

**Clinical trial results:****EFFECTS OF ESLICARBAZEPINE ACETATE (BIA 2-093) ON COGNITIVE FUNCTION IN CHILDREN WITH PARTIAL ONSET SEIZURES: AN ADD-ON, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER CLINICAL TRIAL****Summary**

| | |
|--------------------------|----------------|
| EudraCT number | 2008-005606-39 |
| Trial protocol | NL PL IT |
| Global end of trial date | 27 May 2013 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 22 July 2016 |
| First version publication date | 06 August 2015 |
| Version creation reason | |
| Summary attachment (see zip file) | BIA-2093-208_Synopsis_part I-II (BIA-2093-208_Synopsis_part I-II.pdf) BIA-2093-208_Synopsis_part III (BIA-2093-208_Synopsis_part III.pdf) |

Trial information**Trial identification**

| | |
|-----------------------|--------------|
| Sponsor protocol code | BIA-2093-208 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01527513 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | BIAL - Portela & Ca SA |
| Sponsor organisation address | À Av. Siderurgia Nacional, Coronado, Portugal, 4745-457 |
| Public contact | André Garrido, BIAL - Portela & Ca, S.A., 00351 229866100, andre.garrido@bial.com |
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Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000696-PIP02-10 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 September 2013 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 21 March 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 27 May 2013 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary: To evaluate the effects of ESL on cognition in comparison with placebo as adjunctive therapy in children aged 6 to 16 years old with refractory partial-onset seizures over a 12-week DB period.

Protection of trial subjects:

The trial was conducted in accordance with the International Conference on Harmonisation (ICH), Good Clinical Practices (GCP), Good Manufacturing Practice (GMP), the ethical principles of the Declaration of Helsinki and with applicable local regulations. This trial was conducted by qualified persons who respected the rights and welfare of the subjects and after the review and approval of the protocol by an EC. Adverse events were collected throughout the trial and subject was followed by 28 days after the completion of the study.

Background therapy:

Concomitant AED therapy (1 or 2 AEDs). Concomitant AED therapy will be kept stable during the whole study.

Evidence for comparator:

-

| | |
|---|----------------|
| Actual start date of recruitment | 10 August 2010 |
| 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: 18 |
| Country: Number of subjects enrolled | Poland: 18 |
| Country: Number of subjects enrolled | Russian Federation: 47 |
| Country: Number of subjects enrolled | Ukraine: 40 |
| Worldwide total number of subjects | 123 |
| EEA total number of subjects | 36 |

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) | 54 |
| Adolescents (12-17 years) | 69 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled in 27 sites in Italy, Poland, Russia and the Ukraine.

Pre-assignment

Screening details:

Subjects who met all the inclusion criteria and none of the exclusion criteria. 133 subjects were enrolled to the trial and 10 subjects were screening failures.

Pre-assignment period milestones

| | |
|------------------------------|--------------------|
| Number of subjects started | 133 ^[1] |
| Number of subjects completed | 123 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|---|
| Reason: Number of subjects | Did not meet the inclusion/exclusion criteria: 10 |
|----------------------------|---|

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects reported to have started the pre-assignment period is the number of enrolled subjects; The worldwide number is number of treated subjects.

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Part I |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--------------|
| Arm title | Part I - ESL |
|------------------|--------------|

Arm description:

Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Eslicarbazepine acetate (BIA 2-093) |
| Investigational medicinal product code | |
| Other name | Eslicarbazepine acetate |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosages were as follows:

- During the 4-week titration period, ESL 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks, to a maximum dose of 1200 mg/day.
- During the 8-week maintenance period, ESL 30 mg/kg/day to a maximum dose of 1200 mg/day.
- During the tapering-off period, patients were tapered off in 10 mg/kg/day steps every 2 weeks. The duration of this period depended on the dose that the patient was taking at the end of the maintenance period (30, 20, or 10 mg/kg/day).

ESL was provided as 200 mg tablets. Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored).

| | |
|------------------|------------------|
| Arm title | Part I - Placebo |
|------------------|------------------|

Arm description:

Placebo Once-Daily (QD)

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|--|----------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosages were as follows:

- During the 4-week titration period, Placebo 10 mg/kg/day for 2 weeks followed by 20 mg/kg/day for 2 weeks, to a maximum dose of 1200 mg/day.
- During the 8-week maintenance period, Placebo 30 mg/kg/day to a maximum dose of 1200 mg/day.
- During the tapering-off period, patients were tapered off in 10 mg/kg/day steps every 2 weeks. The duration of this period depended on the dose that the patient was taking at the end of the maintenance period (30, 20, or 10 mg/kg/day).

Placebo was provided as 200 mg tablets. Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored).

| Number of subjects in period 1 | Part I - ESL | Part I - Placebo |
|--------------------------------|--------------|------------------|
| Started | 83 | 40 |
| Completed | 75 | 37 |
| Not completed | 8 | 3 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | 2 | 1 |
| Adverse event, non-fatal | 4 | - |
| Other | - | 1 |
| Non-Compliance of Patient | 1 | 1 |

Period 2

| | |
|------------------------------|----------------|
| Period 2 title | Part II |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|-----------|---------------|
| Arm title | Part II - ESL |
|-----------|---------------|

Arm description:

Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day).

| | |
|--|-------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Eslicarbazepine acetate (BIA 2-093) |
| Investigational medicinal product code | |
| Other name | Eslicarbazepine acetate |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosages were as follows:

All patients who entered Period II initially received a dose of 10 mg/kg/day ESL, but this dose was

titrated by the investigator according to clinical response, with a dose range from 10 to 30 mg/kg/day (maximum allowed dose of 1200 mg QD). Doses were rounded to the nearest 100 mg unit. Half tablets could be used for dosage adjustment, if necessary (tablets were scored). Down-titration was allowed according to clinical response or in case of intolerable AEs, as often as needed.

| Number of subjects in period 2 | Part II - ESL |
|--------------------------------|---------------|
| Started | 112 |
| Completed | 95 |
| Not completed | 17 |
| Consent withdrawn by subject | 12 |
| Physician decision | 1 |
| Other | 2 |
| Non-Compliance of Patient | 1 |
| Lack of efficacy | 1 |

Period 3

| | |
|------------------------------|----------------|
| Period 3 title | Part III |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|--|-------------------------------------|
| Arm title | Part III - ESL |
| Arm description: | |
| Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day). | |
| Arm type | Experimental |
| Investigational medicinal product name | Eslicarbazepine acetate (BIA 2-093) |
| Investigational medicinal product code | |
| Other name | Eslicarbazepine acetate |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Dosages were as follows:

The dose range was 10 to 30 mg/kg/day (maximum allowed ESL dose of 1200 mg QD), and was titrated up or down by the investigator according to clinical response or in case of intolerable adverse events (AEs). Upon completion of this extension, patients were tapered off ESL in 10 mg/kg/day steps every 2 weeks.

| Number of subjects in period 3 ^[2] | Part III - ESL |
|--|----------------|
| | |
| Started | 42 |
| Completed | 31 |
| Not completed | 11 |
| Switches to commercial ESL | 1 |
| Consent withdrawn by subject | 6 |
| Physician decision | 1 |
| Adverse event, non-fatal | 1 |
| Completion status was not recorded | 1 |
| Lost to follow-up | 1 |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Number of subjects 95 completed the Part II and 53 of them did not start Part III.

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Part I - ESL |
| Reporting group description: Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day). | |
| Reporting group title | Part I - Placebo |
| Reporting group description: Placebo Once-Daily (QD) | |

| Reporting group values | Part I - ESL | Part I - Placebo | Total |
|--|--------------|------------------|-------|
| Number of subjects | 83 | 40 | 123 |
| Age Categorical | | | |
| Age Categorical Characteristic | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | 0 |
| Preterm newborn- gestational age < 37 wk | 0 | 0 | 0 |
| Newborns (0-27days) | 0 | 0 | 0 |
| Infants and toddlers (28days – 23months) | 0 | 0 | 0 |
| Children (2-11 years) | 36 | 18 | 54 |
| Adolescents (12-17 year) | 47 | 22 | 69 |
| From 18 - 64 years | 0 | 0 | 0 |
| From 65 – 84 years | 0 | 0 | 0 |
| Over 85 years | 0 | 0 | 0 |
| Age Continuous | | | |
| Age Continuous Characteristic | | | |
| Units: Years | | | |
| arithmetic mean | 11.8 | 11.6 | |
| standard deviation | ± 3.14 | ± 2.79 | - |
| Gender Categorical | | | |
| Gender Categorical Characteristic | | | |
| Units: Subjects | | | |
| Female | 36 | 14 | 50 |
| Male | 47 | 26 | 73 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Part I - ESL |
| Reporting group description: Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day). | |
| Reporting group title | Part I - Placebo |
| Reporting group description: Placebo Once-Daily (QD) | |
| Reporting group title | Part II - ESL |
| Reporting group description: Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day). | |
| Reporting group title | Part III - ESL |
| Reporting group description: Eslicarbazepine acetate (BIA 2-093): ESL 10-30 mg/kg/day QD (maximum 1200 mg/day). | |
| Subject analysis set title | Part I - ESL x Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomized patients who received at least one dose of study treatment after randomization. | |
| Subject analysis set title | Part I - Placebo x Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All randomized patients who received at least one dose of study treatment after randomization. | |
| Subject analysis set title | Part II - ESL x Safety |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: All patients who entered Part II and who received at least one dose of study treatment. | |
| Subject analysis set title | Part I - ESL x Modified Cognitive ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline assessment of cognition. | |
| Subject analysis set title | Part I - Placebo x Modified Cognitive ITT |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline assessment of cognition. | |
| Subject analysis set title | Part I - ESL x Cognitive PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not IPDs with respect to the primary cognitive endpoint. | |
| Subject analysis set title | Part I - Placebo x Cognitive PP |
| Subject analysis set type | Per protocol |
| Subject analysis set description: All patients in the Modified Cognitive ITT population who completed the 8-week maintenance period and were not IPDs with respect to the primary cognitive endpoint. | |
| Subject analysis set title | Part I - ESL x Modified Efficacy ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment.

| | |
|----------------------------|--|
| Subject analysis set title | Part I - Placebo x Modified Efficacy ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All randomized patients who received at least one dose of study treatment after randomization and had at least one post-baseline seizure frequency assessment.

| | |
|----------------------------|---------------------------------------|
| Subject analysis set title | Part II - ESL x Modified Efficacy ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All patients who entered Part II, who received at least one dose of study treatment and had at least one post-baseline seizure frequency assessment during Part II

| | |
|----------------------------|-------------------------|
| Subject analysis set title | Part III - ESL x Safety |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All patients who entered Part III and who received at least one dose of study treatment.

| | |
|----------------------------|--|
| Subject analysis set title | Part III - ESL x Modified Efficacy ITT |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

All patients who entered Part III, who received at least one dose of study treatment and had at least one post-baseline Clinical Global Impression-Severity (CGI-S) scale assessment during Part III.

Primary: Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed.

| | |
|-----------------|---|
| End point title | Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed. |
|-----------------|---|

End point description:

Change from baseline to the end of the Part I (DB period) in the composite Power of Attention measure, in order to assess information processing speed and attention/psychomotor speed by treatment group for the Modified Cognitive ITT

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

End point timeframe:

From baseline to the end of the Part I

| End point values | Part I - ESL x Modified Cognitive ITT | Part I - Placebo x Modified Cognitive ITT | Part I - ESL x Cognitive PP | Part I - Placebo x Cognitive PP |
|--|---------------------------------------|---|-----------------------------|---------------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 73 | 37 | 59 | 33 |
| Units: Power of Attention measure arithmetic mean (standard deviation) | | | | |
| Baseline(V2) | 1733.976 (± 582.46) | 1724.103 (± 443.4066) | 1699.186 (± 531.0453) | 1759.848 (± 456.0726) |
| End of Part I | 1818.474 (± 605.688) | 1824.383 (± 568.5121) | 1759.485 (± 544.0179) | 1868.03 (± 584.2275) |

| | | | | |
|---------------------------------------|--------------------------|---------------------------|--------------------------|---------------------------|
| Change from Baseline at End of Part I | 84.013 (\pm 403.3595) | 101.937 (\pm 422.4147) | 59.122 (\pm 403.4904) | 111.085 (\pm 445.6327) |
|---------------------------------------|--------------------------|---------------------------|--------------------------|---------------------------|

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Non-Inferiority: ESL vs Placebo Mod. Cognitive ITT |
| Statistical analysis description: | |
| Analysis of change from baseline at end of double-blind period based on an ANCOVA model including treatment and country as fixed effects, baseline Power of Attention (ms) score and sex as covariates. | |
| Comparison groups | Part I - ESL x Modified Cognitive ITT v Part I - Placebo x Modified Cognitive ITT |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.977 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | -2.2085 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -154.451 |
| upper limit | 150.034 |

| | |
|---|---|
| Statistical analysis title | Non-Inferiority: ESL vs Placebo Cognitive PP |
| Statistical analysis description: | |
| Analysis of change from baseline at end of double-blind period based on an ANCOVA model including treatment and country as fixed effects, baseline Power of Attention (ms) score and sex as covariates. | |
| Comparison groups | Part I - ESL x Cognitive PP v Part I - Placebo x Cognitive PP |
| Number of subjects included in analysis | 92 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.7 |
| Method | ANCOVA |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 33.2001 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -137.593 |
| upper limit | 203.993 |

Secondary: Change From Baseline in Standardized Seizure Frequency- Part I

| | |
|-----------------|--|
| End point title | Change From Baseline in Standardized Seizure Frequency- Part I |
|-----------------|--|

End point description:

Standardized seizure frequency change from baseline in Part I by treatment group for the Modified Efficacy ITT

End point type Secondary

End point timeframe:

Baseline, Maintenance Period

| End point values | Part I - ESL x Modified Efficacy ITT | Part I - Placebo x Modified Efficacy ITT | | |
|--------------------------------------|--------------------------------------|--|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 83 | 40 | | |
| Units: Number of seizures | | | | |
| arithmetic mean (standard deviation) | | | | |
| Number of seizures | -31.03 (\pm 87.963) | -9.13 (\pm 75.602) | | |

Statistical analyses

Statistical analysis title Equivalence: ESL vs Placebo Mod. Efficacy ITT

Statistical analysis description:

Results from the non-parametric analysis are based on an ANCOVA model on ranked data with ranked baseline, age group and sex as covariates and treatment and country as fixed effects.

Comparison groups Part I - ESL x Modified Efficacy ITT v Part I - Placebo x Modified Efficacy ITT

Number of subjects included in analysis 123

Analysis specification Pre-specified

Analysis type equivalence

P-value < 0.001

Method ANCOVA

Secondary: Change From Baseline in Seizure Frequency During OL period (Part II)

End point title Change From Baseline in Seizure Frequency During OL period (Part II)

End point description:

Standardized seizure frequency change from baseline during OL period (Part II) for the Modified Efficacy ITT

End point type Secondary

End point timeframe:

Weeks 1 to \geq 41 weeks

| End point values | Part II - ESL x Modified Efficacy ITT | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 112 | | | |
| Units: Number of seizures | | | | |
| arithmetic mean (standard deviation) | | | | |
| Number of seizures | -3.03 (± 31.37) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment retention time as actual time treated (Part III)

| | |
|---|--|
| End point title | Treatment retention time as actual time treated (Part III) |
| End point description: Treatment retention time as actual time on treatment during Part III of the study using Kaplan-Meier methods for the Modified Efficacy ITT | |
| End point type | Secondary |
| End point timeframe: 2 years | |

| End point values | Part III - ESL x Modified Efficacy ITT | | | |
|----------------------------------|--|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 41 | | | |
| Units: Treatment retention time | | | | |
| median (confidence interval 95%) | | | | |
| Overall | 735 (728 to 741) | | | |
| 6-11 years | 738 (716 to 770) | | | |
| 12-16 years | 735 (728 to 755) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: CGI-S scale change from baseline (Part III)

| | |
|---|---|
| End point title | CGI-S scale change from baseline (Part III) |
| End point description: Change from baseline (OL7) to last assessment in continuous CGI-S scale score during the 2-year open-label extension for the Modified Efficacy ITT | |
| End point type | Secondary |

End point timeframe:

2 years

| | | | | |
|--------------------------------------|--|--|--|--|
| End point values | Part III - ESL x Modified Efficacy ITT | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 41 | | | |
| Units: CGI-S Scale Score | | | | |
| arithmetic mean (standard deviation) | | | | |
| Severity of Illness | -0.5 (± 0.85) | | | |
| Global Improvement | -0.1 (± 0.69) | | | |
| Therapeutic Effect | 0 (± 0.56) | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up to 28 days after the completion of the study.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 13.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------|
| Reporting group title | Part I - ESL x Safety |
|-----------------------|-----------------------|

Reporting group description:

Subject in the Safety Set treated with ESL in Part I

| | |
|-----------------------|-------------------------|
| Reporting group title | Part III - ESL x Safety |
|-----------------------|-------------------------|

Reporting group description:

Subject in the Safety Set treated with ESL in Part III

| | |
|-----------------------|------------------------|
| Reporting group title | Part II - ESL x Safety |
|-----------------------|------------------------|

Reporting group description:

Subject in the Safety Set treated with ESL in Part II

| | |
|-----------------------|---------------------------|
| Reporting group title | Part I - Placebo x Safety |
|-----------------------|---------------------------|

Reporting group description:

Subject in the Safety Set treated with Placebo in Part I

| Serious adverse events | Part I - ESL x Safety | Part III - ESL x Safety | Part II - ESL x Safety |
|---|-----------------------|-------------------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 2 / 42 (4.76%) | 8 / 112 (7.14%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Mitral valve incompetence | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (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 |
| Surgical and medical procedures | | | |
| Brain operation | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (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 |
| Nervous system disorders | | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (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 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 3 / 112 (2.68%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Status epilepticus | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatitis infectious mononucleosis | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (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 |

| Serious adverse events | Part I - Placebo x Safety | | |
|---|------------------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Injury, poisoning and procedural complications | | | |
| Radius fracture | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Mitral valve incompetence | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Surgical and medical procedures | | | |
| Brain operation | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status epilepticus | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatitis infectious mononucleosis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|----------------|--|--|
| Metabolism and nutrition disorders | | | |
| Type 1 diabetes mellitus | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Part I - ESL x Safety | Part III - ESL x Safety | Part II - ESL x Safety |
|---|-----------------------|-------------------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 33 / 83 (39.76%) | 8 / 42 (19.05%) | 41 / 112 (36.61%) |
| Vascular disorders | | | |
| Pallor | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Feeling abnormal | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Irritability | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 1 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 3 / 42 (7.14%) | 4 / 112 (3.57%) |
| occurrences (all) | 1 | 3 | 6 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Reproductive system and breast disorders | | | |
| Hypomenorrhoea | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------|----------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 2 / 42 (4.76%) | 2 / 112 (1.79%) |
| occurrences (all) | 0 | 2 | 2 |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Apathy | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nervousness | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Electrocardiogram T wave abnormal | | | |

| | | | |
|---|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Excoriation subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Face injury subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Foot fracture subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 1 / 42 (2.38%) 1 | 0 / 112 (0.00%) 0 |
| Head injury subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 2 / 112 (1.79%) 2 |
| Skin laceration subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Thermal burn subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Cardiac disorders | | | |
| Ventricular extrasystoles subjects affected / exposed occurrences (all) | 1 / 83 (1.20%) 1 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Nervous system disorders | | | |
| Ataxia subjects affected / exposed occurrences (all) | 1 / 83 (1.20%) 1 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Convulsion | | | |

| | | | |
|--------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 0 / 42 (0.00%) | 2 / 112 (1.79%) |
| occurrences (all) | 3 | 0 | 2 |
| Headache | | | |
| subjects affected / exposed | 8 / 83 (9.64%) | 1 / 42 (2.38%) | 6 / 112 (5.36%) |
| occurrences (all) | 8 | 1 | 7 |
| Hemianopia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mental retardation | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Monocytosis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 3 / 112 (2.68%) |
| occurrences (all) | 0 | 0 | 3 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vertigo | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Eye disorders | | | |
| Astigmatism | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diplopia | | | |
| subjects affected / exposed | 3 / 83 (3.61%) | 0 / 42 (0.00%) | 2 / 112 (1.79%) |
| occurrences (all) | 4 | 0 | 2 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 5 | 0 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 83 (2.41%) | 0 / 42 (0.00%) | 2 / 112 (1.79%) |
| occurrences (all) | 2 | 0 | 4 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 83 (6.02%) | 0 / 42 (0.00%) | 4 / 112 (3.57%) |
| occurrences (all) | 6 | 0 | 5 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis allergic | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 4 / 83 (4.82%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 5 | 0 | 1 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypothalamo-pituitary disorder | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypothyroidism | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 2 / 112 (1.79%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|----------------------------------|----------------|----------------|-----------------|
| Bronchitis | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 3 / 112 (2.68%) |
| occurrences (all) | 1 | 0 | 3 |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 2 / 112 (1.79%) |
| occurrences (all) | 2 | 0 | 2 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 1 | 0 | 1 |
| Herpes simplex | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 3 / 112 (2.68%) |
| occurrences (all) | 1 | 0 | 3 |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 0 / 112 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 3 / 112 (2.68%) |
| occurrences (all) | 0 | 1 | 3 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 0 / 42 (0.00%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 0 | 1 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 83 (0.00%) | 1 / 42 (2.38%) | 1 / 112 (0.89%) |
| occurrences (all) | 0 | 1 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 83 (1.20%) | 0 / 42 (0.00%) | 0 / 112 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|----------------------|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 83 (4.82%) 4 | 0 / 42 (0.00%) 0 | 3 / 112 (2.68%) 3 |
| Respiratory tract infection viral subjects affected / exposed occurrences (all) | 3 / 83 (3.61%) 3 | 1 / 42 (2.38%) 1 | 5 / 112 (4.46%) 5 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Rubella subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Scarlet fever subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Varicella subjects affected / exposed occurrences (all) | 1 / 83 (1.20%) 1 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 0 / 83 (0.00%) 0 | 0 / 42 (0.00%) 0 | 1 / 112 (0.89%) 1 |
| Obesity subjects affected / exposed occurrences (all) | 1 / 83 (1.20%) 1 | 0 / 42 (0.00%) 0 | 0 / 112 (0.00%) 0 |

| | | | |
|---|------------------------------|--|--|
| Non-serious adverse events | Part I - Placebo x Safety | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 19 / 40 (47.50%) | | |
| Vascular disorders Pallor subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |
| General disorders and administration | | | |

| | | | |
|---|----------------|--|--|
| site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Feeling abnormal | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Irritability | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Reproductive system and breast disorders | | | |
| Hypomenorrhoea | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Cough | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Respiratory disorder | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Apathy | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 2 | | |
| Nervousness | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood creatine phosphokinase increased | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Electrocardiogram QT prolonged | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Electrocardiogram T wave abnormal | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |
| Arthropod sting | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Excoriation | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Face injury | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Foot fracture | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Head injury | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin laceration | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thermal burn | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cardiac disorders | | | |
| Ventricular extrasystoles | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Headache | | | |
| subjects affected / exposed | 6 / 40 (15.00%) | | |
| occurrences (all) | 8 | | |
| Hemianopia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Mental retardation | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Somnolence | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 2 / 40 (5.00%) 2 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Monocytosis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Splenomegaly | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |
| Astigmatism | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |

| | | | |
|--|----------------|--|--|
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastritis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 2 | | |
| Vomiting | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 2 | | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |
| Endocrine disorders | | | |
| Autoimmune thyroiditis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypothalamo-pituitary disorder | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypothyroidism | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Acute tonsillitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Chronic tonsillitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Ear infection | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal viral infection | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Herpes simplex | | | |

| | | | |
|-----------------------------------|----------------|--|--|
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Influenza | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 2 / 40 (5.00%) | | |
| occurrences (all) | 3 | | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 1 / 40 (2.50%) | | |
| occurrences (all) | 1 | | |
| Rubella | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Scarlet fever | | | |
| subjects affected / exposed | 0 / 40 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |
| Varicella subjects affected / exposed occurrences (all) | 1 / 40 (2.50%) 1 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |
| Obesity subjects affected / exposed occurrences (all) | 0 / 40 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 16 April 2010 | Amendment 1: <ul style="list-style-type: none">•The list of participating countries were changed.•The list of Inclusion/exclusion criterion was updated.•Some wording and definitions in the protocol was changed•A few tests were added to the applicable study visits.•A few analyses were clarified/ updated/ added. |
| 24 March 2011 | Amendment 2: <ul style="list-style-type: none">•The list of Inclusion/exclusion criterion was updated.•Some therapy was deleted/added.•Clarification for some procedures, IMP dosing and concomitant medication use were added.•Changed subject(s) to patient(s) throughout the protocol except in the Introduction. |
| 03 October 2011 | Amendment 3: <ul style="list-style-type: none">•Added an additional two-year, OL treatment extension (Part III) with ESL.•Added changes arising from the inclusion of Part III.• Criteria for patient withdrawal/Statistical analysis/Informed Consent and Assent were updated. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported