



## Clinical trial results:

### A Prospective, Open-label, Interventional Phase IIIb Clinical Trial to Investigate the Effectiveness of an Additional Course of Alemtuzumab in Relapsing Remitting Multiple Sclerosis Patients After 2 Courses of Alemtuzumab

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2016-000464-42 |
| Trial protocol           | DE             |
| Global end of trial date | 28 May 2019    |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 11 June 2020 |
| First version publication date | 11 June 2020 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | ALEMLL08091 |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                                     |
|------------------------------------|-------------------------------------|
| ISRCTN number                      | -                                   |
| ClinicalTrials.gov id (NCT number) | -                                   |
| WHO universal trial number (UTN)   | U1111-1185-1377                     |
| Other trial identifiers            | Sponsor abbreviated name: LemCourse |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Genzyme Corporation  |
| Sponsor organisation address | 500 Kendall Street, Cambridge, MA, United States, 02142                                  |
| Public contact               | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi aventis recherche & développement, Contact-US@sanofi.com |

Notes:

##### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 15 August 2019 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 28 May 2019    |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

Evaluation of effectiveness of an additional alemtuzumab course in subjects with relapsing remitting multiple sclerosis (RRMS) with disease activity after 2 courses with respect to the annualised relapse rate (ARR).

Protection of trial subjects:

Subjects were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject and considering the local culture. During the course of the trial, subjects were provided with individual subject cards indicating the nature of the trial in which the subject is participating, contact details and any information needed in the event of a medical emergency. Collected personal data and human biological samples were processed in compliance with the Sanofi-Aventis Group Personal Data Protection Charter ensuring that the Group abides by the laws governing personal data protection in force in all countries in which it operates.

Background therapy: -

Evidence for comparator: -

|   |                 |
|---|-----------------|
| Actual start date of recruitment                          | 04 October 2016 |
| 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 | Germany: 56 |
| Worldwide total number of subjects   | 56          |
| EEA total number of subjects         | 56          |

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) | 56 |
| From 65 to 84 years  | 0  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at multiple sites in Germany between 04-October-2016 to 28-May-2019.

### Pre-assignment

Screening details:

A total of 56 subjects were included in the study.

### Period 1

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

### Arms

|           |             |
|-----------|-------------|
| Arm title | Alemtuzumab |
|-----------|-------------|

Arm description:

Subjects who had previously (before enrollment in this study) received 2 courses of alemtuzumab, received intravenous (IV) infusion of alemtuzumab in this study at a dose of 12 milligram per day (mg/day) for 3 consecutive days, at least 12 months after prior treatment course.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | Alemtuzumab                           |
| Investigational medicinal product code | Lemtrada                              |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

IV infusion of alemtuzumab at a dose of 12 mg/day for 3 consecutive days (total dose-36 mg) at least 12 months after prior treatment course in a supervised medical setting.

| Number of subjects in period 1                    | Alemtuzumab |
|---|-------------|
| Started   | 56          |
| Completed   | 54          |
| Not completed                                     | 2           |
| Adverse Event (AE)                                | 1           |
| Subject did not meet inclusion/exclusion criteria | 1           |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Alemtuzumab |
|-----------------------|-------------|

Reporting group description:

Subjects who had previously (before enrollment in this study) received 2 courses of alemtuzumab, received intravenous (IV) infusion of alemtuzumab in this study at a dose of 12 milligram per day (mg/day) for 3 consecutive days, at least 12 months after prior treatment course.

| Reporting group values  | Alemtuzumab   | Total |  |
|---|---------------|-------|--|
| Number of subjects  | 56            | 56    |  |
| Age categorical<br>Units: Subjects                                      |               |       |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 35.8<br>± 9.2 | -     |  |
| Gender categorical<br>Units: Subjects                                   |               |       |  |
| Female  | 44            | 44    |  |
| Male  | 12            | 12    |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Alemtuzumab  |
| Reporting group description:<br>Subjects who had previously (before enrollment in this study) received 2 courses of alemtuzumab, received intravenous (IV) infusion of alemtuzumab in this study at a dose of 12 milligram per day (mg/day) for 3 consecutive days, at least 12 months after prior treatment course. |  |
| Subject analysis set title   | Alemtuzumab (1-year period prior to 3rd course of treatment) |
| Subject analysis set type  | Modified intention-to-treat                                  |
| Subject analysis set description:<br>Subjects who, after receiving 2nd course of treatment with alemtuzumab, were in a year-long period of observation before administration of 3rd treatment course with alemtuzumab.   |  |
| Subject analysis set title   | Alemtuzumab (1-year period after 3rd course of treatment)    |
| Subject analysis set type  | Modified intention-to-treat                                  |
| Subject analysis set description:<br>Subjects who were observed for up to one year after administration of 1st infusion of the 3rd treatment course with alemtuzumab.  |  |

### Primary: Annualized Number of Relapses During the 1-year Period of Observation Before and After Third Treatment Course With Alemtuzumab

|   |  |
|---|--|
| End point title   | Annualized Number of Relapses During the 1-year Period of Observation Before and After Third Treatment Course With Alemtuzumab |
| End point description:<br>Relapse was defined as new neurological or worsening of previous neurological symptoms with an objective change on neurological examination. These symptoms were attributable to multiple sclerosis, lasting at least 48 hours, be present at normal body temperature (i.e., no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 30 days of clinical stability. Analysis was performed on modified intent-to-treat (mITT) population which included all subjects who had received at least one infusion of the 3rd treatment course with alemtuzumab with non-missing information regarding duration of follow-up after 1st infusion of the 3rd treatment course with alemtuzumab and number of relapses during this follow-up. |  |
| End point type  | Primary  |
| End point timeframe:<br>Up to 12 months before and after 3rd treatment course of alemtuzumab  |  |

| End point values                              | Alemtuzumab (1-year period prior to 3rd course of treatment) | Alemtuzumab (1-year period after 3rd course of treatment) |  |  |
|---|--|---|--|--|
| Subject group type                            | Subject analysis set   | Subject analysis set                                      |  |  |
| Number of subjects analysed                   | 56   | 56  |  |  |
| Units: Normalised number of relapses per year |  |   |  |  |
| arithmetic mean (standard deviation)          | 1.34 (± 0.824)   | 0.58 (± 0.924)  |  |  |

## Statistical analyses

|  |   |
|--|---|
| <b>Statistical analysis title</b>  | Rate ratio  |
| Statistical analysis description:  |   |
| System sums group Ns for "N in analysis", actual N=56. Repeated measures negative binomial regression model compared relapses in year after 3rd treatment course with relapses in year prior with independent factor gender, covariate age and logarithm of duration of corresponding follow-up time as offset variable. Estimates were provided for ARR in the 2 periods and rate ratio (after/before) of ARRs. Null hypothesis H0:RR ≥1 was tested versus H1:RR <1 at 0.025 level. |   |
| Comparison groups  | Alemtuzumab (1-year period prior to 3rd course of treatment)<br>v Alemtuzumab (1-year period after 3rd course of treatment) |
| Number of subjects included in analysis  | 112   |
| Analysis specification   | Pre-specified   |
| Analysis type  | other   |
| P-value  | < 0.0001  |
| Method   | binomial regression   |
| Parameter estimate   | Rate ratio  |
| Point estimate   | 0.42  |
| Confidence interval  |   |
| level  | 95 %  |
| sides  | 2-sided   |
| lower limit  | 0.29  |
| upper limit  | 0.6   |
| Variability estimate   | Standard error of the mean  |
| Dispersion value   | 0.186   |

### Primary: Number of Subjects With Sustained Accumulation of Disability (SAD)

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Sustained Accumulation of Disability (SAD) <sup>[1]</sup> |
|-----------------|---|

End point description:

SAD was defined as an increase of at least 1 point on the expanded disability status scale (EDSS) from baseline EDSS score ≥1.0 (1.5 point increase for subjects with baseline EDSS of 0). An EDSS was an ordinal clinical rating scale which ranges from 0 (normal neurologic examination) to 10 (death due to multiple sclerosis) in half-point increments, where lower score indicated less severity. Analysis was performed on mITT population. Here, "number of subjects analysed" signifies subjects evaluable for this endpoint.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

12 months post 3rd treatment course of alemtuzumab

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: The endpoint is descriptive in nature, no statistical analysis is provided.

|                             |                 |  |  |  |
|-----------------------------|-----------------|--|--|--|
| <b>End point values</b>     | Alemtuzumab     |  |  |  |
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 55              |  |  |  |
| Units: subjects             |                 |  |  |  |
| number (not applicable)     |                 |  |  |  |
| Yes                         | 7               |  |  |  |
| No                          | 48              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects Without Relapse at Month 12

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Without Relapse at Month 12 |
|-----------------|--|

End point description:

Relapse was defined as new neurological or worsening of previous neurological symptoms with an objective change on neurological examination. These symptoms were attributable to multiple sclerosis, lasting at least 48 hours, be present at normal body temperature (i.e., no infection, excessive exercise, or excessively high ambient temperature), and be preceded by at least 30 days of clinical stability. Analysis was performed on mITT population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Month 12

|                               |                 |  |  |  |
|-------------------------------|-----------------|--|--|--|
| <b>End point values</b>       | Alemtuzumab     |  |  |  |
| Subject group type            | Reporting group |  |  |  |
| Number of subjects analysed   | 56              |  |  |  |
| Units: percentage of subjects |                 |  |  |  |
| number (not applicable)       | 66.1            |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change From Baseline in Expanded Disability Status Scale Scores at Months 6 and 12

|                 |  |
|-----------------|--|
| End point title | Change From Baseline in Expanded Disability Status Scale Scores at Months 6 and 12 |
|-----------------|--|

End point description:

The EDSS was used as the standard for assessing disability in subjects with multiple sclerosis. It was an ordinal clinical rating scale which ranges from 0 (normal neurologic examination) to 10 (death due to multiple sclerosis) in half-point increments where lower score indicated less severity. EDSS steps 1.0 to 4.5 referred to subject with multiple sclerosis who were fully ambulatory, while EDSS steps 5.0 to 9.5 were defined by the impairment to ambulation. Analysis was performed on mITT population. Here, "number of subjects analysed" signifies subjects evaluable for this endpoint.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Months 6 and 12



|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Alemtuzumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 55              |  |  |  |
| Units: score on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Month 6                              | -0.2 (± 0.73)   |  |  |  |
| Month 12                             | -0.1 (± 0.86)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Brain Magnetic Resonance Imaging (MRI) Assessment: Percentage of Subjects With Active Lesions

|                 |   |
|-----------------|---|
| End point title | Brain Magnetic Resonance Imaging (MRI) Assessment: Percentage of Subjects With Active Lesions |
|-----------------|---|

End point description:

The MRI was used to evaluate the efficacy of drug modifying therapies (DMTs) by measuring the number of unique active lesion (UALs): Gadolinium-enhancing (Gd)(+)-lesions seen in T1-weighted images plus unenhanced new and enlarging T2-hyperintense lesions, identified on relatively infrequent sequential imaging. Change of number of Gd(+)-lesions and number of new and enlarging lesions found on T2-weighted images were evaluated at Month 12 as compared to Baseline. Analysis was performed on mITT population.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Month 12

|                                   |                 |  |  |  |
|-----------------------------------|-----------------|--|--|--|
| <b>End point values</b>           | Alemtuzumab     |  |  |  |
| Subject group type                | Reporting group |  |  |  |
| Number of subjects analysed       | 56              |  |  |  |
| Units: percentage of subjects     |                 |  |  |  |
| number (not applicable)           |                 |  |  |  |
| New Gd lesions: Baseline          | 35.7            |  |  |  |
| New Gd lesions: Month 12          | 12.5            |  |  |  |
| New T2 lesions: Baseline          | 37.5            |  |  |  |
| New T2 lesions: Month 12          | 14.3            |  |  |  |
| New lesions (Gd or T2): Baseline  | 53.6            |  |  |  |
| New lesions (Gd or T2): Month 12  | 19.6            |  |  |  |
| Any enlarging T2 lesion: Month 12 | 8.9             |  |  |  |

## Statistical analyses

**Secondary: Brain Magnetic Resonance Imaging Assessment: Change from Baseline in Number of Active Gadolinium-enhancing and T2 Lesions at Month 12**

|                 |   |
|-----------------|---|
| End point title | Brain Magnetic Resonance Imaging Assessment: Change from Baseline in Number of Active Gadolinium-enhancing and T2 Lesions at Month 12 |
|-----------------|---|

## End point description:

The MRI was used to evaluate the efficacy of DMTs by measuring the number of UALs: Gd(+)-lesions seen in T1-weighted images plus unenhanced new and enlarging T2-hyperintense lesions, identified on relatively infrequent sequential imaging. Change of number of Gd(+)-lesions and number of new and enlarging lesions found on T2-weighted images were evaluated at Month 12 as compared to Baseline. Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Month 12

| End point values                     | Alemtuzumab     |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 56              |  |  |  |
| Units: lesions                       |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| New Gd lesions: (n=53)               | -0.77 (± 3.017) |  |  |  |
| New T2 lesions: (n=54)               | -2.37 (± 8.295) |  |  |  |
| New lesions (Gd+T2): (n=53)          | -3.19 (± 9.058) |  |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change From Baseline in Cognition Measured by Symbol Digit Modalities Test (SDMT) Scores at Months 6 and 12**

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Cognition Measured by Symbol Digit Modalities Test (SDMT) Scores at Months 6 and 12 |
|-----------------|---|

## End point description:

SDMT was developed to identify subjects with neurological impairment and had demonstrated remarkable sensitivity in detecting changes in cognitive functioning over time and in response to treatment. The SDMT involves a simple substitution task. Using a reference key, the subject had 90 seconds to identify nine different symbols corresponding to the numbers 1 through 9, paired specific numbers with given geometric figures, and practiced writing the correct number under the corresponding symbol. The total number of symbols to recognise was 120 corresponding to a maximal score of 120, where the lower score indicated more cognitive impairment. Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified time point.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

## End point timeframe:

Baseline, Months 6 and 12

|                                      |                 |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| <b>End point values</b>              | Alemtuzumab     |  |  |  |
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 56              |  |  |  |
| Units: scores on a scale             |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Month 6 (n=54)                       | 1 (± 14.6)      |  |  |  |
| Month 12 (n=53)                      | 3 (± 17.3)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline in Patient Reported Outcome Indices for Multiple Sclerosis (PRIMUS) Questionnaire at Months 6 and 12

|                 |   |
|-----------------|---|
| End point title | Change From Baseline in Patient Reported Outcome Indices for Multiple Sclerosis (PRIMUS) Questionnaire at Months 6 and 12 |
|-----------------|---|

End point description:

The PRIMUS was a disease specific subject-reported outcome questionnaire that measured the quality of life (QoL) of subjects suffering from multiple sclerosis. The PRIMUS scores were evaluated by assessment of QoL, activity limitations, and symptoms. The questionnaire contained 22 questions on QoL, 15 on activity limitations and 8 on symptoms. A rank was associated to each answer: symptom questions: Yes=1; No=0, activity questions: could without difficulty=0; could with difficulty=1; could not=2, and QoL questions: Not correct=0; Correct=1. The ranks were then summed by specific domains (QoL, activity limitations, and symptoms) and overall. These sums were normalised on the maximum possible scores and presented as percentage (%), where higher score on any of these scales indicated lower quality of life due to the disease. Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified time point.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Months 6 and 12

|  |                 |  |  |  |
|--|-----------------|--|--|--|
| <b>End point values</b>                | Alemtuzumab     |  |  |  |
| Subject group type                     | Reporting group |  |  |  |
| Number of subjects analysed            | 56              |  |  |  |
| Units: scores on a scale               |                 |  |  |  |
| arithmetic mean (standard deviation)   |                 |  |  |  |
| Symptom Score: Month 6 (n=55)          | -2.8 (± 16.62)  |  |  |  |
| Symptom Score: Month 12 (n=53)         | -1.5 (± 17.84)  |  |  |  |
| Activity Score: Month 6 (n=55)         | -1.0 (± 12.89)  |  |  |  |
| Activity Score: Month 12 (n=53)        | 0.3 (± 13.21)   |  |  |  |
| Quality-of-Life Score: Month 6 (n=55)  | -5.0 (± 20.00)  |  |  |  |
| Quality-of-Life Score: Month 12 (n=53) | -3.3 (± 17.95)  |  |  |  |
| Overall Score: Month 6 (n=55)          | -2.7 (± 12.22)  |  |  |  |
| Overall Score: Month 12 (n=53)         | -1.3 (± 12.26)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes From Baseline in Euro Quality of life (EQ-5D-3L) at Months 6 and 12- Index Scores

|                 |   |
|-----------------|---|
| End point title | Changes From Baseline in Euro Quality of life (EQ-5D-3L) at Months 6 and 12- Index Scores |
|-----------------|---|

End point description:

An EQ-5D was a standardised measure to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D 3L consisted of 2 pages: a descriptive system and a visual analogue scale (EQ VAS). The descriptive system had 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each had 3 levels of severity (no problems, some problems, and extreme problems). The 5-dimensional 3-level systems were converted into a single index utility score between 0 to 1, where higher score indicates a better health state. Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified time point.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Months 6 and 12

| End point values                     | Alemtuzumab      |  |  |  |
|--------------------------------------|------------------|--|--|--|
| Subject group type                   | Reporting group  |  |  |  |
| Number of subjects analysed          | 56               |  |  |  |
| Units: score on a scale              |                  |  |  |  |
| arithmetic mean (standard deviation) |                  |  |  |  |
| At Month 6 (n=54)                    | 0.040 (± 0.1514) |  |  |  |
| At Month 12 (n=52)                   | 0.040 (± 0.1568) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Changes From Baseline in Euro Quality of life at Months 6 and 12- Visual Analogue Scale Scores

|                 |  |
|-----------------|--|
| End point title | Changes From Baseline in Euro Quality of life at Months 6 and 12- Visual Analogue Scale Scores |
|-----------------|--|

End point description:

EQ-5D was a standardised measure of health status to provide a simple, generic measure of health for clinical and economic appraisal. EQ-5D-3L-VAS recorded the subject's self-rated health on a vertical VAS that allowed the subjects to indicate their health state that could range from 0 (worst imaginable) to 100 (best imaginable). Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified time point.

|                           |           |
|---------------------------|-----------|
| End point type            | Secondary |
| End point timeframe:      |           |
| Baseline, Months 6 and 12 |           |

| End point values                     | Alemtuzumab     |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 56              |  |  |  |
| Units: score on a scale              |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| At Month 6 (n=55)                    | 1 (± 15.8)      |  |  |  |
| At Month 12 (n=53)                   | 3 (± 17.8)      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes From Baseline in Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH) Scores at Months 6 and 12

|                 |  |
|-----------------|--|
| End point title | Changes From Baseline in Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH) Scores at Months 6 and 12 |
|-----------------|--|

End point description:

WPAI-GH consisted of 6 questions (Q): 1=currently employed; 2=hours missed due to health problems; 3=hours missed because of other reasons; 4=hours actually worked; 5=degree health affected productivity while working (using 0 to 10 VAS); 6=degree health affected productivity in regular unpaid activities (VAS). 4 outcomes were generated, expressed in % by multiplying scores by 100: 1) Work time % missed due to health=Q2/(Q2 + Q4) for currently employed; 2) Impairment % while working due to health=Q5/10 for currently employed and actually worked in past 7 days; 3) Overall work impairment % due to health Q2/(Q2+Q4)+([1-Q2/(Q2+Q4)]\*[Q5/10]) for currently employed; 4) Activity impairment % due to health Q6/10 for all respondents. Subjects who missed work/did not work in past 7 days, overall work impairment % due to health was equal to work time % missed due to health. Analysis was performed on mITT population. Here, "n" signifies number of subjects analysed for each specified time point.

|                           |           |
|---------------------------|-----------|
| End point type            | Secondary |
| End point timeframe:      |           |
| Baseline, Months 6 and 12 |           |

| End point values                     | Alemtuzumab     |  |  |  |
|--------------------------------------|-----------------|--|--|--|
| Subject group type                   | Reporting group |  |  |  |
| Number of subjects analysed          | 56              |  |  |  |
| Units: scores on a scale             |                 |  |  |  |
| arithmetic mean (standard deviation) |                 |  |  |  |
| Score 1: Month 6 (n=15)              | -5.4 (± 27.13)  |  |  |  |
| Score 1: Month 12 (n=15)             | -9.6 (± 45.92)  |  |  |  |
| Score 2: Month 6 (n=21)              | -3.3 (± 20.08)  |  |  |  |
| Score 2: Month 12 (n=21)             | -7.1 (± 22.83)  |  |  |  |

|                          |                 |  |  |  |
|--------------------------|-----------------|--|--|--|
| Score 3: Month 6 (n=14)  | -0.6 (± 23.46)  |  |  |  |
| Score 3: Month 12 (n=14) | -12.3 (± 31.13) |  |  |  |
| Score 4: Month 6 (n=55)  | -5.6 (± 22.09)  |  |  |  |
| Score 4: Month 12 (n=51) | -5.1 (± 27.88)  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)/Serious Adverse Events (SAEs)/Adverse Events of Special Interest (AESIs)

|  |  |
|--|--|
| End point title  | Number of Subjects With Treatment-emergent Adverse Events (TEAEs)/Serious Adverse Events (SAEs)/Adverse Events of Special Interest (AESIs) |
| End point description:   |  |
| An AE was any untoward medical occurrence in subject or clinical investigation subject administered a pharmaceutical product and which did not necessarily had a causal relationship with this treatment. A TEAE was AE that occurred from the start of the 1st infusion of 3rd treatment course up to 1 year after 1st infusion of 3rd treatment course. An SAE was any untoward medical occurrence that at any dose: resulted in death, was life-threatening, required inpatient hospitalisation/prolongation of existing hospitalisation, resulted in persistent or significant disability/incapacity, was congenital anomaly/birth defect, or medically important event. An AESI was an AE (serious/non-serious) of scientific and medical concern specific to Sponsor's product or program, for which ongoing monitoring and immediate notification by Investigator to Sponsor was required. Analysis was performed on safety population that included all subjects who had received at least 1 infusion of 3rd treatment course. |  |
| End point type   | Secondary  |
| End point timeframe:   |  |
| From Baseline up to 12 months  |  |

| End point values            | Alemtuzumab     |  |  |  |
|-----------------------------|-----------------|--|--|--|
| Subject group type          | Reporting group |  |  |  |
| Number of subjects analysed | 56              |  |  |  |
| Units: subjects             |                 |  |  |  |
| TEAEs                       | 52              |  |  |  |
| SAEs                        | 17              |  |  |  |
| AESIs                       | 17              |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs were collected from signature of the informed consent form up to 12 months regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are the treatment-emergent adverse events, that is, AEs that developed/worsened during the 'treatment emergent period' (the time from the first dose of study drug up to the 12 months post third course of treatment). Analysis was performed on safety population.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Alemtuzumab |
|-----------------------|-------------|

Reporting group description:

Subjects who had previously (before enrollment in this study) received 2 courses of alemtuzumab, received IV infusion of alemtuzumab in this study at a dose of 12 mg/day for 3 consecutive days, at least 12 months after prior treatment course.

| Serious adverse events                            | Alemtuzumab      |  |  |
|---|------------------|--|--|
| Total subjects affected by serious adverse events |                  |  |  |
| subjects affected / exposed                       | 17 / 56 (30.36%) |  |  |
| number of deaths (all causes)                     | 0                |  |  |
| number of deaths resulting from adverse events    | 0                |  |  |
| Investigations                                    |                  |  |  |
| Nuclear Magnetic Resonance Imaging Brain Abnormal |                  |  |  |
| subjects affected / exposed                       | 1 / 56 (1.79%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Surgical and medical procedures                   |                  |  |  |
| Multiple Sclerosis Relapse Prophylaxis            |                  |  |  |
| subjects affected / exposed                       | 1 / 56 (1.79%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |
| Thyroidectomy                                     |                  |  |  |
| subjects affected / exposed                       | 1 / 56 (1.79%)   |  |  |
| occurrences causally related to treatment / all   | 0 / 1            |  |  |
| deaths causally related to treatment / all        | 0 / 0            |  |  |

|   |                                    |  |  |
|---|------------------------------------|--|--|
| Nervous system disorders<br>Multiple Sclerosis Relapse<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all          | 9 / 56 (16.07%)<br>0 / 15<br>0 / 0 |  |  |
| General disorders and administration site conditions<br>Pyrexia<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | 1 / 56 (1.79%)<br>0 / 1<br>0 / 0   |  |  |
| Eye disorders<br>Endocrine Ophthalmopathy<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                       | 1 / 56 (1.79%)<br>0 / 1<br>0 / 0   |  |  |
| Endocrine disorders<br>Hyperthyroidism<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                          | 1 / 56 (1.79%)<br>0 / 1<br>0 / 0   |  |  |
| Thyrotoxic Crisis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all   | 1 / 56 (1.79%)<br>0 / 1<br>0 / 0   |  |  |
| Infections and infestations<br>Chest Wall Abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all               | 1 / 56 (1.79%)<br>0 / 1<br>0 / 0   |  |  |

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



| <b>Non-serious adverse events</b>                     | Alemtuzumab      |  |  |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 41 / 56 (73.21%) |  |  |
| Nervous system disorders                              |                  |  |  |
| Headache  |                  |  |  |
| subjects affected / exposed                           | 14 / 56 (25.00%) |  |  |
| occurrences (all)                                     | 17               |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Fatigue   |                  |  |  |
| subjects affected / exposed                           | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Pyrexia   |                  |  |  |
| subjects affected / exposed                           | 6 / 56 (10.71%)  |  |  |
| occurrences (all)                                     | 6                |  |  |
| Gastrointestinal disorders                            |                  |  |  |
| Diarrhoea   |                  |  |  |
| subjects affected / exposed                           | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                                     | 5                |  |  |
| Nausea  |                  |  |  |
| subjects affected / exposed                           | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Skin and subcutaneous tissue disorders                |                  |  |  |
| Alopecia  |                  |  |  |
| subjects affected / exposed                           | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Rash  |                  |  |  |
| subjects affected / exposed                           | 5 / 56 (8.93%)   |  |  |
| occurrences (all)                                     | 5                |  |  |
| Musculoskeletal and connective tissue disorders       |                  |  |  |
| Arthralgia  |                  |  |  |
| subjects affected / exposed                           | 3 / 56 (5.36%)   |  |  |
| occurrences (all)                                     | 3                |  |  |
| Back Pain   |                  |  |  |
| subjects affected / exposed                           | 4 / 56 (7.14%)   |  |  |
| occurrences (all)                                     | 4                |  |  |
| Muscle Spasms   |                  |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 3 / 56 (5.36%)<br>3 |  |  |
| Infections and infestations                      |                     |  |  |
| Nasopharyngitis                                  |                     |  |  |
| subjects affected / exposed                      | 12 / 56 (21.43%)    |  |  |
| occurrences (all)                                | 13                  |  |  |
| Sinusitis  |                     |  |  |
| subjects affected / exposed                      | 4 / 56 (7.14%)      |  |  |
| occurrences (all)                                | 4                   |  |  |
| Urinary Tract Infection                          |                     |  |  |
| subjects affected / exposed                      | 4 / 56 (7.14%)      |  |  |
| occurrences (all)                                | 5                   |  |  |
| Metabolism and nutrition disorders               |                     |  |  |
| Hyperglycaemia                                   |                     |  |  |
| subjects affected / exposed                      | 3 / 56 (5.36%)      |  |  |
| occurrences (all)                                | 4                   |  |  |

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported