



Clinical trial results: An Open-Label Phase I/IIa Study of Intravenous BAL101553 in Adult Patients with Advanced Solid Tumors

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-024237-23 |
| Trial protocol | GB |
| Global end of trial date | 06 April 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 01 February 2019 |
| First version publication date | 01 February 2019 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | CDI-CS-001 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01397929 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Basilea Pharmaceutica International Ltd. |
| Sponsor organisation address | Grenzacherstrasse 487, Basel, Switzerland, |
| Public contact | Medical Information, Basilea Pharmaceutical International Ltd., +41 6061400, medical.information@basilea.com |
| Scientific contact | Medical Information, Basilea Pharmaceutical International Ltd., +41 6061400, medical.information@basilea.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 | 07 February 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|---------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 06 April 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the maximum tolerated dose (MTD) and to characterize dose-limiting toxicities (DLT) of BAL101553 administered intravenously as single agent on days 1, 8 and 15 of an every 28 day treatment cycle in adults with advanced or recurrent solid tumors, who have failed standard therapy or for whom no effective standard therapy is available

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) and applicable national and regional regulations/guidelines regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 10 June 2011 |
| 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 | United Kingdom: 73 |
| Worldwide total number of subjects | 73 |
| EEA total number of subjects | 73 |

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) | 50 |
| From 65 to 84 years | 23 |

| | |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 4 Phase 1 study centers in the United Kingdom.

Pre-assignment

Screening details:

Total of 104 subjects were screened, out of which 25 subjects failed screening. Seventy-nine subjects were assigned to treatment of which 73 received at least one dose.

Period 1

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

Arms

| | |
|------------------------------|---------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | BAL101553: 15 mg/m ² |

Arm description:

BAL101553 was administered at 15 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAL101553 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BAL101553 15 mg/m² intravenously over 2 hours on Days 1, 8 and 15 of each 28-day treatment cycle.

| | |
|------------------|---------------------------------|
| Arm title | BAL101553: 30 mg/m ² |
|------------------|---------------------------------|

Arm description:

BAL101553 was administered at 30 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|--|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAL101553 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

BAL101553 30 mg/m² intravenously over 2 hours on Days 1, 8 and 15 of each 28-day treatment cycle.

| | |
|------------------|---------------------------------|
| Arm title | BAL101553: 45 mg/m ² |
|------------------|---------------------------------|

Arm description:

BAL101553 was administered at 45 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|---|----------------------------------|
| Investigational medicinal product name | BAL101553 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| BAL101553 45 mg/m ² intravenously over 2 hours on Days 1, 8 and 15 of each 28-day treatment cycle. | |
| Arm title | BAL101553: 60 mg/m ² |

Arm description:

BAL101553 was administered at 60 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|---|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAL101553 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| BAL101553 60 mg/m ² intravenously over 2 hours on Days 1, 8 and 15 of each 28-day treatment cycle. | |
| Arm title | BAL101553: 80 mg/m ² |

Arm description:

BAL101553 was administered at 80 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|---|----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | BAL101553 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| BAL101553 80 mg/m ² intravenously over 2 hours on Days 1, 8 and 15 of each 28-day treatment cycle. | |

| Number of subjects in period 1 | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² |
|---------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Started | 1 | 36 | 8 |
| Completed | 0 | 0 | 0 |
| Not completed | 1 | 36 | 8 |
| Consent withdrawn by subject | - | 1 | - |
| Disease progression | 1 | 30 | 7 |
| Death | - | 1 | - |
| Admin/ other | - | 1 | - |
| AE, intercurrent illness | - | 2 | 1 |
| Protocol deviation | - | 1 | - |

| Number of subjects in period 1 | BAL101553: 60 mg/m ² | BAL101553: 80 mg/m ² |
|---------------------------------------|---------------------------------|---------------------------------|
|---------------------------------------|---------------------------------|---------------------------------|

| | | |
|------------------------------|----|---|
| Started | 21 | 7 |
| Completed | 0 | 0 |
| Not completed | 21 | 7 |
| Consent withdrawn by subject | 1 | 2 |
| Disease progression | 18 | 3 |
| Death | - | - |
| Admin/ other | - | - |
| AE, intercurrent illness | 2 | 2 |
| Protocol deviation | - | - |

Baseline characteristics

Reporting groups

| | |
|---|---------------------------------|
| Reporting group title | BAL101553: 15 mg/m ² |
| Reporting group description: BAL101553 was administered at 15 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 30 mg/m ² |
| Reporting group description: BAL101553 was administered at 30 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 45 mg/m ² |
| Reporting group description: BAL101553 was administered at 45 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 60 mg/m ² |
| Reporting group description: BAL101553 was administered at 60 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 80 mg/m ² |
| Reporting group description: BAL101553 was administered at 80 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |

| Reporting group values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² |
|---------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Number of subjects | 1 | 36 | 8 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 1 | 26 | 2 |
| From 65-84 years | 0 | 10 | 6 |
| Age continuous Units: years | | | |
| median | 51 | 60 | 67 |
| full range (min-max) | 51 to 51 | 32 to 79 | 47 to 76 |
| Gender categorical Units: Subjects | | | |
| Female | 1 | 16 | 3 |
| Male | 0 | 20 | 5 |

| Reporting group values | BAL101553: 60 mg/m ² | BAL101553: 80 mg/m ² | Total |
|------------------------------------|---------------------------------|---------------------------------|-------|
| Number of subjects | 21 | 7 | 73 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 16 | 5 | 50 |
| From 65-84 years | 5 | 2 | 23 |

| | | | |
|----------------------|----------|----------|----|
| Age continuous | | | |
| Units: years | | | |
| median | 57 | 55 | |
| full range (min-max) | 29 to 80 | 45 to 70 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 11 | 3 | 34 |
| Male | 10 | 4 | 39 |

End points

End points reporting groups

| | |
|---|---------------------------------|
| Reporting group title | BAL101553: 15 mg/m ² |
| Reporting group description: BAL101553 was administered at 15 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 30 mg/m ² |
| Reporting group description: BAL101553 was administered at 30 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 45 mg/m ² |
| Reporting group description: BAL101553 was administered at 45 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 60 mg/m ² |
| Reporting group description: BAL101553 was administered at 60 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |
| Reporting group title | BAL101553: 80 mg/m ² |
| Reporting group description: BAL101553 was administered at 80 mg/m ² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met. | |

Primary: Maximum tolerated dose (MTD)

| | |
|--|---|
| End point title | Maximum tolerated dose (MTD) ^[1] |
| End point description: MTD: highest dose level of BAL101553 at which no more than 1 of 6 MTD-evaluable subjects experienced dose limiting toxicities (DLT). DLT: an adverse event or abnormal laboratory value as defined in the protocol that is related to BAL101553. MTD-evaluable subjects: Phase 1 subjects who received at least one dose of BAL101553 and experienced a DLT, or patients who received all three doses of BAL101553 in Cycle 1 without a DLT. | |
| End point type | Primary |
| End point timeframe: Cycle 1 (28 days) | |

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

| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
|-----------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 3 | 3 | 6 |
| Units: Subjects with DLTs | 0 | 0 | 0 | 1 |

| | | | | |
|-----------------------------|------------------------------------|--|--|--|
| End point values | BAL101553: 80 mg/m ² | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Subjects with DLTs | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: AUC of BAL101553 and BAL27862 (the active metabolite)

| | |
|---|---|
| End point title | PK Parameter: AUC of BAL101553 and BAL27862 (the active metabolite) |
| End point description: | |
| Area under the plasma concentration time curve from time point zero to infinity | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 of Cycle 1 | |

| | | | | |
|---|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 36 | 8 | 21 |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 917 (± 0) | 2520 (± 44.0) | 2340 (± 257) | 3440 (± 47.8) |
| BAL27862 | 2110 (± 0) | 3620 (± 55.7) | 5090 (± 62.9) | 7180 (± 44.5) |

| | | | | |
|---|------------------------------------|--|--|--|
| End point values | BAL101553: 80 mg/m ² | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: h*ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 5640 (± 36.5) | | | |
| BAL27862 | 7950 (± 40.5) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Cmax of BAL101553 and BAL27862 (the active metabolite)

| | |
|------------------------|--|
| End point title | PK Parameter: Cmax of BAL101553 and BAL27862 (the active metabolite) |
| End point description: | Maximum drug concentration observed in plasma |
| End point type | Secondary |
| End point timeframe: | Day 1 of Cycle 1 |

| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
|---|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 36 | 8 | 21 |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 556 (± 0) | 1060 (± 51.7) | 1130 (± 350) | 1320 (± 137) |
| BAL27862 | 154 (± 0) | 267 (± 19.8) | 346 (± 26.3) | 484 (± 25.1) |

| End point values | BAL101553: 80 mg/m ² | | | |
|---|---------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: ng/mL | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 3250 (± 24.8) | | | |
| BAL27862 | 601 (± 13.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Tmax of BAL101553 and BAL27862 (the active metabolite)

| | |
|------------------------|--|
| End point title | PK Parameter: Tmax of BAL101553 and BAL27862 (the active metabolite) |
| End point description: | Time to maximum plasma concentration |
| End point type | Secondary |

End point timeframe:

Day 1 of Cycle 1

| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
|--|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 36 | 8 | 21 |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 1.05 (± 0) | 1.94 (± 15.9) | 1.80 (± 39.6) | 1.75 (± 36.9) |
| BAL27862 | 2.50 (± 0) | 2.13 (± 16.7) | 2.30 (± 28.8) | 2.34 (± 23.8) |

| End point values | BAL101553: 80 mg/m ² | | | |
|--|------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 1.54 (± 32.9) | | | |
| BAL27862 | 2.33 (± 14.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: PK Parameter: Terminal half-life of BAL101553 and BAL27862 (the active metabolite)

| | |
|-----------------|---|
| End point title | PK Parameter: Terminal half-life of BAL101553 and BAL27862 (the active metabolite) |
|-----------------|---|

End point description:

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

End point timeframe:

Day 1 of Cycle 1

| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
|---|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 36 | 8 | 21 |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 0.908 (± 0) | 1.96 (± 44.1) | 1.54 (± 20.7) | 1.51 (± 33.1) |
| BAL27862 | 18.1 (± 0) | 12.6 (± 57.2) | 12.5 (± 47.7) | 13.8 (± 26.5) |

| End point values | BAL101553: 80 mg/m ² | | | |
|---|------------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: hours | | | | |
| geometric mean (geometric coefficient of variation) | | | | |
| BAL101553 | 1.49 (± 15.2) | | | |
| BAL27862 | 12.5 (± 26.7) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Best overall response in EEP

| | |
|---|------------------------------|
| End point title | Best overall response in EEP |
| End point description: | |
| The best overall response is the best response recorded from the start of the treatment until disease progression. | |
| Efficacy evaluable population (EEP): all patients who completed Cycle 1 dosing and who underwent at least one on-study clinical tumor assessment or a radiological assessment by RECIST v1.1. | |
| End point type | Secondary |
| End point timeframe: | |
| Assessed every 8 weeks from time of first dose until disease progression. | |

| End point values | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² | BAL101553: 60 mg/m ² |
|-----------------------------|------------------------------------|------------------------------------|------------------------------------|------------------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 31 | 7 | 15 |
| Units: Number of subjects | | | | |
| Complete response | 0 | 0 | 0 | 0 |
| Partial response | 0 | 1 | 0 | 0 |
| Stable disease | 1 | 5 | 3 | 5 |
| Progressive disease | 0 | 25 | 4 | 10 |

| | | | | |
|-----------------------------|------------------------------------|--|--|--|
| End point values | BAL101553: 80 mg/m ² | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Number of subjects | | | | |
| Complete response | 0 | | | |
| Partial response | 0 | | | |
| Stable disease | 0 | | | |
| Progressive disease | 3 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first administration of BAL101553 up to 28 days after the last administration.

Adverse event reporting additional description:

Treatment-emergent adverse events and serious adverse events

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 17 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | BAL101553: 15 mg/m ² |
|-----------------------|---------------------------------|

Reporting group description:

BAL101553 was administered at 15 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|-----------------------|---------------------------------|
| Reporting group title | BAL101553: 30 mg/m ² |
|-----------------------|---------------------------------|

Reporting group description:

BAL101553 was administered at 30 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|-----------------------|---------------------------------|
| Reporting group title | BAL101553: 45 mg/m ² |
|-----------------------|---------------------------------|

Reporting group description:

BAL101553 was administered at 45 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|-----------------------|---------------------------------|
| Reporting group title | BAL101553: 60 mg/m ² |
|-----------------------|---------------------------------|

Reporting group description:

BAL101553 was administered at 60 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| | |
|-----------------------|---------------------------------|
| Reporting group title | BAL101553: 80 mg/m ² |
|-----------------------|---------------------------------|

Reporting group description:

BAL101553 was administered at 80 mg/m² as an IV infusion over 2 hours on Days 1, 8 and 15 of a 28 day treatment Cycle. Treatment Cycles were continued until disease progression, unacceptable toxicity, or other discontinuation criteria met.

| Serious adverse events | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 14 / 36 (38.89%) | 3 / 8 (37.50%) |
| number of deaths (all causes) | 0 | 2 | 1 |
| number of deaths resulting from adverse events | 0 | 2 | 1 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |

| | | | |
|--|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |

| | | | |
|---|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Incorrect drug administration rate | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------|----------------|----------------|
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocarditis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myasthenia gravis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain upper | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Constipation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Nausea | | | |

| | | | |
|---|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Jaundice | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (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 |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Mobility decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---------------------------------|----------------------------------|----------------------------------|
| Infections and infestations Biliary sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 1 (0.00%) 0 / 0 0 / 0 | 1 / 36 (2.78%) 0 / 1 0 / 0 | 0 / 8 (0.00%) 0 / 0 0 / 0 |
| Device related infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 1 (0.00%) 0 / 0 0 / 0 | 1 / 36 (2.78%) 0 / 2 0 / 0 | 0 / 8 (0.00%) 0 / 0 0 / 0 |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 1 (0.00%) 0 / 0 0 / 0 | 1 / 36 (2.78%) 0 / 1 0 / 0 | 1 / 8 (12.50%) 0 / 1 0 / 0 |
| Urinary tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 1 (0.00%) 0 / 0 0 / 0 | 0 / 36 (0.00%) 0 / 0 0 / 0 | 0 / 8 (0.00%) 0 / 0 0 / 0 |
| Metabolism and nutrition disorders Dehydration subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 1 (0.00%) 0 / 0 0 / 0 | 1 / 36 (2.78%) 0 / 1 0 / 0 | 0 / 8 (0.00%) 0 / 0 0 / 0 |

| Serious adverse events | BAL101553: 60 mg/m ² | BAL101553: 80 mg/m ² | |
|---|---------------------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 21 (66.67%) | 5 / 7 (71.43%) | |
| number of deaths (all causes) | 2 | 0 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypertension | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Disease progression | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 7 (28.57%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleuritic pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Electrocardiogram T wave inversion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Clavicle fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Incorrect drug administration rate | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Radiation pneumonitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocarditis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myasthenia gravis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Ascites | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large intestinal obstruction | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 21 (4.76%) | 2 / 7 (28.57%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Bile duct obstruction | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholangitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Mobility decreased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Biliary sepsis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |

| | | | |
|---|----------------|---------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | BAL101553: 15 mg/m ² | BAL101553: 30 mg/m ² | BAL101553: 45 mg/m ² |
|---|---------------------------------|---------------------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 35 / 36 (97.22%) | 8 / 8 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypertension | | | |

| | | | |
|--|-----------------|------------------|----------------|
| subjects affected / exposed | 1 / 1 (100.00%) | 6 / 36 (16.67%) | 3 / 8 (37.50%) |
| occurrences (all) | 1 | 18 | 7 |
| Hypotension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 2 / 8 (25.00%) |
| occurrences (all) | 0 | 2 | 3 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 13 / 36 (36.11%) | 4 / 8 (50.00%) |
| occurrences (all) | 0 | 15 | 6 |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Infusion site erythema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 2 / 8 (25.00%) |
| occurrences (all) | 0 | 1 | 3 |
| Infusion site pruritus | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infusion site reaction | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 4 / 36 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 10 | 0 |
| Infusion site thrombosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Non-cardiac chest pain | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Puncture site erythema | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Puncture site pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 2 | 2 |
| Reproductive system and breast disorders | | | |
| Genital swelling | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 3 / 8 (37.50%) |
| occurrences (all) | 0 | 4 | 4 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 2 | 1 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Tachypnoea | | | |

| | | | |
|--|--------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 36 (0.00%) 0 | 1 / 8 (12.50%) 1 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Depressed mood | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 6 / 36 (16.67%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 6 | 0 |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cells in urine | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| QRS axis abnormal | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 4 | 1 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Palpitations | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Sinus tachycardia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 2 |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Dysgeusia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 4 / 36 (11.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 5 | 1 |
| Lethargy | | | |

| | | | |
|--------------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 4 | 1 |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Migraine | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 3 / 8 (37.50%) |
| occurrences (all) | 0 | 2 | 3 |
| Nystagmus | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 1 / 36 (2.78%) | 1 / 8 (12.50%) |
| occurrences (all) | 1 | 1 | 1 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 9 / 36 (25.00%) | 2 / 8 (25.00%) |
| occurrences (all) | 0 | 9 | 3 |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Abdominal distension | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Abdominal pain | | | |

| | | | |
|--|-----------------|------------------|----------------|
| subjects affected / exposed | 1 / 1 (100.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 3 | 0 |
| Abdominal pain lower | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 10 / 36 (27.78%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 12 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 10 / 36 (27.78%) | 4 / 8 (50.00%) |
| occurrences (all) | 1 | 14 | 4 |
| Dry mouth | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 1 | 1 |
| Nausea | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 12 / 36 (33.33%) | 4 / 8 (50.00%) |
| occurrences (all) | 2 | 18 | 6 |
| Oesophageal haemorrhage | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Proctalgia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 7 / 36 (19.44%) | 2 / 8 (25.00%) |
| occurrences (all) | 2 | 10 | 4 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Alopecia | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 4 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 5 / 36 (13.89%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Rash macular | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin reaction | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 1 / 1 (100.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 5 | 0 |
| Back pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 8 / 36 (22.22%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 11 | 0 |
| Flank pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle spasms | | | |

| | | | |
|-----------------------------------|---------------|-----------------|----------------|
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 1 / 36 (2.78%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 4 / 36 (11.11%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 2 | 1 |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 2 / 36 (5.56%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 3 / 36 (8.33%) | 0 / 8 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Paronychia | | | |
| subjects affected / exposed | 0 / 1 (0.00%) | 0 / 36 (0.00%) | 1 / 8 (12.50%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|------------------------|---------------------|
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 4 / 36 (11.11%) 4 | 1 / 8 (12.50%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 2 | 2 / 36 (5.56%) 3 | 0 / 8 (0.00%) 0 |
| Urinary tract infection bacterial subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 0 / 36 (0.00%) 0 | 0 / 8 (0.00%) 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | 11 / 36 (30.56%) 13 | 1 / 8 (12.50%) 1 |
| Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 36 (5.56%) 2 | 0 / 8 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 1 / 1 (100.00%) 1 | 1 / 36 (2.78%) 1 | 1 / 8 (12.50%) 1 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 4 / 36 (11.11%) 4 | 1 / 8 (12.50%) 1 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 36 (5.56%) 2 | 0 / 8 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 1 (0.00%) 0 | 2 / 36 (5.56%) 2 | 1 / 8 (12.50%) 1 |

| | | | |
|---|------------------------------------|------------------------------------|--|
| Non-serious adverse events | BAL101553: 60 mg/m ² | BAL101553: 80 mg/m ² | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 21 / 21 (100.00%) | 7 / 7 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Tumour pain subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 2 | 0 / 7 (0.00%) 0 | |

| | | | |
|--|------------------|----------------|--|
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Flushing | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 6 / 7 (85.71%) | |
| occurrences (all) | 30 | 10 | |
| Hypotension | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 7 (14.29%) | |
| occurrences (all) | 5 | 2 | |
| Fatigue | | | |
| subjects affected / exposed | 12 / 21 (57.14%) | 4 / 7 (57.14%) | |
| occurrences (all) | 17 | 4 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Infusion site erythema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infusion site pruritus | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Infusion site reaction | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Infusion site thrombosis | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Puncture site erythema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Puncture site pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Pyrexia | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | 1 / 7 (14.29%) | |
| occurrences (all) | 7 | 3 | |
| Reproductive system and breast disorders | | | |
| Genital swelling | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) | |
| occurrences (all) | 1 | 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 2 / 7 (28.57%) | |
| occurrences (all) | 4 | 2 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Haemoptysis | | | |

| | | | |
|--------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Tachypnoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 1 / 7 (14.29%) | |
| occurrences (all) | 4 | 1 | |
| Depressed mood | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 0 / 7 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood albumin decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cells in urine | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 | |
| Lymphocyte count decreased subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 | |
| QRS axis abnormal subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 7 (14.29%) 1 | |
| Injury, poisoning and procedural complications Contusion subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 7 (0.00%) 0 | |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 7 (28.57%) 3 | |
| Palpitations subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 7 (0.00%) 0 | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 7 (14.29%) 1 | |
| Tachycardia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 7 (0.00%) 0 | |
| Nervous system disorders Ataxia subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 7 (0.00%) 0 | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 3 | 2 / 7 (28.57%) 2 | |
| Dysgeusia | | | |

| | | | |
|--------------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 4 / 21 (19.05%) | 1 / 7 (14.29%) | |
| occurrences (all) | 4 | 1 | |
| Headache | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 2 / 7 (28.57%) | |
| occurrences (all) | 14 | 2 | |
| Lethargy | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Memory impairment | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Migraine | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 2 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 5 / 7 (71.43%) | |
| occurrences (all) | 5 | 6 | |
| Nystagmus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 7 (14.29%) | |
| occurrences (all) | 2 | 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 0 / 7 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Leukocytosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |

| | | |
|----------------------------------|------------------|-----------------|
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 7 (14.29%) |
| occurrences (all) | 2 | 2 |
| Abdominal distension | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 7 (14.29%) |
| occurrences (all) | 1 | 1 |
| Abdominal pain | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 1 / 7 (14.29%) |
| occurrences (all) | 8 | 5 |
| Abdominal pain lower | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Abdominal pain upper | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 7 (14.29%) |
| occurrences (all) | 6 | 1 |
| Constipation | | |
| subjects affected / exposed | 11 / 21 (52.38%) | 3 / 7 (42.86%) |
| occurrences (all) | 14 | 3 |
| Diarrhoea | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 4 / 7 (57.14%) |
| occurrences (all) | 22 | 6 |
| Dry mouth | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) |
| occurrences (all) | 2 | 0 |
| Nausea | | |
| subjects affected / exposed | 14 / 21 (66.67%) | 7 / 7 (100.00%) |
| occurrences (all) | 31 | 12 |
| Oesophageal haemorrhage | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) |
| occurrences (all) | 0 | 1 |
| Proctalgia | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) |
| occurrences (all) | 0 | 0 |
| Rectal haemorrhage | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 21 (61.90%) | 7 / 7 (100.00%) | |
| occurrences (all) | 22 | 12 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pruritus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Rash macular | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash papular | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Skin reaction | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Back pain | | | |

| | | | |
|-----------------------------------|-----------------|----------------|--|
| subjects affected / exposed | 7 / 21 (33.33%) | 2 / 7 (28.57%) | |
| occurrences (all) | 10 | 3 | |
| Flank pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Muscle tightness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Neck pain | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |

| | | | |
|------------------------------------|------------------|----------------|--|
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Paronychia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 7 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 7 (14.29%) | |
| occurrences (all) | 0 | 1 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 21 (52.38%) | 3 / 7 (42.86%) | |
| occurrences (all) | 13 | 3 | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 7 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 7 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 7 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 7 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 31 January 2012 | Change of the infusion carrier solution to Ringer Lactate and addition of optional pre- and post-dose and/or parallel-infusion with Ringer Lactate or physiologic saline. |
| 18 July 2012 | Exclusion of patients with uncontrolled baseline hypertension or with history of cerebral hemorrhage, cerebral aneurysm, ischemic stroke or transient ischemic attack. Increased frequency of BP, ECG, and cardiac troponin assessments. |
| 12 May 2014 | Definition of Phase 2a design: inclusion of 40 evaluable patients with specific tumor types; randomization (1:1) to 60 mg/m ² or 30 mg/m ² ; introduction of optional functional imaging. |
| 11 May 2015 | Definition of patient number per tumor type; changed definition of the Efficacy Evaluable Population (EEP); changed patient replacement criteria. |
| 02 June 2015 | Randomization to 30 mg/m ² or 45 mg/m ² instead of 60 mg/m ² because of cardiac safety concerns at 60 mg/m ² . Introduction of additional troponin and ECG assessments. |
| 27 November 2015 | Clarification of EEP definition, patient replacement criteria, and treatment of missing RECIST data. |
| 02 December 2015 | Treatment of all patients at 30 mg/m ² following observation of myocardial injury in one patient at 45 mg/m ² . |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported