



## Clinical trial results:

**Clinical Evaluation of lamotrigine in Epilepsy-Mutual Recognition-D2012-6595-Study only identified as requiring Article 46 submission-30 July 2012 (as part of r/co-administration retrospective exercise)**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2015-004901-18 |
| Trial protocol           | Outside EU/EEA |
| Global end of trial date | 26 March 2009  |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 23 December 2016 |
| First version publication date | 23 December 2016 |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | LAM107844 |
|-----------------------|-----------|

#### Additional study identifiers

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

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GlaxoSmithKline  |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact               | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |
| Scientific contact           | GSK Response Center, GlaxoSmithKline, 1 866-435-7343,      |

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? | Yes |

Notes:

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**Results analysis stage**

|  |               |
|--|---------------|
| Analysis stage                                       | Final         |
| Date of interim/final analysis                       | 11 June 2009  |
| Is this the analysis of the primary completion data? | Yes           |
| Primary completion date                              | 26 March 2009 |
| Global end of trial reached?                         | Yes           |
| Global end of trial date                             | 26 March 2009 |
| Was the trial ended prematurely?                     | No            |

Notes:

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**General information about the trial**

Main objective of the trial:

TBD

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 07 August 2006 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | No             |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |            |
|--------------------------------------|------------|
| Country: Number of subjects enrolled | Japan: 102 |
| Worldwide total number of subjects   | 102        |
| EEA total number of subjects         | 0          |

Notes:

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**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)                     | 35 |
| Adolescents (12-17 years)                 | 22 |
| Adults (18-64 years)                      | 45 |
| From 65 to 84 years                       | 0  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 102 participants were enrolled in the study. Of these, 99 participants completed the maintenance phase, and 97 participants entered the continuation phase.

### Period 1

|                              |                                      |
|------------------------------|--------------------------------------|
| Period 1 title               | Escalation Phase + Maintenance Phase |
| Is this the baseline period? | Yes                                  |
| Allocation method            | Not applicable                       |
| Blinding used                | Not blinded                          |

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Adults: LTG |

Arm description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | BW430C (Lamotrigine) 2 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 5 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 25 mg  |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 100 mg |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Adolescents: LTG |
|------------------|------------------|

Arm description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | BW430C (Lamotrigine) 2 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 5 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 25 mg  |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 100 mg |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

| Number of subjects in period 1 | Adults: LTG | Adolescents: LTG |
|--------------------------------|-------------|------------------|
| Started                        | 51          | 51               |
| Completed                      | 50          | 49               |
| Not completed                  | 1           | 2                |
| Adverse event, non-fatal       | 1           | 2                |

## Period 2

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

## Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Adults: LTG |

### Arm description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | BW430C (Lamotrigine) 2 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

### Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 5 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

### Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 25 mg  |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

### Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and

adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 100 mg |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|                  |                  |
|------------------|------------------|
| <b>Arm title</b> | Adolescents: LTG |
|------------------|------------------|

Arm description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

|  |                             |
|--|-----------------------------|
| Arm type                               | Experimental                |
| Investigational medicinal product name | BW430C (Lamotrigine) 2 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 5 mg   |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 25 mg  |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

|  |                             |
|--|-----------------------------|
| Investigational medicinal product name | BW430C (Lamotrigine) 100 mg |
| Investigational medicinal product code |                             |
| Other name                             |                             |
| Pharmaceutical forms                   | Chewable/dispersible tablet |
| Routes of administration               | Oral use                    |

Dosage and administration details:

BW430C (Lamotrigine) tablet taken orally once daily or twice daily depending on study phase and adjusted dose.

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Adults: LTG | Adolescents: LTG |
|---|-------------|------------------|
| Started   | 49          | 48               |
| Completed   | 34          | 35               |
| Not completed                                       | 15          | 13               |
| Consent withdrawn by subject                        | -           | 2                |
| Adverse event, non-fatal                            | 1           | -                |
| Withdrawal Due to Wishes of Family                  | 1           | -                |
| Poor Compliance                                     | 1           | -                |
| Lack of efficacy                                    | 12          | 11               |

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Notes:

[1] - 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: A total of 99 participants (50 adults and 49 children) completed the maintenance phase. Of these, 97 participants (49 adults and 48 children) entered the continuation phase and 2 participants (1 adult and 1 child) discontinued the study due to lack of efficacy.

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Adults: LTG |
|-----------------------|-------------|

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Adolescents: LTG |
|-----------------------|------------------|

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

| Reporting group values | Adults: LTG | Adolescents: LTG | Total |
|------------------------|-------------|------------------|-------|
| Number of subjects     | 51          | 51               | 102   |
| Age categorical        |             |                  |       |
| Units: Subjects        |             |                  |       |

|                            |       |       |     |
|----------------------------|-------|-------|-----|
| Age continuous             |       |       |     |
| Units: years               |       |       |     |
| arithmetic mean            | 29    | 8.2   |     |
| standard deviation         | ± 9.9 | ± 4.1 | -   |
| Gender categorical         |       |       |     |
| Units: Subjects            |       |       |     |
| Female                     | 23    | 25    | 48  |
| Male                       | 28    | 26    | 54  |
| Race/Ethnicity, Customized |       |       |     |
| Units: Subjects            |       |       |     |
| Asian-Japanese             | 51    | 51    | 102 |



## End points

### End points reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Adults: LTG |
|-----------------------|-------------|

#### Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Adolescents: LTG |
|-----------------------|------------------|

#### Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

|                       |             |
|-----------------------|-------------|
| Reporting group title | Adults: LTG |
|-----------------------|-------------|

#### Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Adolescents: LTG |
|-----------------------|------------------|

#### Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

|                            |            |
|----------------------------|------------|
| Subject analysis set title | Total: LTG |
|----------------------------|------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

#### Subject analysis set description:

Adult participants were initiated on 12.5 mg/day, and adolescents were initiated on 0.15 mg/kg/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking VPA or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. During the MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

**Primary: Number of participants with any rash event (including Stevens–Johnson syndrome [SJS] and any other serious drug eruption) during the initial 8 weeks of study treatment**

|                 |   |
|-----------------|---|
| End point title | Number of participants with any rash event (including Stevens–Johnson syndrome [SJS] and any other serious drug eruption) during the initial 8 weeks of study treatment |
|-----------------|---|

## End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

Safety Population: all participants enrolled in the study who received at least one dose of study medication

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

End point timeframe:

8 weeks

| End point values            | Adults: LTG       | Adolescents: LTG  | Total: LTG           |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 51 <sup>[1]</sup> | 51 <sup>[2]</sup> | 102 <sup>[3]</sup>   |  |
| Units: participants         | 2                 | 3                 | 5                    |  |

Notes:

[1] - Safety Population

[2] - Safety Population

[3] - Safety Population

**Statistical analyses**

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

The estimated value represents the percentage of participants with rash events.

|   |   |
|---|---|
| Comparison groups                       | Adults: LTG v Adolescents: LTG v Total: LTG |
| Number of subjects included in analysis | 204   |
| Analysis specification                  | Pre-specified                               |
| Analysis type                           | other                                       |
| Parameter estimate                      | Percentage of participants                  |
| Point estimate                          | 4.9   |
| Confidence interval                     |   |
| level                                   | 95 %  |
| sides                                   | 2-sided                                     |
| lower limit                             | 1.6   |
| upper limit                             | 11.1  |

**Primary: Number of participants with any rash event (including SJS and any other serious drug eruption) up to the end of the maintenance phase**

|                 |   |
|-----------------|---|
| End point title | Number of participants with any rash event (including SJS and |
|-----------------|---|

any other serious drug eruption) up to the end of the maintenance phase<sup>[4]</sup>

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

End point type Primary

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

Notes:

[4] - 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: There are no statistical data to report

| End point values            | Adults: LTG       | Adolescents: LTG  | Total: LTG           |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 51 <sup>[5]</sup> | 51 <sup>[6]</sup> | 102 <sup>[7]</sup>   |  |
| Units: participants         | 2                 | 3                 | 5                    |  |

Notes:

[5] - Safety Population

[6] - Safety Population

[7] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of rash events experienced (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

|                 |   |
|-----------------|---|
| End point title | Number of rash events experienced (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment |
|-----------------|---|

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

End point type Secondary

End point timeframe:

8 weeks

| End point values            | Adults: LTG      | Adolescents: LTG | Total: LTG           |  |
|-----------------------------|------------------|------------------|----------------------|--|
| Subject group type          | Reporting group  | Reporting group  | Subject analysis set |  |
| Number of subjects analysed | 2 <sup>[8]</sup> | 3 <sup>[9]</sup> | 5 <sup>[10]</sup>    |  |
| Units: rash events          | 3                | 4                | 7                    |  |

Notes:

[8] - Safety Population

[9] - Safety Population

[10] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

|                 |   |
|-----------------|---|
| End point title | Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment |
|-----------------|---|

End point description:

The rash events (including SJS and any other serious drug eruption) were classified into severe (rash prevents participant from leading a normal life), moderate (participant's discomfort due to rash interferes with daily life), and mild (no interference with participant's daily life due to rash), based on the intensity of the event.

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

End point timeframe:

8 weeks

| End point values            | Total: LTG           |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 5 <sup>[11]</sup>    |  |  |  |
| Units: participants         |                      |  |  |  |
| Severe                      | 0                    |  |  |  |
| Moderate                    | 2                    |  |  |  |
| Mild                        | 3                    |  |  |  |

Notes:

[11] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of drug-related and not related rash events (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment

|                 |  |
|-----------------|--|
| End point title | Number of drug-related and not related rash events (including SJS and any other serious drug eruption) during the initial 8 weeks of study treatment |
|-----------------|--|

End point description:

The adverse event of rash was considered to be drug-related when the Investigator answered "Yes" to the following question: "Is there a reasonable possibility that the adverse event may have been caused by the investigational product?".

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

End point timeframe:

8 weeks

| End point values            | Total: LTG           |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 5 <sup>[12]</sup>    |  |  |  |
| Units: rash events          |                      |  |  |  |
| Drug related                | 3                    |  |  |  |
| Not related to drug         | 4                    |  |  |  |

Notes:

[12] - Safety Population

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of participants with at least a 50 percent reduction in seizure frequency for the indicated types of seizures

|                 |  |
|-----------------|--|
| End point title | Percentage of participants with at least a 50 percent reduction in seizure frequency for the indicated types of seizures |
|-----------------|--|

End point description:

Partial seizures are seizures that affect only a part of the brain at onset. Tonic-clonic seizures (grand mal seizures) affect the entire brain and are characterized by a generalized involuntary muscular contraction and cessation of respiration followed by tonic and clonic spasms of the muscles. Lennox-Gastaut syndrome (LGS) is a pediatric epilepsy syndrome characterized by multiple seizure types; mental retardation or regression; and abnormal findings on an electroencephalogram (EEG), with paroxysms of fast activity and generalized slow spike-and-wave discharges.

Full Analysis Set (FAS) Population: all enrolled participants except those who had no assessments of the main efficacy variable (percent reduction in seizure frequency).

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

End point timeframe:

8 weeks

| End point values                            | Adults: LTG        | Adolescents: LTG   | Total: LTG           |  |
|---|--------------------|--------------------|----------------------|--|
| Subject group type                          | Reporting group    | Reporting group    | Subject analysis set |  |
| Number of subjects analysed                 | 28 <sup>[13]</sup> | 25 <sup>[14]</sup> | 53 <sup>[15]</sup>   |  |
| Units: percentage of participants           |                    |                    |                      |  |
| number (not applicable)                     |                    |                    |                      |  |
| All Partial Seizures, n=28, 25, 53          | 17.9               | 20                 | 18.9                 |  |
| Tonic-clonic Seizures, n=5, 4, 9            | 60                 | 0                  | 33.3                 |  |
| Generalized Seizures with LGS, n=25, 25, 50 | 16                 | 20                 | 18                   |  |

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent change in seizure frequency of the indicated types of seizures

|                 |  |
|-----------------|--|
| End point title | Percent change in seizure frequency of the indicated types of seizures |
|-----------------|--|

End point description:

Percent change in seizure frequency was calculated as  $100 * (\text{pre-treatment seizures minus MP seizures}) / \text{pre-treatment seizures}$ . Partial seizures are seizures that affect only a part of the brain at onset. Tonic-clonic seizures (grand mal seizures) affect the entire brain and are characterized by a generalized involuntary muscular contraction and cessation of respiration followed by tonic and clonic spasms of the muscles. Lennox-Gastaut syndrome (LGS) is a pediatric epilepsy syndrome characterized by multiple seizure types, mental retardation or regression, and abnormal findings on an ECG.

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

End point timeframe:

Pre-treatment (Day 0) and Week 8 of the Maintenance Phase (Study Week 14)

| End point values                            | Adults: LTG            | Adolescents: LTG       | Total: LTG           |  |
|---|------------------------|------------------------|----------------------|--|
| Subject group type                          | Reporting group        | Reporting group        | Subject analysis set |  |
| Number of subjects analysed                 | 28 <sup>[16]</sup>     | 25 <sup>[17]</sup>     | 53 <sup>[18]</sup>   |  |
| Units: percent change                       |                        |                        |                      |  |
| median (confidence interval 95%)            |                        |                        |                      |  |
| All Partial Seizures, n=28, 25, 53          | 6.3 (-44.8 to 28.7)    | -11.1 (-46.6 to 34.6)  | -9.8 (-42.3 to 28.6) |  |
| Tonic-clonic Seizures, n=5, 4, 9            | 83.3 (-99999 to 99999) | 27.4 (-99999 to 99999) | 36.5 (-47.9 to 100)  |  |
| Generalized Seizures with LGS, n=25, 25, 50 | 18.6 (-16.2 to 32.2)   | 10.1 (-24.9 to 28.8)   | 12.4 (5.8 to 27.6)   |  |

Notes:

[16] - FAS Population

[17] - FAS Population

[18] - FAS Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of rash events experienced (including SJS and any other serious drug eruption) up to the end of the maintenance phase

|                 |  |
|-----------------|--|
| End point title | Number of rash events experienced (including SJS and any other serious drug eruption) up to the end of the maintenance phase |
|-----------------|--|

End point description:

Any rash event (including SJS or any other serious drug eruption) includes: all event terms containing "rash"; drug eruption; SJS; toxic epidermal necrolysis; rash generalized; and events grouped into the "Skin and Subcutaneous Tissue Disorders" system organ class per the Medical Dictionary for Regulatory Activities (MedDRA), including the above-mentioned events that the GSK medical advisors judged to be included as any rash event. SJS, also called as erythema multiforme, is a skin disorder resulting from an allergic reaction or infection.

Safety Population. Only those participants who had experienced any rash event were evaluated.

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

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

| End point values            | Adults: LTG       | Adolescents: LTG  | Total: LTG           |  |
|-----------------------------|-------------------|-------------------|----------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed | 2 <sup>[19]</sup> | 3 <sup>[20]</sup> | 5 <sup>[21]</sup>    |  |
| Units: rash events          | 3                 | 4                 | 7                    |  |

Notes:

[19] - Safety Population

[20] - Safety Population

[21] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) up to the end of the maintenance phase

|                 |  |
|-----------------|--|
| End point title | Number of participants with the indicated intensity of rash (including SJS and any other serious drug eruption) up to the end of the maintenance phase |
|-----------------|--|

End point description:

The rash events (including SJS and any other serious drug eruption) were classified into severe (rash prevents participant from leading a normal life), moderate (participant's discomfort due to rash interferes with daily life), and mild (no interference with participant's daily life due to rash), based on the intensity of the event.

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

End point timeframe:

Up to Week 8 of the Maintenance Phase (Study Week 14)

| End point values            | Total: LTG           |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 5 <sup>[22]</sup>    |  |  |  |
| Units: participants         |                      |  |  |  |
| Severe                      | 0                    |  |  |  |
| Moderate                    | 2                    |  |  |  |
| Mild                        | 3                    |  |  |  |

Notes:

[22] - Safety Population

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of drug-related and not related rash events (including SJS and any other serious drug eruption) up to the end of the maintenance phase

|                 |   |
|-----------------|---|
| End point title | Number of drug-related and not related rash events (including SJS and any other serious drug eruption) up to the end of the maintenance phase |
|-----------------|---|

End point description:

The adverse event of rash was considered to be drug-related when the Investigator answered "Yes" to the following question: "Is there a reasonable possibility that the adverse event may have been caused by the investigational product?".

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                  |           |
| Up to Week 8 of the Maintenance Phase (Study Week 14) |           |

|                             |                      |  |  |  |
|-----------------------------|----------------------|--|--|--|
| <b>End point values</b>     | Total: LTG           |  |  |  |
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 5 <sup>[23]</sup>    |  |  |  |
| Units: rash events          |                      |  |  |  |
| Drug related                | 3                    |  |  |  |
| Not related to drug         | 4                    |  |  |  |

Notes:

[23] - Safety Population

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of rash events (including SJS and any other serious drug eruption) adjudicated by the rash adjudication committee in participants taking VPA

|                 |   |
|-----------------|---|
| End point title | Number of rash events (including SJS and any other serious drug eruption) adjudicated by the rash adjudication committee in participants taking VPA |
|-----------------|---|

End point description:

The rash adjudication committee reviewed all rash events from a dermatologic standpoint based on the nature, onset site, affected area, time to onset, outcome, and the investigator's comments to adjudicate whether or not the reported event was a drug eruption. A drug eruption is an eruption or a solitary lesion caused by a drug taken internally, often a result of allergic sensitization.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:                                  |           |
| Up to Week 8 of the Maintenance Phase (Study Week 14) |           |

|                                |                   |                   |                      |  |
|--------------------------------|-------------------|-------------------|----------------------|--|
| <b>End point values</b>        | Adults: LTG       | Adolescents: LTG  | Total: LTG           |  |
| Subject group type             | Reporting group   | Reporting group   | Subject analysis set |  |
| Number of subjects analysed    | 2 <sup>[24]</sup> | 3 <sup>[25]</sup> | 5 <sup>[26]</sup>    |  |
| Units: adjudicated rash events | 1                 | 2                 | 3                    |  |

Notes:

[24] - Safety Population

[25] - Safety Population

[26] - Safety Population

### Statistical analyses



No statistical analyses for this end point

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**Secondary: Percentage of participants with monocyte values outside the normal range (shifted high) at Weeks 4 and 8**

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|                 |  |
|-----------------|--|
| End point title | Percentage of participants with monocyte values outside the normal range (shifted high) at Weeks 4 and 8 |
|-----------------|--|

End point description:

Monocytes are a type of white blood cell (WBC; typically comprising 2%-8% of total WBCs) and are a part of the immune system. The normal range for adults is  $0.2$  to  $0.95 \times 10^3$  cells per microliter ( $\mu\text{L}$ ); the normal range for adolescents is  $0$  to  $0.8 \times 10^3$  cells per  $\mu\text{L}$ . The monocyte count may increase during chronic inflammation, stress response, immune-mediated disease, viral fever, etc. The percentage of participants (par.) with monocyte values outside the normal range was calculated as  $100 \times (\text{number of par. with monocyte values outside the normal range}) / \text{total number of par.}$

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

End point timeframe:

Week 4 and Week 8

---

| End point values                  | Total: LTG           |  |  |  |
|-----------------------------------|----------------------|--|--|--|
| Subject group type                | Subject analysis set |  |  |  |
| Number of subjects analysed       | 102 <sup>[27]</sup>  |  |  |  |
| Units: percentage of participants |                      |  |  |  |
| number (not applicable)           |                      |  |  |  |
| Week 4                            | 15.2                 |  |  |  |
| Week 8                            | 16.2                 |  |  |  |

Notes:

[27] - Safety Population

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

First day of study drug administration and the end of the maintenance phase-Week 8.

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 9.1 |
|--------------------|-----|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Adults: LTG |
|-----------------------|-------------|

Reporting group description:

Adult participants were initiated on 12.5 milligrams per day (mg/day) of BW430C (lamotrigine [LTG]) (as a tablet taken orally) once daily. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (maintenance phase [MP]). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking valproic acid (VPA) or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative antiepileptic drugs (AEDs) were available were allowed to continue treatment with LTG until the drug is marketed (continuation phase).

|                       |            |
|-----------------------|------------|
| Reporting group title | Total: LTG |
|-----------------------|------------|

Reporting group description:

Adult participants were initiated on 12.5 mg/day, and adolescents were initiated on 0.15 mg/kg/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, participants received up to a maximum of 200 mg/day for adults taking VPA or up to a maximum of 400 mg/day for adults not taking VPA plus an inducer of LTG glucuronidation. During the MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Adolescents: LTG |
|-----------------------|------------------|

Reporting group description:

Adolescent participants were initiated on 0.15 mg/kilogram (kg)/day. Participants had their dose increased to an optimal maintenance dose (escalation phase) and then were maintained at that dose for 8 weeks (MP). During the 8-week MP, adolescents taking VPA alone received up to a maximum of 3 mg/kg/day, adolescents taking VPA with an inducer of LTG glucuronidation received up to a maximum of 5 mg/kg/day, and adolescents not taking VPA with an inducer of LTG glucuronidation received up to a maximum of 15 mg/kg/day. Participants who achieved adequate seizure control at the end of the MP and for whom no alternative AEDs were available were allowed to continue treatment with BW430C until the drug is marketed (continuation phase).

| Serious adverse events                            | Adults: LTG    | Total: LTG      | Adolescents: LTG |
|---|----------------|-----------------|------------------|
| Total subjects affected by serious adverse events |                |                 |                  |
| subjects affected / exposed                       | 5 / 51 (9.80%) | 7 / 102 (6.86%) | 2 / 51 (3.92%)   |
| number of deaths (all causes)                     | 0              | 0               | 0                |
| number of deaths resulting from adverse events    | 0              | 0               | 0                |
| Injury, poisoning and procedural complications    |                |                 |                  |
| Therapeutic agent toxicity                        |                |                 |                  |

|  |                |                 |                |
|--|----------------|-----------------|----------------|
| subjects affected / exposed                          | 1 / 51 (1.96%) | 1 / 102 (0.98%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Nervous system disorders                             |                |                 |                |
| Somnolence   |                |                 |                |
| subjects affected / exposed                          | 1 / 51 (1.96%) | 1 / 102 (0.98%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Status epilepticus                                   |                |                 |                |
| subjects affected / exposed                          | 1 / 51 (1.96%) | 1 / 102 (0.98%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Convulsion   |                |                 |                |
| subjects affected / exposed                          | 0 / 51 (0.00%) | 1 / 102 (0.98%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| General disorders and administration site conditions |                |                 |                |
| Pyrexia  |                |                 |                |
| subjects affected / exposed                          | 0 / 51 (0.00%) | 1 / 102 (0.98%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 1           | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Gastrointestinal disorders                           |                |                 |                |
| Vomiting   |                |                 |                |
| subjects affected / exposed                          | 1 / 51 (1.96%) | 1 / 102 (0.98%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all      | 1 / 1          | 1 / 1           | 0 / 0          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Skin and subcutaneous tissue disorders               |                |                 |                |
| Drug eruption  |                |                 |                |
| subjects affected / exposed                          | 0 / 51 (0.00%) | 1 / 102 (0.98%) | 1 / 51 (1.96%) |
| occurrences causally related to treatment / all      | 0 / 0          | 1 / 1           | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0           | 0 / 0          |
| Infections and infestations                          |                |                 |                |
| Pneumonia  |                |                 |                |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed                     | 1 / 51 (1.96%) | 1 / 102 (0.98%) | 0 / 51 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1           | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Adults: LTG      | Total: LTG        | Adolescents: LTG |
|---|------------------|-------------------|------------------|
| Total subjects affected by non-serious adverse events |                  |                   |                  |
| subjects affected / exposed                           | 37 / 51 (72.55%) | 83 / 102 (81.37%) | 46 / 51 (90.20%) |
| Injury, poisoning and procedural complications        |                  |                   |                  |
| Contusion   |                  |                   |                  |
| subjects affected / exposed                           | 8 / 51 (15.69%)  | 12 / 102 (11.76%) | 4 / 51 (7.84%)   |
| occurrences (all)                                     | 9                | 13                | 4                |
| Arthropod sting                                       |                  |                   |                  |
| subjects affected / exposed                           | 1 / 51 (1.96%)   | 10 / 102 (9.80%)  | 9 / 51 (17.65%)  |
| occurrences (all)                                     | 1                | 16                | 15               |
| Excoriation   |                  |                   |                  |
| subjects affected / exposed                           | 6 / 51 (11.76%)  | 8 / 102 (7.84%)   | 2 / 51 (3.92%)   |
| occurrences (all)                                     | 6                | 8                 | 2                |
| Nervous system disorders                              |                  |                   |                  |
| Somnolence  |                  |                   |                  |
| subjects affected / exposed                           | 6 / 51 (11.76%)  | 17 / 102 (16.67%) | 11 / 51 (21.57%) |
| occurrences (all)                                     | 9                | 20                | 11               |
| Dizziness   |                  |                   |                  |
| subjects affected / exposed                           | 10 / 51 (19.61%) | 12 / 102 (11.76%) | 2 / 51 (3.92%)   |
| occurrences (all)                                     | 11               | 13                | 2                |
| General disorders and administration site conditions  |                  |                   |                  |
| Pyrexia   |                  |                   |                  |
| subjects affected / exposed                           | 7 / 51 (13.73%)  | 12 / 102 (11.76%) | 5 / 51 (9.80%)   |
| occurrences (all)                                     | 7                | 13                | 6                |
| Gastrointestinal disorders                            |                  |                   |                  |
| Diarrhoea   |                  |                   |                  |
| subjects affected / exposed                           | 3 / 51 (5.88%)   | 14 / 102 (13.73%) | 11 / 51 (21.57%) |
| occurrences (all)                                     | 3                | 16                | 13               |
| Vomiting  |                  |                   |                  |

|   |                        |                         |                        |
|---|------------------------|-------------------------|------------------------|
| subjects affected / exposed<br>occurrences (all)  | 3 / 51 (5.88%)<br>3    | 10 / 102 (9.80%)<br>13  | 7 / 51 (13.73%)<br>10  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 3 / 51 (5.88%)<br>3    | 7 / 102 (6.86%)<br>7    | 4 / 51 (7.84%)<br>4    |
| Respiratory, thoracic and mediastinal disorders<br>Upper respiratory tract inflammation<br>subjects affected / exposed<br>occurrences (all) | 5 / 51 (9.80%)<br>6    | 20 / 102 (19.61%)<br>27 | 15 / 51 (29.41%)<br>21 |
| Skin and subcutaneous tissue disorders<br>Erythema<br>subjects affected / exposed<br>occurrences (all)                                      | 1 / 51 (1.96%)<br>3    | 7 / 102 (6.86%)<br>11   | 6 / 51 (11.76%)<br>8   |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 10 / 51 (19.61%)<br>12 | 24 / 102 (23.53%)<br>33 | 14 / 51 (27.45%)<br>21 |

## **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