



Clinical trial results:

A Phase II, open label, dose escalation study to investigate the pharmacokinetics, pharmacodynamics, safety and clinical activity of beigelomab 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) | EMA-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 Biological Dose (OBD). The starting dose level was 4 mg/m², the second dose level 8 mg/m² and the third dose level was 16 mg/m². 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/m².

| | |
|--|---------------------------------------|
| 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/m².

| | |
|--|---------------------------------------|
| 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/m². 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/m² 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/m² 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 beigelomab 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 | beigelomab 4 mg/m ² FAS | beigelomab 8 mg/m ² FAS | beigelomab 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 | begecomab 4 mg/m ² FAS | begecomab 8 mg/m ² FAS | begecomab 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/m² FAS" and "4mg/m² 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 | beigelomab 4 mg/m ² FAS | beigelomab 8 mg/m ² FAS | beigelomab 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/m².

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/m².

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/m². 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 occurrences (all) | 3 / 8 (37.50%) 7 | 5 / 11 (45.45%) 12 | 10 / 31 (32.26%) 15 |
| Metabolism and nutrition disorders any subjects affected / exposed occurrences (all) | 8 / 8 (100.00%) 25 | 5 / 11 (45.45%) 13 | 19 / 31 (61.29%) 40 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 21 May 2018 | <p>Main changes include:</p> <ul style="list-style-type: none">- Updated staging system reference used for aGvHD and cGvHD determination- Inclusion/Exclusion criteria updated:<ul style="list-style-type: none">- 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 | <p>Main changes include:</p> <ul style="list-style-type: none">- Study Phase changed from I-II to II, with rationale explanation in the study protocol- Inclusion/Exclusion Criteria updated:<ul style="list-style-type: none">- 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