# Clinical trial results:
# Phase 3b Study for Management of Ocular Side Effects in Subjects with EGFR-amplified Glioblastoma Receiving Depatuxizumab Mafodotin (ABT-414)

## Summary

| | |
|---|---|
| EudraCT number | 2017-003171-64 |
| Trial protocol | GB NL DE |
| Global end of trial date | 03 March 2020 |

**Results information**

| | |
|---|---|
| Result version number | v1 |
| This version publication date | 04 March 2021 |
| First version publication date | 04 March 2021 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | M16-534 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03419403 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | AbbVie |
| Sponsor organisation address | AbbVie House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB |
| Public contact | AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com |
| Scientific contact | AbbVie, Global Medical Services, 001 8006339110, abbvieclinicaltrials@abbvie.com |

Notes:

**Paediatric regulatory details**

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

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 03 March 2020 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 03 March 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The objective of this Phase 3b open-label, randomized, exploratory study was to evaluate the effect of several ophthalmologic prophylactic treatment strategies for the management of ocular side effects (OSEs) in subjects with epidermal growth factor receptor (EGFR)-amplified glioblastoma (GBM) treated with depatuxizumab mafodotin (ABT-414). All subjects received ABT-414 during both phases of the treatment period plus 1 of 3 prophylactic ophthalmologic treatments (standard steroids; standard steroids with vasoconstrictors and cold compress; and enhanced steroids with vasoconstrictors and cold compress. The study had a screening period of up to 7 weeks after surgery, a 6-week concomitant Chemoradiation Phase (radiation plus temozolomide [RT/TMZ]), an Adjuvant Phase (TMZ) beginning approximately 4 weeks after completion of chemoradiation, and a Follow-Up Phase. The study was terminated because clinical development of ABT-414 in glioblastoma was stopped due to lack of survival benefit.

Protection of trial subjects:

Subjects must have voluntarily signed and dated an informed consent form, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 30 July 2018 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Germany: 1 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Country: Number of subjects enrolled | United States: 30 |
| Worldwide total number of subjects | 40 |
| EEA total number of subjects | 1 |

Notes:

### Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |

| | |
|---|---|
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 33 |
| From 65 to 84 years | 7 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All randomized subjects; two subjects were randomized to the study but received no doses of depatuxizumab mafodotin or prophylactic eye treatments.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Standard Steroids |

Arm description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Steroid eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Intraocular use |

Dosage and administration details:

1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days;

| | |
|---|---|
| Investigational medicinal product name | Depatuxizumab mafodotin |
| Investigational medicinal product code | |
| Other name | ABT-414 |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

During the Chemoradiation Phase, participants were to receive depatuxizumab mafodotin at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). During the Adjuvant Therapy Phase, participants were to receive depatuxizumab mafodotin at 1.25 mg/kg on Day 1 (± 2 days) and Day 15 (± 2 days) of each 28-day cycle as a 30 – 40 minute infusion for 12 cycles.

| | |
|---|---|
| Investigational medicinal product name | Temozolomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Temozolomide was to be administered according to the local standard of care. Duration of treatment was to be 6 – 12 cycles in the adjuvant phase and at the discretion of the investigator as supported by local standard of care.

| | |
|---|---|
| **Arm title** | Standard Steroids + Vasoconstrictor + Cold Compress |

Arm description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin

infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the participant was uncomfortable).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Steroid eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Intraocular use |

Dosage and administration details:

1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days;

| | |
|---|---|
| Investigational medicinal product name | Vasoconstrictor eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Intraocular use |

Dosage and administration details:

1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion;

| | |
|---|---|
| Investigational medicinal product name | Depatuxizumab mafodotin |
| Investigational medicinal product code | |
| Other name | ABT-414 |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

During the Chemoradiation Phase, participants were to receive depatuxizumab mafodotin at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). During the Adjuvant Therapy Phase, participants were to receive depatuxizumab mafodotin at 1.25 mg/kg on Day 1 (± 2 days) and Day 15 (± 2 days) of each 28-day cycle as a 30 – 40 minute infusion for 12 cycles.

| | |
|---|---|
| Investigational medicinal product name | Temozolomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Temozolomide was to be administered according to the local standard of care. Duration of treatment was to be 6 – 12 cycles in the adjuvant phase and at the discretion of the investigator as supported by local standard of care.

| | |
|---|---|
| **Arm title** | Enhanced Steroids + Vasoconstrictor + Cold Compress |

Arm description:

Enhanced steroid eye drops: 1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Ophthalmic Steroid Ointment; applied to each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. Cold compress was to be applied

in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Steroid eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Intraocular use |

Dosage and administration details:

1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days;

| | |
|---|---|
| Investigational medicinal product name | Vasoconstrictor eye drops |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Intraocular use |

Dosage and administration details:

1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion;

| | |
|---|---|
| Investigational medicinal product name | Ophthalmic steroid ointment |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Ocular use |

Dosage and administration details:

Applied to each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days;

| | |
|---|---|
| Investigational medicinal product name | Depatuxizumab mafodotin |
| Investigational medicinal product code | |
| Other name | ABT-414 |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

During the Chemoradiation Phase, participants were to receive depatuxizumab mafodotin at 2.0 mg/kg IV infusion over 30 – 40 minutes once every 2 weeks (Day 1 of Weeks 1, 3, and 5 of the 6-week regimen). During the Adjuvant Therapy Phase, participants were to receive depatuxizumab mafodotin at 1.25 mg/kg on Day 1 (± 2 days) and Day 15 (± 2 days) of each 28-day cycle as a 30 – 40 minute infusion for 12 cycles.

| | |
|---|---|
| Investigational medicinal product name | Temozolomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Temozolomide was to be administered according to the local standard of care. Duration of treatment was to be 6 – 12 cycles in the adjuvant phase and at the discretion of the investigator as supported by local standard of care.

| **Number of subjects in period 1[1]** | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress |
|---|---|---|---|
| Started | 14 | 12 | 12 |
| Completed | 2 | 3 | 0 |
| Not completed | 12 | 9 | 12 |
| Left study due to COVID-19 restrictions | 1 | 1 | - |
| Progressive disease (per protocol) | - | 2 | 2 |
| Other, not specified | 6 | 4 | 5 |
| Withdrawal by subject | 5 | 2 | 5 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two subjects were randomized to the study but received no doses of depatuxizumab mafodotin or prophylactic eye treatments and are not included in any treatment group.

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Standard Steroids |
| Reporting group description: | |
| Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days | |
| Reporting group title | Standard Steroids + Vasoconstrictor + Cold Compress |
| Reporting group description: | |
| Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the participant was uncomfortable). | |
| Reporting group title | Enhanced Steroids + Vasoconstrictor + Cold Compress |
| Reporting group description: | |
| Enhanced steroid eye drops: 1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Ophthalmic Steroid Ointment; applied to each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. Cold compress was to be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable). | |

| **Reporting group values** | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress |
|---|---|---|---|
| Number of subjects | 14 | 12 | 12 |
| Age categorical<br>Units: Subjects | | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 47.6 | 55.2 | 57.3 |
| standard deviation | ± 9.85 | ± 10.53 | ± 8.69 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 3 | 4 | 1 |
| Male | 11 | 8 | 11 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 38 | | |
| Age categorical<br>Units: Subjects | | | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | -<br> | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 8 | | |
| Male | 30 | | |

## End points

### End points reporting groups

| Reporting group title | Standard Steroids |
|---|---|

Reporting group description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days

| Reporting group title | Standard Steroids + Vasoconstrictor + Cold Compress |
|---|---|

Reporting group description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. The cold compress should be applied in increments no longer than 30 min (could be shorter if the participant was uncomfortable).

| Reporting group title | Enhanced Steroids + Vasoconstrictor + Cold Compress |
|---|---|

Reporting group description:

Enhanced steroid eye drops: 1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Ophthalmic Steroid Ointment; applied to each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. Cold compress was to be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

### Primary: Percentage of Participants Who Required a Change in Ocular Side Effect (OSE) Management

| End point title | Percentage of Participants Who Required a Change in Ocular Side Effect (OSE) Management[1] |
|---|---|

End point description:

Inadequate control of ocular side effects (OSE) was defined as either a ≥ 3-line decline from baseline (≥ +0.3 on LogMAR scale) in visual acuity (with baseline correction determined at the screening ophthalmology visit)) or ≥ Grade 3 OSE severity on the Corneal Epithelial Adverse Event (CEAE) scale.

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

End point timeframe:

Within 8 weeks after the initial dose of depatuxizumab mafodotin

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Treatment differences were not evaluated due to small sample size.

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[2] | 12[3] | 12[4] | |
| Units: percentage of participants | | | | |

| | | | | |
|---|---|---|---|---|
| number (not applicable) | | | | |
| Bilateral vision | 50.0 | 27.3 | 41.7 | |
| Vision in worst eye | 64.3 | 72.7 | 50.0 | |

Notes:

[2] - Subjects rcvd ≥1 ABT-414 dose + ≥1 post-baseline value w/in 8 wks after 1st dose for LogMAR or CEAE

[3] - Subjects rcvd ≥1 ABT-414 dose + ≥1 post-baseline value w/in 8 wks after 1st dose for LogMAR or CEAE

[4] - Subjects rcvd ≥1 ABT-414 dose + ≥1 post-baseline value w/in 8 wks after 1st dose for LogMAR or CEAE

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change From Baseline In Logarithm of the Minimum Angle of Resolution (LogMAR) Scale After Bandage Contact Lens (BCL) Intervention

| | |
|---|---|
| End point title | Change From Baseline In Logarithm of the Minimum Angle of Resolution (LogMAR) Scale After Bandage Contact Lens (BCL) Intervention |

End point description:

The change on the LogMAR Scale from last assessment prior to BCL intervention to 2 weeks after BCL intervention was calculated. The LogMAR scale measures visual acuity on a continuous scale, with a LogMAR value of 0 equivalent to 20/20 visual acuity. Normal vision is considered to be from -0.2 - 0.1; higher values indicate visual impairment. In the table below, a value of 999 indicates not calculable due to insufficient number of participants with events.

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

End point timeframe:

Up to approximately 18 weeks after initial dose of depatuxizumab mafodotin

| **End point values** | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[5] | 12[6] | 12[7] | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| W/in 8 wks of 1st dose:Bilateral vision (n= 4,2,3) | 0.325 (± 0.1248) | 0.13 (± 0.099) | 0.54 (± 0.1442) | |
| W/in 8 wks of 1st dose:Worst eye (n= 4,2,3) | 0.435 (± 0.0574) | 0.52 (± 0.3111) | 0.867 (± 0.2914) | |
| W/in 8 wks of 1st adj dose:Bil vision (n= 1,2,0) | -0.1 (± 999) | 0.41 (± 0.2404) | 999 (± 999) | |
| W/in 8 wks of 1st adj dose:Worst eye (n= 1,2,0) | -0.1 (± 999) | 0.33 (± 0.0141) | 999 (± 999) | |

Notes:

[5] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[6] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[7] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Cumulative Dose of Depatuxizumab Mafodotin Received During Chemoradiation and During Adjuvant Treatment

| End point title | Cumulative Dose of Depatuxizumab Mafodotin Received During Chemoradiation and During Adjuvant Treatment |
|---|---|

End point description:

The cumulative dose of depatuxizumab mafodotin administered was tabulated.

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

End point timeframe:

Up to 9 months

| **End point values** | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[8] | 12[9] | 12[10] | |
| Units: mg/kg | | | | |
| arithmetic mean (standard deviation) | 8.5 (± 5.86) | 10.5 (± 7.35) | 7.0 (± 3.67) | |

Notes:

[8] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[9] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[10] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Bandage Contact Lens (BCL) Intervention

| End point title | Time to Bandage Contact Lens (BCL) Intervention |
|---|---|

End point description:

The time to initiation of bandage contact lenses for those participants who required intervention due to inadequate control of ocular side effects (OSE) was calculated. In the table below, a value of 999 indicates not calculable due to insufficient number of participants with events

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

End point timeframe:

Up to 9 months after the first dose of depatuxizumab mafodotin

| **End point values** | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[11] | 12[12] | 12[13] | |
| Units: months | | | | |
| median (confidence interval 95%) | 999 (1.1 to | 3.6 (1.1 to | 2.1 (1.1 to | |

| | | | |
|---|---|---|---|
| | 999) | 999) | 999) |

Notes:

[11] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[12] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[13] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Ocular Side Effect (OSE) Symptom Resolution After Drug Discontinuation (Reversibility)

| End point title | Time to Ocular Side Effect (OSE) Symptom Resolution After Drug Discontinuation (Reversibility) |
|---|---|

End point description:

The time from discontinuation of depatuxizumab mafodotin to OSE symptom resolution (reversibility) was to be recorded.

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

End point timeframe:

From the first dose of study drug until 49 days after last depatuxizumab mafodotin administration, up to 47 weeks

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[14] | 0[15] | 0[16] | |
| Units: weeks | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | ( to ) | |

Notes:

[14] - Data were not collected for this outcome (due to early termination of the study)

[15] - Data were not collected for this outcome (due to early termination of the study)

[16] - Data were not collected for this outcome (due to early termination of the study)

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Restart Depatuxizumab Mafodotin if Interrupted Due to Ocular Side Effects After Bandage Contact Lens (BCL) Intervention

| End point title | Time to Restart Depatuxizumab Mafodotin if Interrupted Due to Ocular Side Effects After Bandage Contact Lens (BCL) Intervention |
|---|---|

End point description:

The time to restart depatuxizumab mafodotin treatment if it was interrupted due to ocular side effects after BCL Intervention was tabulated.

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

End point timeframe:

From the last assessment prior to BCL intervention to the end of BCL intervention

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[17] | 0[18] | 0[19] | |
| Units: weeks | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | ( to ) | |

Notes:

[17] - Data were not collected for this outcome (due to early termination of the study)

[18] - Data were not collected for this outcome (due to early termination of the study)

[19] - Data were not collected for this outcome (due to early termination of the study)

### Statistical analyses

No statistical analyses for this end point

## Secondary: Treatment-Emergent Corneal Epithelial Adverse Event (CEAE) Grade at Each Visit

| End point title | Treatment-Emergent Corneal Epithelial Adverse Event (CEAE) Grade at Each Visit |
|---|---|

End point description:

The corneal epithelial adverse event (CEAE) rating scale is designed to record symptoms associated with corneal epitheliopathy caused by antibody-drug conjugates and to grade the severity of findings. The overall CEAE grade is measured on a scale of 0 to 5, with higher values being more severe, reflecting the impact of corneal abnormalities on visual activities of daily living (ADLs). Additional detailed information is collected for specific domains that are commonly affected, with the following ranges (each in order of increasing severity): ocular discomfort (0 - 4), photophobia (0 - 3), and reading (1 - 3).

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

End point timeframe:

Up to 63 weeks

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[20] | 12[21] | 12[22] | |
| Units: participants | | | | |
| Week 1: Grade 0 | 10 | 8 | 5 | |
| Week 1: Grade 1 | 1 | 3 | 1 | |
| Week 3: Grade 0 | 4 | 5 | 7 | |
| Week 3: Grade 1 | 10 | 6 | 3 | |
| Week 3: Grade 2 | 0 | 0 | 1 | |
| Week 5: Grade 0 | 1 | 0 | 2 | |
| Week 5: Grade 1 | 7 | 5 | 6 | |
| Week 5: Grade 2 | 1 | 3 | 2 | |

| | | | | |
|---|---|---|---|---|
| Week 5: Grade 3 | 4 | 2 | 2 | |
| Week 7: Grade 0 | 0 | 0 | 2 | |
| Week 7: Grade 1 | 3 | 4 | 0 | |
| Week 7: Grade 2 | 4 | 6 | 5 | |
| Week 7: Grade 3 | 2 | 0 | 2 | |
| Week 9: Grade 0 | 1 | 0 | 1 | |
| Week 9: Grade 1 | 1 | 2 | 0 | |
| Week 9: Grade 2 | 3 | 5 | 4 | |
| Week 9: Grade 3 | 2 | 0 | 1 | |
| Week 11: Grade 0 | 0 | 0 | 1 | |
| Week 11: Grade 1 | 2 | 1 | 0 | |
| Week 11: Grade 2 | 2 | 0 | 3 | |
| Week 11: Grade 3 | 1 | 0 | 1 | |
| Week 11: Grade 4 | 1 | 0 | 0 | |
| Week 13: Grade 1 | 1 | 0 | 1 | |
| Adj Week 1: Grade 0 | 0 | 1 | 0 | |
| Adj Week 1: Grade 1 | 1 | 3 | 2 | |
| Adj Week 1: Grade 2 | 3 | 2 | 2 | |
| Adj Week 1: Grade 3 | 1 | 0 | 0 | |
| Adj Week 5: Grade 0 | 0 | 2 | 2 | |
| Adj Week 5: Grade 1 | 1 | 3 | 0 | |
| Adj Week 5: Grade 2 | 4 | 0 | 1 | |
| Adj Week 5: Grade 3 | 1 | 1 | 0 | |
| Adj Week 9: Grade 0 | 0 | 1 | 0 | |
| Adj Week 9: Grade 1 | 0 | 2 | 1 | |
| Adj Week 9: Grade 2 | 2 | 2 | 2 | |
| Adj Week 9: Grade 3 | 1 | 1 | 0 | |
| Adj Week 13: Grade 0 | 0 | 1 | 0 | |
| Adj Week 13: Grade 1 | 0 | 2 | 0 | |
| Adj Week 13: Grade 2 | 2 | 2 | 2 | |
| Adj Week 13: Grade 3 | 1 | 0 | 0 | |
| Adj Week 17: Grade 0 | 0 | 0 | 1 | |
| Adj Week 17: Grade 1 | 0 | 1 | 0 | |
| Adj Week 17: Grade 2 | 2 | 3 | 0 | |
| Adj Week 21: Grade 1 | 0 | 0 | 1 | |
| Adj Week 21: Grade 2 | 2 | 3 | 0 | |
| Adj Week 25: Grade 1 | 0 | 2 | 0 | |
| Adj Week 25: Grade 2 | 1 | 1 | 0 | |
| Adj Week 29: Grade 2 | 1 | 0 | 0 | |
| Adj Week 29: Grade 4 | 0 | 1 | 0 | |

Notes:

[20] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[21] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[22] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants That Recovered to <3-line Decline From

## Baseline (≤ +0.3 LogMAR) in Visual Acuity After Bandage Contact Lens (BCL) Intervention

| End point title | Percentage of Participants That Recovered to <3-line Decline From Baseline (≤ +0.3 LogMAR) in Visual Acuity After Bandage Contact Lens (BCL) Intervention |
|---|---|

End point description:

Recovery was defined as return to <3-line decline from baseline (≤ +0.3 LogMAR) in visual acuity after BCL intervention.

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

End point timeframe:

From the last assessment prior to BCL intervention to the end of BCL intervention

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[23] | 0[24] | 0[25] | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[23] - Data were not collected for this outcome (due to early termination of the study)

[24] - Data were not collected for this outcome (due to early termination of the study)

[25] - Data were not collected for this outcome (due to early termination of the study)

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Depatuxizumab Mafodotin Dose Modifications Due to Ocular Side Effects (OSE)

| End point title | Number of Participants With Depatuxizumab Mafodotin Dose Modifications Due to Ocular Side Effects (OSE) |
|---|---|

End point description:

Dose modifications included depatuxizumab mafodotin withdrawal, interruption, and reductions in dose initiated due to OSEs.

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

End point timeframe:

From the first dose of study drug until 49 days after last depatuxizumab mafodotin administration, up to 47 weeks

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[26] | 12[27] | 12[28] | |
| Units: participants | 2 | 3 | 2 | |

Notes:

[26] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[27] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[28] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants With Depatuxizumab Mafodotin Dose Modifications to Ocular Side Effects After Bandage Contact Lens (BCL) Intervention

| End point title | Number of Participants With Depatuxizumab Mafodotin Dose Modifications to Ocular Side Effects After Bandage Contact Lens (BCL) Intervention |
|---|---|

End point description:

Dose modifications included depatuxizumab mafodotin withdrawal, interruption, and reductions in dose initiated due to OSEs after BCL intervention.

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

End point timeframe:

From the last assessment prior to BCL intervention to the end of BCL intervention, up to 38 weeks

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 14[29] | 12[30] | 12[31] | |
| Units: participants | 2 | 1 | 0 | |

Notes:

[29] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[30] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[31] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Maximum Change From Baseline on the Logarithm of the Minimum Angle of Resolution (LogMAR) Scale

| End point title | Maximum Change From Baseline on the Logarithm of the Minimum Angle of Resolution (LogMAR) Scale |
|---|---|

End point description:

The LogMAR scale measures visual acuity on a continuous scale, with a LogMAR value of 0 equivalent to 20/20 visual acuity. Normal vision is considered to be from -0.2 - 0.1; higher values indicate visual impairment. The baseline observation is defined as the last non-missing measurement collected prior to the first dose of depatuxizumab mafodotin.

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

End point timeframe:

Within 8 weeks after the initial dose of depatuxizumab mafodotin

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12[32] | 10[33] | 9[34] | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Bilateral vision | 0.353 (± 0.1888) | 0.402 (± 0.1985) | 0.272 (± 0.3888) | |
| Vision in worst eye | 0.482 (± 0.2028) | 0.528 (± 0.3073) | 0.430 (± 0.5120) | |

Notes:

[32] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[33] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[34] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Treatment Emergent Corneal Epithelial Adverse Event (CEAE) Grade at Each Visit After Bandage Contact Lens (BCL) Intervention

| End point title | Treatment Emergent Corneal Epithelial Adverse Event (CEAE) Grade at Each Visit After Bandage Contact Lens (BCL) Intervention |
|---|---|

End point description:

The corneal epithelial adverse event (CEAE) rating scale is designed to record symptoms associated with corneal epitheliopathy caused by antibody-drug conjugates and to grade the severity of findings. The overall CEAE grade is measured on a scale of 0 to 5, with higher values being more severe, reflecting the impact of corneal abnormalities on visual activities of daily living (ADLs). Additional detailed information is collected for specific domains that are commonly affected, with the following ranges (each in order of increasing severity): ocular discomfort (0 - 4), photophobia (0 - 3), and reading (1 - 3).

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

End point timeframe:

From the last assessment prior to BCL intervention to the end of BCL intervention, up to 38 weeks

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 7[35] | 4[36] | 4[37] | |
| Units: participants | | | | |
| Week 5: Grade 1 | 2 | 0 | 0 | |
| Week 7: Grade 2 | 1 | 1 | 0 | |

| | | | | |
|---|---|---|---|---|
| Week 9: Grade 2 | 1 | 1 | 1 | |
| Week 11: Grade 2 | 0 | 0 | 2 | |
| Week 11: Grade 3 | 1 | 0 | 0 | |
| Week 13: Grade 1 | 1 | 0 | 0 | |
| Adj Week 1: Grade 1 | 0 | 0 | 1 | |
| Adj Week 1: Grade 2 | 0 | 0 | 1 | |
| Adj Week 5: Grade 0 | 0 | 1 | 1 | |
| Adj Week 5: Grade 1 | 0 | 1 | 0 | |
| Adj Week 5: Grade 2 | 1 | 0 | 1 | |
| Adj Week 5: Grade 3 | 1 | 0 | 0 | |
| Adj Week 9: Grade 0 | 0 | 1 | 0 | |
| Adj Week 9: Grade 1 | 0 | 0 | 1 | |
| Adj Week 9: Grade 2 | 0 | 0 | 1 | |
| Adj Week 9: Grade 3 | 1 | 0 | 0 | |
| Adj Week 13: Grade 0 | 0 | 2 | 0 | |
| Adj Week 13: Grade 1 | 0 | 1 | 0 | |
| Adj Week 13: Grade 2 | 1 | 0 | 1 | |
| Adj Week 13: Grade 3 | 1 | 0 | 0 | |
| Adj Week 17: Grade 1 | 0 | 1 | 0 | |
| Adj Week 17: Grade 2 | 1 | 1 | 0 | |
| Adj Week 21: Grade 2 | 2 | 1 | 0 | |
| Adj Week 25: Grade 1 | 0 | 1 | 0 | |
| Adj Week 25: Grade 2 | 1 | 0 | 0 | |
| Adj Week 29: Grade 2 | 1 | 0 | 0 | |

Notes:

[35] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[36] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

[37] - Safety population: randomized subjects who rcvd ≥1 dose of ABT-414 with available data

### Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Re-initiation of Depatuxizumab Mafodotin After Dose Interruption

| End point title | Time to Re-initiation of Depatuxizumab Mafodotin After Dose Interruption |
|---|---|

End point description:

The time from dose interruption until re-initiation or permanent discontinuation of depatuxizumab mafodotin was to be recorded.

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

End point timeframe:

Up to 9 months

| End point values | Standard Steroids | Standard Steroids + Vasoconstrictor + Cold Compress | Enhanced Steroids + Vasoconstrictor + Cold Compress | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0[38] | 0[39] | 0[40] | |
| Units: weeks | | | | |
| median (confidence interval 95%) | ( to ) | ( to ) | ( to ) | |

Notes:

[38] - Data were not collected for this outcome (due to early termination of the study)

[39] - Data were not collected for this outcome (due to early termination of the study)

[40] - Data were not collected for this outcome (due to early termination of the study)

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) collected from 1st dose of ABT-414 until 49 d after last dose, up to 47 wks. SAEs and protocol-related nonserious AEs were collected from the time the subject signed consent.

Adverse event reporting additional description:

TEAEs and SAEs are defined as any AE or SAE with onset or worsening reported by a participant from the time that the first dose of depatuxizumab mafodotin is administered until 49 days have elapsed following discontinuation of study drug. TEAEs were collected whether elicited or spontaneously reported by the participant.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 22.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Standard Steroids |

Reporting group description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days

| | |
|---|---|
| Reporting group title | Enhanced Steroids + Vasoconstrictor + Cold Compress |

Reporting group description:

Enhanced steroid eye drops: 1 drop each eye, 6 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Ophthalmic Steroid Ointment; applied to each eye once daily before sleep, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4 – 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin
infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. Cold compress was to be applied in increments no longer than 30 min (could be shorter if the patient is uncomfortable).

| | |
|---|---|
| Reporting group title | Standard Steroids + Vasoconstrictor + Cold Compress |

Reporting group description:

Steroid eye drops: 1 drop each eye, 3 times/day, starting 2 days prior to depatuxizumab mafodotin infusion and continuing until 4 days after infusion, for a total of 7 days; Vasoconstrictor Eye Drops: 1 drop each eye 4– 6 times on day of infusion in total (5 – 10 minutes before infusion; at end of infusion; and 2 – 4 times during the remainder of the infusion day). Continuing 4 – 6 times/day on Day 1 and Day 2 after each depatuxizumab mafodotin infusion; Cold Compress: Starting 5 minutes prior to start of infusion and continuing for 30 minutes past end of infusion, and then use at least 2 hours total/day on Days 1 – 3 with each depatuxizumab mafodotin infusion. The cold compress was to be applied in increments no longer than 30 min (could be shorter if the
participant was uncomfortable).

| **Serious adverse events** | Standard Steroids | Enhanced Steroids + Vasoconstrictor + Cold Compress | Standard Steroids + Vasoconstrictor + Cold Compress |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 14 (42.86%) | 4 / 12 (33.33%) | 4 / 12 (33.33%) |
| number of deaths (all causes) | 1 | 1 | 1 |
| number of deaths resulting from adverse events | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| MALIGNANT NEOPLASM PROGRESSION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| TUMOUR PSEUDOPROGRESSION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Vascular disorders | | | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| HAEMATOMA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Nervous system disorders | | | |
| HEADACHE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| HEMIPARESIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SEIZURE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| STATUS EPILEPTICUS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Blood and lymphatic system disorders | | | |
| FEBRILE NEUTROPENIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| PYREXIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 0 / 12 (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 |
| Eye disorders | | | |
| ULCERATIVE KERATITIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| VOMITING | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| PULMONARY EMBOLISM | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| Infections and infestations | | | |
| CELLULITIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| EYE INFECTION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| LOWER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (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 |
| PNEUMONIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | Standard Steroids | Enhanced Steroids + Vasoconstrictor + Cold Compress | Standard Steroids + Vasoconstrictor + Cold Compress |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 14 / 14 (100.00%) | 12 / 12 (100.00%) | 12 / 12 (100.00%) |
| Vascular disorders | | | |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| HYPOTENSION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| General disorders and administration | | | |

| | | | |
|---|---|---|---|
| site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| CHEST PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| FATIGUE | | | |
| subjects affected / exposed | 6 / 14 (42.86%) | 7 / 12 (58.33%) | 9 / 12 (75.00%) |
| occurrences (all) | 10 | 8 | 10 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| PYREXIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Immune system disorders | | | |
| HYPERSENSITIVITY | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Reproductive system and breast disorders | | | |
| MENSTRUATION IRREGULAR | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| PROSTATIC OBSTRUCTION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 4 |
| DYSPNOEA EXERTIONAL | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| OROPHARYNGEAL PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| PLEURITIC PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| PULMONARY OEDEMA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| RHINITIS ALLERGIC | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| AGITATION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| ANXIETY | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 1 | 3 |
| CONFUSIONAL STATE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| DEPRESSION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| INSOMNIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| Investigations | | | |
| ALANINE AMINOTRANSFERASE INCREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 14 (14.29%) | 3 / 12 (25.00%) | 5 / 12 (41.67%) |
| occurrences (all) | 2 | 4 | 7 |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 4 / 14 (28.57%) | 2 / 12 (16.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 4 | 3 | 2 |
| BLOOD BILIRUBIN ABNORMAL | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BLOOD CALCIUM INCREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BLOOD CREATININE INCREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BLOOD PHOSPHORUS DECREASED | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| CARDIAC MURMUR | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| GAMMA-GLUTAMYLTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| INTRAOCULAR PRESSURE INCREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| LYMPHOCYTE COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 3 / 12 (25.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 7 | 0 |
| NEUTROPHIL COUNT DECREASED | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| NEUTROPHIL COUNT INCREASED | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| WEIGHT DECREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| WHITE BLOOD CELL COUNT DECREASED | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Injury, poisoning and procedural complications | | | |
| ARTHROPOD BITE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| CORNEAL ABRASION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| FALL | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| INCISION SITE PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| INFUSION RELATED REACTION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| RADIATION NECROSIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| RADIATION SKIN INJURY | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 2 | 0 | 1 |
| SKIN ABRASION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac disorders | | | |

| | | | |
|---|---|---|---|
| CARDIOMEGALY | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| TACHYCARDIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| Nervous system disorders | | | |
| APHASIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| APRAXIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BALANCE DISORDER | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| BRAIN OEDEMA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 12 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 2 | 1 |
| CEREBRAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| DIZZINESS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 2 |
| DYSGEUSIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 3 |
| HEADACHE | | | |
| subjects affected / exposed | 5 / 14 (35.71%) | 4 / 12 (33.33%) | 3 / 12 (25.00%) |
| occurrences (all) | 5 | 5 | 3 |
| HEMIPARESIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 12 (16.67%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| MEMORY IMPAIRMENT | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 1 | 1 |
| SEIZURE | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 12 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 3 | 1 |
| SYNCOPE | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| TREMOR | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| VASOGENIC CEREBRAL OEDEMA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 2 / 12 (16.67%) |
| occurrences (all) | 1 | 1 | 2 |
| LEUKOPENIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| LYMPHOPENIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 2 | 2 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 3 / 12 (25.00%) | 5 / 12 (41.67%) |
| occurrences (all) | 4 | 7 | 7 |
| Ear and labyrinth disorders | | | |
| EAR PAIN | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| HYPOACUSIS | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 2 |
| Eye disorders | | | |
| ACQUIRED EPIBLEPHARON | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| CONJUNCTIVITIS ALLERGIC | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| DIPLOPIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| DRY EYE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| EYELID PTOSIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| FOREIGN BODY SENSATION IN EYES | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| VISION BLURRED | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ANAL INCONTINENCE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| CONSTIPATION | | | |
| subjects affected / exposed | 5 / 14 (35.71%) | 2 / 12 (16.67%) | 4 / 12 (33.33%) |
| occurrences (all) | 5 | 2 | 4 |
| DIARRHOEA | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 1 | 0 | 1 |
| DRY MOUTH | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| DUODENAL ULCER | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| DYSPHAGIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| GASTRITIS EROSIVE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| HAEMORRHOIDAL HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| MOUTH ULCERATION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| NAUSEA | | | |
| subjects affected / exposed | 6 / 14 (42.86%) | 3 / 12 (25.00%) | 6 / 12 (50.00%) |
| occurrences (all) | 7 | 3 | 7 |
| STOMATITIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| VOMITING | | | |
| subjects affected / exposed | 5 / 14 (35.71%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 5 | 1 | 1 |
| Hepatobiliary disorders | | | |
| DRUG-INDUCED LIVER INJURY | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 3 |

| | | | |
|---|---|---|---|
| Skin and subcutaneous tissue disorders | | | |
| ALOPECIA | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 5 / 12 (41.67%) | 2 / 12 (16.67%) |
| occurrences (all) | 2 | 7 | 2 |
| DERMATITIS | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| DERMATITIS ACNEIFORM | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| DRY SKIN | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ERYTHEMA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 12 (16.67%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 2 | 1 |
| PETECHIAE | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| RASH | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 4 | 0 | 1 |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| RASH PRURITIC | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| SCAR PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Renal and urinary disorders | | | |
| NOCTURIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| URINARY INCONTINENCE | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| ARTHRALGIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| MUSCULAR WEAKNESS | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 5 | 0 | 0 |
| MUSCULOSKELETAL CHEST PAIN | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| NECK PAIN | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infections and infestations | | | |
| BALANITIS CANDIDA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| NASOPHARYNGITIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ORAL CANDIDIASIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| ORAL HERPES | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| SINUSITIS | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| UPPER RESPIRATORY TRACT INFECTION | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 3 / 14 (21.43%) | 3 / 12 (25.00%) | 3 / 12 (25.00%) |
| occurrences (all) | 4 | 3 | 5 |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all) | 0 | 0 | 2 |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 0 / 12 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| HYPOKALAEMIA | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 12 (8.33%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 1 | 1 |
| HYPONATRAEMIA | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 12 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| MALNUTRITION | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 12 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 02 July 2018 | Version 2.0<br><br>•Implemented safety measures for subjects with hepatic laboratory abnormalities due to a Grade 5 acute liver injury in a patient receiving depatuxizumab mafodotin in an ongoing study<br>•Provided guidelines for depatuxizumab mafodotin dose modifications due to hepatic laboratory abnormalities<br>•Provided guidelines for management and evaluation of severe hepatic laboratory abnormalities and for data collection<br>•Provided clarification on measurements of visual acuity (VA)<br>•Primary measure of interest, used for assessing the VA component of primary endpoint and other changes from baseline in VA, defined as VA with baseline correction, to be determined at the initial ophthalmology examination and used throughout the study<br>•Provided additional flexibility in OSE management once endpoints for study objectives were assessed<br>•Allowed subjects to transition to the Investigator Discretion Phase once key period of interest for OSE observation has ended (after 8 wks of adjuvant therapy) regardless of CEAE grade or prior intervention with BCLs<br>•Increased frequency of vasoconstrictor eye drop administration, as consistent with labeling information<br>•Clarified sequence of steroid eye drop substitution: initial eye drop is Prednisolone acetate 1% suspension and substitution with 0.1% dexamethasone phosphate is allowed after emergency of ocular side effects, if deemed necessary<br>•Provided clarification on supportive care measures allowed or prohibited during Initial Prophylaxis and BCL Intervention phases of OSE management<br>•Clarified language describing optional biomarker study<br>•Clarified purpose of optional cornea collection: histopathologic evaluation of the post-mortem<br>corneal tissue will be assessed to further characterize histopathologic features of OSEs<br>•Specified that non-corrective (plano) bandage contact lenses are to be used in the study<br>•Provided clarification on adverse event reporting by following current template language |

| | |
|---|---|
| 14 December 2018 | Version 3.0<br><br>•Updated Benefits and Risks to patients to reflect clinical study data reported in current Investigator Brochure and updated Reference for IB<br>•Added active infection with hepatitis B virus, hepatitis C virus, or HIV as exclusion criteria<br>•Provided updated contraception language to be consistent with AbbVie protocol template<br>•Prohibited use of live attenuated vaccines during study and for 49 days after end of study drug administration<br>•Clarified instructions for withdrawal of subjects and discontinuation of study<br>•Clarified use of vasoconstrictor eye drops 4 - 6 times in total on day of infusion, including 2-4 times during remainder of infusion day, and 4 - 6 times/day in total on Day 1 - Day 2 after infusion<br>•Clarified that all adverse events reported will be collected from the time of study drug administration until 49 days after last depatuxizumab mafodotin administration; clarified that administration of depatuxizumab mafodotin must be discontinued immediately in the event that a subject becomes pregnant during the study<br>•Included instructions for Toxicity Management in Protocol; moved from Operations Manual.<br>•Updated CTCAE to version 5.0 for grading of clinical toxicity in order to use most recent version.<br>•Specified that study drug should be permanently discontinued if subject develops corneal ulceration with impending perforation (CU) or corneal perforation (CP)<br>•Clarified end of study as the date of subject's last visit<br>•Added time points for collection of visual quality of life questionnaire and visual symptoms questionnaire; added time points for collection of perception of treatment value question; provided clarification on timing and type of pregnancy tests; added randomization visit with prophylactic treatment for OSE; clarified timing of central lab tests during Follow Up 35 Day visit and not at Follow Up 49 Day visit; added Post-Treatment Follow Up visit at 49 Day |
| 28 May 2019 | Version 4.0<br><br>•Added brief summary of results for the protocol-specified interim efficacy analysis for INTELLANCE-1 in the Introduction<br>•Provided modified study procedures and instructions for depatuxizumab mafodotin dosing in for those subjects who were currently receiving depatuxizumab mafodotin and who choose to continue depatuxizumab mafodotin. No additional efficacy data was to be collected, and procedures were minimized to include those necessary for study drug dosing, safety monitoring and collection of safety data related to adverse events. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported