third dose level was 16mg/m^2. OBD has been reached at this dose level, therefore the second stage of the study (dose expansion phase) has been performed at the same dose level.	
Subject analysis set title	4mg/m^2 Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects registered in the 4.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.	
Subject analysis set title	8mg/m^2 Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects registered in the 8.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.	
Subject analysis set title	16mg/m^2 Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects registered in the 16.0 mg/m^2 cohort who completed at least the treatment period and had no major protocol deviations that could impact on the data were included in the analysis.	
Subject analysis set title	4mg/m^2 Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who provided informed consent receiving at least one dose of study medication in the 4.0 mg/m^2 cohort were included in the analysis.	
Subject analysis set title	8mg/m^2 Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who provided informed consent receiving at least one dose of study medication in the 8.0 mg/m^2 cohort were included in the analysis.	
Subject analysis set title	16mg/m^2 Safety Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
All patients who provided informed consent receiving at least one dose of study medication in the 16.0 mg/m^2 cohort were included in the analysis.	
Subject analysis set title	4mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All patients enrolled in the 4.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.	
Subject analysis set title	8mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients enrolled in the 8.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.

Subject analysis set title	16mg/m^2 LOCF FAS
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All patients enrolled in the 16.0 mg/m^2 cohort were included in the analysis for which a Last Observation Carried Forward (LOCF) imputation method is adopted for any missing assessments of Response to Treatment.

Primary: Receptor Occupancy

End point title	Receptor Occupancy[1]

End point description:

Dose of begelomab leading to a maximum Receptor Occupancy as determined with flow cytometry

End point type	Primary

End point timeframe:

Day -1 to Day 180, only day 28 reported

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: Appropriate descriptive statistics has been used for outcome variables. Continuous variables has been presented using the mean, median, standard deviation, minimum and maximum, and were also discretized for practical purposes. For categorical data, frequencies and percentages were presented.

End point values	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS	4mg/m^2 Per Protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	11	31	5
Units: percent				
median (full range (min-max))	33.7 (21.8 to 52.5)	63.8 (22.8 to 80.4)	55.3 (34.7 to 100.6)	33.7 (21.8 to 52.5)

End point values	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	23		
Units: percent				
median (full range (min-max))	63.8 (22.8 to 80.4)	54.15 (34.7 to 96.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cumulative overall response

End point title	Cumulative overall response

End point description:

Overall response is defined as the percentage of patients with graft-versus-host disease (GvHD) complete response (CR) or partial response (PR)

End point type	Secondary

End point timeframe:

Day 28, Day 56, Day 100 and Day 180.

End point values	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS	4mg/m^2 Per Protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	11	31	5
Units: percent				
number (confidence interval 90%)				
Overall Response	62.5 (28.9 to 88.9)	63.6 (35.0 to 86.5)	64.5 (48.2 to 78.7)	100.0 (54.9 to 100.0)
Complete Response	50.0 (19.3 to 80.7)	54.5 (27.1 to 80.0)	41.9 (26.9 to 58.2)	80.0 (34.3 to 99.0)
Partial Response	12.5 (0.6 to 47.1)	9.1 (0.5 to 36.4)	22.6 (11.1 to 38.3)	20.0 (1.0 to 65.7)

End point values	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol	4mg/m^2 LOCF FAS	8mg/m^2 LOCF FAS
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	23	8	11
Units: percent				
number (confidence interval 90%)				
Overall Response	100.0 (65.2 to 100.0)	78.3 (59.6 to 91.0)	62.5 (28.9 to 88.9)	72.7 (43.6 to 92.1)
Complete Response	85.7 (47.9 to 99.3)	47.8 (29.6 to 66.5)	50.0 (19.3 to 80.7)	54.5 (27.1 to 80.0)
Partial Response	14.3 (0.7 to 52.1)	30.4 (15.2 to 49.6)	12.5 (0.6 to 47.1)	18.2 (3.3 to 47.0)

End point values	16mg/m^2 LOCF FAS			
Subject group type	Subject analysis set			
Number of subjects analysed	31			
Units: percent				
number (confidence interval 90%)				
Overall Response	67.7 (51.5 to 81.3)			
Complete Response	41.9 (26.9 to 58.2)			
Partial Response	25.8 (13.5 to 41.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Overall Response

End point title	Duration of Overall Response[2]

End point description:

Defined as the time in days from first response (from Day 28) until GvHD progression or death

End point type	Secondary

End point timeframe:

Day 28 to Day 180

Notes:

[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: Duration of overall response is defined as the time from first response until GvHD progression or death and it is calculated only for patients with disease progression or death. In the "begelomab 4 mg/m^2 FAS" and "4mg/m^2 Per Protocol" groups no patients progressed or died, therefore it is not possible to calculate the endpoint, which is reported as missing in the tables. System only allows to enter numbers in the field, therefore it was decided to exclude groups as "NA" is not reportable.

End point values	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	11	31	7	23
Units: day				
median (full range (min-max))	73.0 (73 to 73)	73.5 (7 to 172)	73 (73 to 73)	73.5 (7 to 172)

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Proportion of participants who survive until Day 28, Day 56, Day 100 and Day 180

End point type	Secondary

End point timeframe:

Day 28 to Day 180

End point values	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS	4mg/m^2 Per Protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	11	31	5
Units: percent				
number (confidence interval 90%)				
Day 28	100 (100 to 100)	90.0 (57.9 to 98.0)	96.8 (84.4 to 99.4)	100.0 (100.0 to 100.0)
Day 56	100 (100 to 100)	90.0 (57.9 to 98.0)	88.7 (73.2 to 95.5)	100.0 (100.0 to 100.0)

Day 100	83.3 (38.8 to 96.5)	80.0 (48.9 to 93.3)	76.6 (59.2 to 87.3)	100.0 (100.0 to 100.0)
Day 180	83.3 (38.8 to 96.5)	70.0 (39.6 to 87.2)	56.5 (38.8 to 70.8)	100.0 (100.0 to 100.0)

End point values	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	23		
Units: percent				
number (confidence interval 90%)				
Day 28	100.0 (100.0 to 100.0)	100.0 (100.0 to 100.0)		
Day 56	100.0 (100.0 to 100.0)	95.2 (77.7 to 99.1)		
Day 100	100.0 (100.0 to 100.0)	85.7 (67.1 to 94.2)		
Day 180	100.0 (100.0 to 100.0)	61.9 (42.2 to 76.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of reduction of steroid dose

End point title	Percentage of reduction of steroid dose
End point description:	
Percentage reduction of the steroid dose compared with respect to initial dosing at Day 28, Day 56, Day 100 and Day 180	
End point type	Secondary
End point timeframe:	
Day 28 to Day 180	

End point values	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS	4mg/m^2 Per Protocol
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	8	11	31	5
Units: percent				
median (full range (min-max))				
Day 28	-16.7 (-58.0 to 150)	-69.0 (-83.0 to -63.0)	-63.0 (-93.0 to 99.0)	-16.7 (-58.0 to 150.0)
Day 56	-80.3 (-83.0 to -78.0)	-83.3 (-86.0 to 15.0)	-70.0 (-97.0 to -20.0)	-80.3 (-83.0 to -78.0)
Day 100	-93.3 (-93.3 to -93.3)	-96.6 (-96.7 to -96.5)	-84.0 (-99.0 to -58.0)	-93.3 (-93.3 to -93.3)
Day 180	291.7 (-67.0 to 650.0)	-98.0 (-98.0 to -85.0)	-62.5 (-80.0 to 400.0)	291.7 (-67.0 to 650.0)

End point values	8mg/m^2 Per Protocol	16mg/m^2 Per Protocol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	23		
Units: percent				
median (full range (min-max))				
Day 28	-71.3 (-83.0 to -67.0)	-63.0 (-93.0 to 40.0)		
Day 56	-84.7 (-86.0 to -83.0)	-68.3 (-97.0 to -20.0)		
Day 100	-96.6 (-96.7 to -96.5)	-84.0 (-99.0 to -58.0)		
Day 180	-98.0 (-98.0 to -85.0)	-66.7 (-80.0 to 400.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AE) and Serious Adverse Events (SAE) incidence from baseline to Days 28, 100 and 180 or last available data

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	begelomab 4 mg/m^2 FAS

Reporting group description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The first dose level was 4mg/m^2.
The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses.

Reporting group title	begelomab 8 mg/m^2 FAS

Reporting group description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The second dose level was 8mg/m^2.
The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses.

Reporting group title	begelomab 16 mg/m^2 FAS

Reporting group description:

In the first stage of the study (dose escalation phase) patients were treated until achievement of the OBD. The third dose level was 16mg/m^2. OBD has been reached at this dose level, therefore the second stage of the study (dose expansion phase) has been performed at the same dose level.
The investigational medicinal product was administered as a 1-hour intravenous infusion into a central vein via a dedicated catheter (i.e. CVC or PICC) once daily for five days after enrolment (Days 1-5) followed by administration every other day for another eleven doses (Days 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27) for a total of 16 doses.

Serious adverse events	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 8 (62.50%)	7 / 11 (63.64%)	14 / 31 (45.16%)
number of deaths (all causes)	1	3	12
number of deaths resulting from adverse events	1	3	12
Investigations			
Platelet count decreased			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
White blood cell count decreased			

subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutrophil count decreased			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Myelofibrosis			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 31 (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
Leukaemia recurrent			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 31 (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
Acute leukaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Injury, poisoning and procedural complications			
Delayed graft function			
subjects affected / exposed	2 / 8 (25.00%)	0 / 11 (0.00%)	0 / 31 (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
Nervous system disorders			
Encephalopathy			
subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 31 (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 and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	1 / 8 (12.50%)	0 / 11 (0.00%)	0 / 31 (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
Microangiopathic haemolytic anaemia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Acute graft versus host disease			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Acute graft versus host disease in intestine			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Acute graft versus host disease in liver			
subjects affected / exposed	0 / 8 (0.00%)	1 / 11 (9.09%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Graft versus host disease			

subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Infections and infestations			
Cerebral toxoplasmosis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Coronavirus infection			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia klebsiella			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sepsis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	2 / 31 (6.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Septic shock			
subjects affected / exposed	0 / 8 (0.00%)	2 / 11 (18.18%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	begelomab 4 mg/m^2 FAS	begelomab 8 mg/m^2 FAS	begelomab 16 mg/m^2 FAS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 8 (100.00%)	10 / 11 (90.91%)	31 / 31 (100.00%)
Vascular disorders			
any			
subjects affected / exposed	3 / 8 (37.50%)	2 / 11 (18.18%)	9 / 31 (29.03%)
occurrences (all)	4	2	9
General disorders and administration site conditions			
any			
subjects affected / exposed	3 / 8 (37.50%)	4 / 11 (36.36%)	13 / 31 (41.94%)
occurrences (all)	5	5	26
Immune system disorders			
any			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	4 / 31 (12.90%)
occurrences (all)	0	0	6
Reproductive system and breast disorders			
any			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	1 / 31 (3.23%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
any			
subjects affected / exposed	2 / 8 (25.00%)	0 / 11 (0.00%)	2 / 31 (6.45%)
occurrences (all)	2	0	3
Psychiatric disorders			
any			
subjects affected / exposed	0 / 8 (0.00%)	0 / 11 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4
Investigations			
any			
subjects affected / exposed	7 / 8 (87.50%)	5 / 11 (45.45%)	18 / 31 (58.06%)
occurrences (all)	37	20	78
Injury, poisoning and procedural complications			
any			
subjects affected / exposed	1 / 8 (12.50%)	1 / 11 (9.09%)	4 / 31 (12.90%)
occurrences (all)	1	1	4
Cardiac disorders			

any subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 11 (0.00%) 0	1 / 31 (3.23%) 1
Nervous system disorders any subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 2	0 / 11 (0.00%) 0	4 / 31 (12.90%) 5
Blood and lymphatic system disorders any subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 6	5 / 11 (45.45%) 8	14 / 31 (45.16%) 35
Eye disorders any subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1	0 / 11 (0.00%) 0	3 / 31 (9.68%) 3
Gastrointestinal disorders any subjects affected / exposed occurrences (all)	2 / 8 (25.00%) 4	1 / 11 (9.09%) 2	15 / 31 (48.39%) 36
Hepatobiliary disorders any subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 11 (0.00%) 0	2 / 31 (6.45%) 2
Skin and subcutaneous tissue disorders any subjects affected / exposed occurrences (all)	0 / 8 (0.00%) 0	0 / 11 (0.00%) 0	8 / 31 (25.81%) 14
Renal and urinary disorders any subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 5	1 / 11 (9.09%) 1	2 / 31 (6.45%) 3
Musculoskeletal and connective tissue disorders any subjects affected / exposed occurrences (all)	4 / 8 (50.00%) 6	1 / 11 (9.09%) 1	3 / 31 (9.68%) 4
Infections and infestations any			

subjects affected / exposed	3 / 8 (37.50%)	5 / 11 (45.45%)	10 / 31 (32.26%)
occurrences (all)	7	12	15
Metabolism and nutrition disorders			
any			
subjects affected / exposed	8 / 8 (100.00%)	5 / 11 (45.45%)	19 / 31 (61.29%)
occurrences (all)	25	13	40

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 May 2018	Main changes include: - Updated staging system reference used for aGvHD and cGvHD determination - Inclusion/Exclusion criteria updated: - Gastrointestinal biopsy is recommended and no longer mandatory - Time window for prior systemic corticosteroid therapy for GvHD has been extended to 48 hours - Spirometry test has been replaced by pulse oximetry assessment of oxygen saturation - Added criteria to exclude the possibility to enroll in the trial patients affected by steroid-resistant GvHD variant - Removed criteria "Patients with signs of steroid-resistance" due to the impossibility to diagnose steroid resistance within the first 48 hours after the start of systemic corticosteroid therapy - The definition of clinically relevant CMV-viremia has been updated according to the current clinical criteria for preemptive treatment and increased from ≥ 5.000 to ≥10.000 copies/mL in whole blood - To specify that both central venous catheter (CVC) and peripherally inserted central catheter (PICC) can be used for IP administration
07 January 2019	Main changes include: - Study Phase changed from I-II to II, with rationale explanation in the study protocol - Inclusion/Exclusion Criteria updated: - removed upper limit for inclusion age (previously < 70Yrs) since data on patients higher than 70 years can be relevant for safety purposes. - Time window for prior systemic corticosteroid therapy for GvHD has been extended to 72 hours to allow the sites more time to complete the screening exams and assessments. - The application of topical steroids for indications other than GvHD is no longer prohibited - Patients with known CNS involvement or pleural effusions/ascites are now eligible

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported