



## Clinical trial results:

### A Phase II/III, Multicenter, Randomized, Placebo-controlled Study of Gemcitabine Plus Cisplatin With or Without Bintrafusp Alfa (M7824) as First-line Treatment of Biliary Tract Cancer

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2019-001992-35   |
| Trial protocol           | DE FR PL ES IT   |
| Global end of trial date | 10 November 2022 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 05 November 2023 |
| First version publication date | 20 October 2022  |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |               |
|-----------------------|---------------|
| Sponsor protocol code | MS200647_0055 |
|-----------------------|---------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT04066491 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Merck Healthcare KGaA, Darmstadt, Germany   |
| Sponsor organisation address | Frankfurter Strasse 250, Darmstadt, Germany, 64293  |
| Public contact               | Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.com |
| Scientific contact           | Communication Centre, Merck Healthcare KGaA, Darmstadt, Germany, +49 6151725200, service@merckgroup.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                       | 10 November 2022 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 10 November 2022 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

The aim of the study was to evaluate whether bintrafusp alfa in combination with the current standard of care (SoC) (gemcitabine plus cisplatin) improves overall survival (OS) in chemotherapy and immunotherapy-naïve subjects with locally advanced or metastatic Biliary Tract Cancer (BTC) compared to placebo, gemcitabine and cisplatin.

Protection of trial subjects:

Subject protection was ensured by following high medical and ethical standards in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 20 September 2019 |
| Long term follow-up planned                               | No                |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | China: 15              |
| Country: Number of subjects enrolled | Japan: 53              |
| Country: Number of subjects enrolled | Korea, Republic of: 91 |
| Country: Number of subjects enrolled | Taiwan: 28             |
| Country: Number of subjects enrolled | Australia: 10          |
| Country: Number of subjects enrolled | France: 10             |
| Country: Number of subjects enrolled | Germany: 7             |
| Country: Number of subjects enrolled | Poland: 12             |
| Country: Number of subjects enrolled | Spain: 20              |
| Country: Number of subjects enrolled | United Kingdom: 1      |
| Country: Number of subjects enrolled | Argentina: 16          |
| Country: Number of subjects enrolled | Brazil: 1              |
| Country: Number of subjects enrolled | Chile: 24              |
| Country: Number of subjects enrolled | United States: 21      |
| Worldwide total number of subjects   | 309                    |
| EEA total number of subjects         | 49                     |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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)                      | 152 |
| From 65 to 84 years                       | 157 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

This study was conducted in 2 parts: Safety run-in part and double-blind part. Subjects who enrolled in safety run-in part of study were not eligible to participate in double-blind part.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Overall Study (overall period)         |
| Is this the baseline period? | Yes                                    |
| Allocation method            | Randomised - controlled                |
| Blinding used                | Double blind                           |
| Roles blinded                | Subject, Investigator, Carer, Assessor |

### Arms

|                              |   |
|------------------------------|---|
| Are arms mutually exclusive? | Yes   |
| <b>Arm title</b>             | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin |

Arm description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square ( $\text{mg}/\text{m}^2$ ) and  $25 \text{ mg}/\text{m}^2$  respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

|  |                                       |
|--|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | M7824                                 |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Subjects received intravenous infusion of M7824 at a dose of 2400 mg Q3W 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of  $25 \text{ mg}/\text{m}^2$  on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Gemcitabine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Subjects received Gemcitabine intravenously at a dose of  $1000 \text{ mg}/\text{m}^2$  on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Double-blinded Part: Placebo + Gemcitabine + Cisplatin |
|------------------|--|

Arm description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2

years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

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

Dosage and administration details:

Subjects received intravenous infusion of M7824 matched placebo, Q3W until 2 years (in case of complete response), otherwise until criterion pre-specified in protocol for discontinuation is met.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Cisplatin                             |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of 25 mg/m<sup>2</sup> on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Gemcitabine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Subjects received Gemcitabine intravenously at a dose of 1000 mg/m<sup>2</sup> on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|                  |  |
|------------------|--|
| <b>Arm title</b> | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |
|------------------|--|

Arm description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

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

Dosage and administration details:

Subjects received Cisplatin intravenously at a dose of 25 mg/m<sup>2</sup> on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | Gemcitabine                           |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

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**Dosage and administration details:**

Subjects received Gemcitabine intravenously at a dose of 1000 mg/m<sup>2</sup> on Day 1 and Day 8 of 21-day cycle, for 8 cycles Q3W.

|  |                                       |
|--|---------------------------------------|
| Investigational medicinal product name | M7824                                 |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

**Dosage and administration details:**

Subjects received intravenous infusion of M7824 at a dose of 2400 mg Q3W 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met.

| <b>Number of subjects in period 1</b> | Safety Run-In Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin | Double-blinded Part:<br>Placebo +<br>Gemcitabine +<br>Cisplatin | Double-blinded Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin |
|---------------------------------------|--|---|---|
| Started                               | 12   | 149   | 148   |
| Treated                               | 12   | 149   | 146   |
| Completed                             | 12   | 149   | 146   |
| Not completed                         | 0  | 0   | 2   |
| Randomized, not treated               | -  | -   | 2   |

## Baseline characteristics

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin |
|-----------------------|---|

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m<sup>2</sup>) and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Double-blinded Part: Placebo + Gemcitabine + Cisplatin |
|-----------------------|--|

Reporting group description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

|                       |  |
|-----------------------|--|
| Reporting group title | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |
|-----------------------|--|

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

| Reporting group values    | Safety Run-In Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin | Double-blinded Part:<br>Placebo +<br>Gemcitabine +<br>Cisplatin | Double-blinded Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin |
|---------------------------|--|---|---|
| Number of subjects        | 12   | 149   | 148   |
| Age categorical<br>Units: |  |   |   |

|   |              |              |              |
|---|--------------|--------------|--------------|
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | 66<br>± 11.9 | 64<br>± 10.6 | 63<br>± 10.8 |
| Sex: Female, Male<br>Units: Subjects                                    |              |              |              |
| Female  | 5            | 78           | 68           |
| Male  | 7            | 71           | 80           |
| Ethnicity (NIH/OMB)<br>Units: Subjects                                  |              |              |              |
| Hispanic or Latino  | 1            | 21           | 22           |
| Not Hispanic or Latino  | 11           | 128          | 126          |
| Unknown or Not Reported   | 0            | 0            | 0            |
| Race (NIH/OMB)<br>Units: Subjects                                       |              |              |              |
| American Indian or Alaska Native  | 0            | 1            | 0            |

|   |   |    |    |
|---|---|----|----|
| Asian                                     | 6 | 93 | 90 |
| Native Hawaiian or Other Pacific Islander | 0 | 1  | 0  |
| Black or African American                 | 0 | 0  | 1  |
| White                                     | 6 | 51 | 51 |
| More than one race                        | 0 | 0  | 1  |
| Unknown or Not Reported                   | 0 | 3  | 5  |

|                               |       |  |  |
|-------------------------------|-------|--|--|
| <b>Reporting group values</b> | Total |  |  |
| Number of subjects            | 309   |  |  |
| Age categorical               |       |  |  |
| Units:                        |       |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age Continuous                            |     |  |  |
| Units: Years                              |     |  |  |
| arithmetic mean                           |     |  |  |
| standard deviation                        | -   |  |  |
| Sex: Female, Male                         |     |  |  |
| Units: Subjects                           |     |  |  |
| Female                                    | 151 |  |  |
| Male                                      | 158 |  |  |
| Ethnicity (NIH/OMB)                       |     |  |  |
| Units: Subjects                           |     |  |  |
| Hispanic or Latino                        | 44  |  |  |
| Not Hispanic or Latino                    | 265 |  |  |
| Unknown or Not Reported                   | 0   |  |  |
| Race (NIH/OMB)                            |     |  |  |
| Units: Subjects                           |     |  |  |
| American Indian or Alaska Native          | 1   |  |  |
| Asian                                     | 189 |  |  |
| Native Hawaiian or Other Pacific Islander | 1   |  |  |
| Black or African American                 | 1   |  |  |
| White                                     | 108 |  |  |
| More than one race                        | 1   |  |  |
| Unknown or Not Reported                   | 8   |  |  |



## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin    |
| Reporting group description:<br>Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m <sup>2</sup> ) and 25 mg/m <sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks.  |  |
| Reporting group title  | Double-blinded Part: Placebo + Gemcitabine + Cisplatin |
| Reporting group description:<br>Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m <sup>2</sup> and 25 mg/m <sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.             |  |
| Reporting group title  | Double-blinded Part: M7824 + Gemcitabine + Cisplatin   |
| Reporting group description:<br>Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m <sup>2</sup> and 25 mg/m <sup>2</sup> respectively on Day 1 and Day 8 of 21-day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision. |  |

### Primary: Safety Run-in Part: Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs)

|   |  |
|---|--|
| End point title   | Safety Run-in Part: Number of Subjects Who Experienced Dose Limiting Toxicities (DLTs) <sup>[1][2]</sup> |
| End point description:<br>DLT: toxicity related to study intervention that meets, following criteria as evaluated in open-label, safety run-in: Grade (Gr) 3/4 Immune-related adverse event (irAE) that needs permanent discontinuation of M7824 treatment; a malignant skin lesion induced by M7824 that is local and can be resected with a negative resection margin is not a DLT; Gr 3/4 nonhematologic toxicity other than irAE, A life threatening hematological toxicity (unless clearly attributable to chemotherapy alone), which is hardly medically manageable, including a bleeding event resulting in urgent intervention and admission to an intensive care unit and Gr5 toxicity. DLT analysis set: all subjects who experienced at least 1 DLT (either by Investigator/by Safety Monitoring Committee (SMC)/who completed safety run-in, receiving at least 1 infusion of M7824 and of both gemcitabine and cisplatin and not being withdrawn during the DLT evaluation period for reasons other than toxicity. |  |
| End point type  | Primary  |
| End point timeframe:<br>Day 1 up to Day 21 of Cycle 1 (each Cycle is of 21 days)  |  |
| Notes:<br>[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.<br>Justification: Only descriptive statistics was planned to be reported for this endpoint.<br>[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.<br>Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.  |  |

|                             |  |  |  |  |
|-----------------------------|--|--|--|--|
| <b>End point values</b>     | Safety Run-In<br>Part: M7824 +<br>Gemcitabine +<br>Cisplatin |  |  |  |
| Subject group type          | Reporting group  |  |  |  |
| Number of subjects analysed | 12   |  |  |  |
| Units: Subjects             | 0  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Double-blind Part: Overall Survival

|                 |   |
|-----------------|---|
| End point title | Double-blind Part: Overall Survival <sup>[3]</sup> <sup>[4]</sup> |
|-----------------|---|

End point description:

Overall Survival was defined as the time from study day 1 to the date of death due to any cause. The overall survival was analyzed by using the Kaplan-Meier method. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

Time from study day 1 up to data cutoff (assessed up to 609 days)

Notes:

[3] - 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: Only descriptive statistics was planned to be reported for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

|                               |   |   |  |  |
|-------------------------------|---|---|--|--|
| <b>End point values</b>       | Double-blinded<br>Part: Placebo +<br>Gemcitabine +<br>Cisplatin | Double-blinded<br>Part: M7824 +<br>Gemcitabine +<br>Cisplatin |  |  |
| Subject group type            | Reporting group   | Reporting group   |  |  |
| Number of subjects analysed   | 18  | 23  |  |  |
| Units: Months                 |   |   |  |  |
| median (full range (min-max)) | 11.5 (0.9 to<br>15.2)   | 11.5 (0.2 to<br>13.9)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Safety Run-in Part: Number of Subjects With Grade Greater than or Equal ( $\geq$ ) 3 Laboratory Abnormalities

|                 |  |
|-----------------|--|
| End point title | Safety Run-in Part: Number of Subjects With Grade Greater than or Equal ( $\geq$ ) 3 Laboratory Abnormalities <sup>[5]</sup> |
|-----------------|--|

End point description:

Laboratory investigation included hematology and biochemistry. The number of subjects with Grade  $\geq$ 3 laboratory abnormalities were reported. Severity of grade 3 or higher TEAEs were graded using

NCI-CTCAE v5.0 toxicity grades, as follows: Grade 3 = Severe; Grade 4 = Life-threatening and Grade 5 = Death. The safety run-in (SRI) analysis set included all subjects from the safety run-in part who were administered any dose of any study intervention.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Time from first treatment up to data cutoff (assessed up to 609 days) |           |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.

|                               |   |  |  |  |
|-------------------------------|---|--|--|--|
| <b>End point values</b>       | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin |  |  |  |
| Subject group type            | Reporting group                                     |  |  |  |
| Number of subjects analysed   | 12  |  |  |  |
| Units: Subjects               |   |  |  |  |
| Hemoglobin low                | 6   |  |  |  |
| Leukocytes low                | 4   |  |  |  |
| Neutrophils low               | 6   |  |  |  |
| Platelets low                 | 3   |  |  |  |
| Alanine Aminotransferase high | 2   |  |  |  |
| Bilirubin high                | 1   |  |  |  |
| Creatinine high               | 1   |  |  |  |
| Lipase high                   | 1   |  |  |  |
| Potassium low                 | 1   |  |  |  |
| Lymphocytes low               | 2   |  |  |  |
| Corrected Calcium high        | 1   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Safety Run-in Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs) and Treatment Related TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0

|                 |  |
|-----------------|--|
| End point title | Safety Run-in Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs) and Treatment Related TEAEs According to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0 <sup>[6]</sup> |
|-----------------|--|

End point description:

Adverse Event (AE) was defined any untoward medical occurrence in a subject administered with a study drug, which does not necessarily had a causal relationship with this treatment. Serious AE was defined AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAE was defined as events with onset date or worsening during the on treatment period. TEAEs included serious TEAEs and non-serious TEAEs. Safety run-in (SRI) analysis set included all subjects from the safety run-in part who were administered any dose of any study intervention.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Time from first treatment up to data cutoff (assessed up to 609 days) |           |

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only safety run-in part. Therefore, other arms has not been selected.

| End point values                      | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin |  |  |  |
|---------------------------------------|---|--|--|--|
| Subject group type                    | Reporting group                                     |  |  |  |
| Number of subjects analysed           | 12  |  |  |  |
| Units: Subjects                       |   |  |  |  |
| Subjects with TEAEs                   | 12  |  |  |  |
| Subjects with Serious TEAEs           | 5   |  |  |  |
| Subjects with Treatment-related TEAEs | 11  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double-blind Part: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

|                 |  |
|-----------------|--|
| End point title | Double-blind Part: Percentage of Subjects With Confirmed Objective Response According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) <sup>[7]</sup> |
|-----------------|--|

End point description:

Percentage of subjects with confirmed objective response that is at least one overall assessment of complete response (CR) or partial response (PR) reported here. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the sum of the longest diameter (SLD) of all lesions. Confirmed CR = at least 2 determinations of CR at least 4 weeks apart and before progression. Confirmed PR = at least 2 determinations of PR at least 4 weeks apart and before progression (and not qualifying for a CR). Confirmed objective response was determined according to RECIST v1.1 and as adjudicated by IRC. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

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

End point timeframe:

Time from randomization of study drug up to data cut off (assessed up to 609 days)

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

| End point values                 | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                                      |  |  |
| Number of subjects analysed      | 77   | 73   |  |  |
| Units: Percentage of subjects    |  |  |  |  |
| number (confidence interval 95%) | 19.5 (11.3 to 30.1)                                    | 31.5 (21.1 to 43.4)                                  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double-blind Part: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) Assessed by Independent Review Committee (IRC)

|                 |   |
|-----------------|---|
| End point title | Double-blind Part: Progression-Free Survival (PFS) According to Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1) Assessed by Independent Review Committee (IRC) <sup>[8]</sup> |
|-----------------|---|

#### End point description:

Progression free survival was defined as the time from randomization of study intervention until the first documentation of disease progression (PD) or death due to any cause in the absence of documented PD, whichever occurred first. PD: At least a 20 percent (%) increase in the sum of the longest diameter (SLD) taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

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

#### End point timeframe:

Time from randomization of study drug until the first documentation of PD or death, assessed up to 609 days

#### Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

| End point values                 | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |  |  |
|----------------------------------|--|--|--|--|
| Subject group type               | Reporting group  | Reporting group                                      |  |  |
| Number of subjects analysed      | 44   | 49   |  |  |
| Units: Months                    |  |  |  |  |
| median (confidence interval 95%) | 5.6 (4.2 to 6.9)                                       | 5.5 (2.8 to 6.7)                                     |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Double-blind Part: Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC)

|                 |  |
|-----------------|--|
| End point title | Double-blind Part: Duration of Response (DOR) According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) as Assessed by Independent Review Committee (IRC) <sup>[9]</sup> |
|-----------------|--|

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**End point description:**

DOR was defined for subjects with objective response, as the time from first documentation of objective response (confirmed Complete Response [CR] or Partial Response [PR]) to the date of first documentation of progression disease (PD) or death due to any cause, whichever occurred first. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. PD: At least a 20 percent (%) increase in the SLD, taking as reference the smallest SLD recorded from baseline or the appearance of 1 or more new lesions. DOR was determined according to RECIST v1.1 and assessed by IRC. Results were calculated based on Kaplan-Meier estimates. Intent-to-Treat analysis set included all randomized subjects. Here, "Number of Subjects Analyzed" signifies those subjects who were evaluable for this endpoint.

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

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**End point timeframe:**

From first documented objective response to PD or death due to any cause, assessed up to 609 days

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**Notes:**

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

| End point values              | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |  |  |
|-------------------------------|--|--|--|--|
| Subject group type            | Reporting group  | Reporting group                                      |  |  |
| Number of subjects analysed   | 7  | 9  |  |  |
| Units: Months                 |  |  |  |  |
| median (full range (min-max)) | 12.5 (2.7 to 12.5)                                     | 7.0 (1.4 to 8.3)                                     |  |  |

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**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Double-blind Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs), Treatment Related TEAEs and Adverse Events of Special Interest (AESIs) According to NCI-CTCAE version 5.0**

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|                 |   |
|-----------------|---|
| End point title | Double-blind Part: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs), Serious TEAEs (SAEs), Treatment Related TEAEs and Adverse Events of Special Interest (AESIs) According to NCI-CTCAE version 5.0 <sup>[10]</sup> |
|-----------------|---|

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**End point description:**

AE: any untoward medical occurrence in a subject administered with a study drug, which does not necessarily had a causal relationship with this treatment. Serious AE: AE that resulted in any of following outcomes: death; life threatening; persistent/significant disability/incapacity; initial/prolonged inpatient hospitalization; congenital anomaly/birth defect. TEAE: events with onset date/worsening during the on-treatment period. TEAEs included serious TEAEs and non-serious TEAEs. Adverse events of special interest (AESI) are serious/non-serious AEs that are of clinical interest and should be closely followed. AESIs include following: Infusion-related reactions including immediate hypersensitivity; Immune-related AEs; Transforming growth factor beta (TGFβ) inhibition mediated skin reactions; Anemia; Bleeding AEs. Safety analysis set: all subjects who were administered at least 1 dose of any study treatment (M7824, placebo, gemcitabine or cisplatin).

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

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**End point timeframe:**

Time from first treatment up to data cutoff (assessed up to 609 days)

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Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

| End point values                      | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |  |  |
|---------------------------------------|--|--|--|--|
| Subject group type                    | Reporting group  | Reporting group                                      |  |  |
| Number of subjects analysed           | 149  | 146  |  |  |
| Units: Subjects                       |  |  |  |  |
| Subjects with TEAEs                   | 145  | 140  |  |  |
| Subjects with Serious TEAEs           | 36   | 58   |  |  |
| Subjects with Treatment-related TEAEs | 136  | 133  |  |  |
| Subjects with AESIs                   | 8  | 16   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Double-blind Part: Durable Response of at least 6 months According to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator

|                 |   |
|-----------------|---|
| End point title | Double-blind Part: Durable Response of at least 6 months According to Response Evaluation Criteria In Solid Tumors (RECIST) Version 1.1 as Assessed by Investigator <sup>[11]</sup> |
|-----------------|---|

End point description:

Durable Response was defined as the number of subjects with confirmed objective response (CR or PR) according to RECIST 1.1, determined by Investigator with duration of at least 6 months. CR: Disappearance of all evidence of target and non-target lesions. PR: At least 30% reduction from baseline in the SLD of all lesions. Based on a review of data conducted by the Independent Data Monitoring Committee (IDMC), Sponsor has decided to discontinue this study as the study is unlikely to achieve the primary objective of overall survival. Subsequently, the data for this endpoint was not collected and analyzed.

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

End point timeframe:

Time from first treatment assessed up to 1148 days

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: It was planned to report data for only double-blind part. Therefore, other arms has not been selected.

| End point values            | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |  |  |
|-----------------------------|--|--|--|--|
| Subject group type          | Reporting group  | Reporting group                                      |  |  |
| Number of subjects analysed | 0 <sup>[12]</sup>                                      | 0 <sup>[13]</sup>                                    |  |  |
| Units: subjects             |  |  |  |  |

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Notes:

[12] - Data for this endpoint was not collected and analyzed.

[13] - Data for this endpoint was not collected and analyzed.

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### **Statistical analyses**

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Time from first treatment up to data cutoff (assessed up to 609 days)

Adverse event reporting additional description:

Safety Run-In Part: The safety run-in (SRI) analysis set includes all subjects from the safety run-in part who were administered any dose of any study intervention and double-blinded part safety analysis set included all randomized subjects who were administered at least one dose of study treatment (M7824, Placebo, Gemcitabine or Cisplatin).

|                 |                |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

### Reporting groups

|                       |  |
|-----------------------|--|
| Reporting group title | Double-blinded Part: Placebo + Gemcitabine + Cisplatin |
|-----------------------|--|

Reporting group description:

Subjects received intravenous infusion of M7824 matched placebo, once every 3 weeks (Q3W) until 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

|                       |   |
|-----------------------|---|
| Reporting group title | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin |
|-----------------------|---|

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of Complete Response), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 milligram per meter square (mg/m<sup>2</sup>) and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks.

|                       |  |
|-----------------------|--|
| Reporting group title | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |
|-----------------------|--|

Reporting group description:

Subjects received intravenous infusion of M7824 at a dose of 2400 milligrams (mg), once every 3 weeks (Q3W) 2 years (in case of CR), otherwise until criterion pre-specified in protocol for discontinuation is met, in combination with intravenous infusion of Gemcitabine and Cisplatin at a dose of 1000 mg/m<sup>2</sup> and 25 mg/m<sup>2</sup> respectively on Day 1 and Day 8 of 21- day cycle, for 8 cycles every 3 weeks. In case of any missed dose for chemotherapy, gemcitabine and cisplatin combination administered on Day 15 of that cycle or at the end of the scheduled 8 cycles (up to 16 administrations of gemcitabine and cisplatin combination). The administration of the missed dose on Day 15 or at the end of 8 cycles is Investigator's clinical decision.

| Serious adverse events  | Double-blinded Part: Placebo + Gemcitabine + Cisplatin | Safety Run-In Part: M7824 + Gemcitabine + Cisplatin | Double-blinded Part: M7824 + Gemcitabine + Cisplatin |
|---|--|---|--|
| Total subjects affected by serious adverse events                   |  |   |  |
| subjects affected / exposed   | 36 / 149 (24.16%)                                      | 5 / 12 (41.67%)                                     | 58 / 146 (39.73%)                                    |
| number of deaths (all causes)                                       | 26   | 7   | 31   |
| number of deaths resulting from adverse events                      |  |   |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |   |  |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Cancer pain                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Metastases to bone                              |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 0 / 12 (0.00%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Squamous cell carcinoma of skin                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Squamous cell carcinoma                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tumour associated fever                         |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Vascular disorders                              |                 |                |                 |
| Embolism  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypertension                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pelvic venous thrombosis                        |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| General disorders and administration            |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| site conditions                                 |                 |                |                 |
| Asthenia  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 12 (8.33%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pyrexia   |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 1 / 12 (8.33%) | 4 / 146 (2.74%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1          | 3 / 4           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Oedema peripheral                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Malaise   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hernia  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Fatigue   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Disease progression                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Death   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 1 / 1           |
| Chills  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Immune system disorders                         |                 |                |                 |
| Anaphylactic shock                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders |                 |                |                 |
| Epistaxis                                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pleural effusion                                |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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 distress                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Respiratory failure                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Product issues                                  |                 |                |                 |
| Device occlusion                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Investigations                                  |                 |                |                 |
| Lymphocyte count decreased                      |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Neutrophil count decreased                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Lipase increased                                |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood sodium decreased                          |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood bilirubin increased                       |                 |                |                 |
| subjects affected / exposed                     | 3 / 149 (2.01%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood albumin decreased                         |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Alanine aminotransferase increased              |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Platelet count decreased                        |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Transaminases increased                         |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 12 (8.33%) | 0 / 146 (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           |
| Injury, poisoning and procedural complications  |                 |                |                 |
| Incisional hernia                               |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Infusion related reaction                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 3 / 146 (2.05%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Traumatic intracranial haemorrhage              |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Cardiac disorders                               |                 |                |                 |
| Cardiac arrest                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Nervous system disorders                        |                 |                |                 |
| Cerebral infarction                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cerebral ischaemia                              |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Encephalopathy                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Haemorrhage intracranial                        |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Ischaemic cerebral infarction                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Facial paralysis                                |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Blood and lymphatic system disorders            |                 |                |                 |
| Anaemia   |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 0 / 12 (0.00%) | 7 / 146 (4.79%) |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0          | 7 / 7           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pancytopenia                                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Neutropenia                                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Febrile neutropenia                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Thrombocytopenia                                |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 1 / 12 (8.33%) | 0 / 146 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1          | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Eye disorders                                   |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Ulcerative keratitis                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastrointestinal disorders                      |                 |                |                 |
| Ascites   |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Abdominal pain upper                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Abdominal pain                                  |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Colitis   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Duodenal ulcer haemorrhage                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 12 (8.33%) | 0 / 146 (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           |
| Gastric haemorrhage                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| 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 haemorrhage                    |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 1 / 12 (8.33%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric ulcer                                   |                 |                |                 |



|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 0           |
| Gastric stenosis                                    |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 1 / 1           |
| Gastrointestinal vascular malformation haemorrhagic |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 0           |
| Intestinal obstruction                              |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 0           |
| Haematochezia                                       |                 |                |                 |
| subjects affected / exposed                         | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Lower gastrointestinal haemorrhage                  |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 0           |
| Upper gastrointestinal haemorrhage                  |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 1           |
| Rectal haemorrhage                                  |                 |                |                 |
| subjects affected / exposed                         | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0          | 0 / 0           |
| Pancreatitis  |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Obstruction gastric                             |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Nausea  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 3 / 146 (2.05%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vomiting  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 3 / 146 (2.05%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 3 / 3           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatobiliary disorders                         |                 |                |                 |
| Cholangitis                                     |                 |                |                 |
| subjects affected / exposed                     | 5 / 149 (3.36%) | 0 / 12 (0.00%) | 6 / 146 (4.11%) |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0          | 0 / 6           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Cholecystitis                                   |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 1 / 12 (8.33%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Cholestasis                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hepatic failure                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Jaundice cholestatic                            |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Biliary obstruction                             |                 |                |                 |
| subjects affected / exposed                     | 3 / 149 (2.01%) | 1 / 12 (8.33%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Bile duct stone                                 |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Bile duct stenosis                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Immune-mediated hepatitis                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Skin and subcutaneous tissue disorders          |                 |                |                 |
| Urticaria                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Erythema multiforme                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Dermatitis                                      |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal and urinary disorders                     |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Dysuria   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Acute kidney injury                             |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 1 / 12 (8.33%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1          | 2 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Haematuria                                      |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Renal failure                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Tubulointerstitial nephritis                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Endocrine disorders                             |                 |                |                 |
| Hypothyroidism                                  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypopituitarism                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypophysitis                                    |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Adrenal insufficiency                           |                 |                |                 |

|  |                 |                |                 |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed                            | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0          | 1 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0          | 0 / 0           |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                |                 |
| Bone pain  |                 |                |                 |
| subjects affected / exposed                            | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| <b>Infections and infestations</b>                     |                 |                |                 |
| Abdominal infection                                    |                 |                |                 |
| subjects affected / exposed                            | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0          | 0 / 0           |
| Bacteraemia  |                 |                |                 |
| subjects affected / exposed                            | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0          | 0 / 0           |
| Biliary sepsis   |                 |                |                 |
| subjects affected / exposed                            | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0          | 0 / 0           |
| Biliary tract infection                                |                 |                |                 |
| subjects affected / exposed                            | 3 / 149 (2.01%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all        | 0 / 3           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all             | 0 / 1           | 0 / 0          | 0 / 0           |
| COVID-19   |                 |                |                 |
| subjects affected / exposed                            | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Diarrhoea infectious                                   |                 |                |                 |
| subjects affected / exposed                            | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0          | 0 / 0           |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| Herpes simplex encephalitis                     |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| Klebsiella infection                            |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Liver abscess                                   |                 |                |                 |
| subjects affected / exposed                     | 2 / 149 (1.34%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Vascular device infection                       |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pneumonia                                       |                 |                |                 |
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Pseudomonas infection                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Sepsis  |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 1           |
| Soft tissue infection                           |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Urinary tract infection                         |                 |                |                 |

|   |                 |                |                 |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed                     | 1 / 149 (0.67%) | 0 / 12 (0.00%) | 0 / 146 (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           |
| <b>Metabolism and nutrition disorders</b>       |                 |                |                 |
| Hyponatraemia                                   |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Hypomagnesaemia                                 |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Dehydration                                     |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 1 / 146 (0.68%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |
| Decreased appetite                              |                 |                |                 |
| subjects affected / exposed                     | 0 / 149 (0.00%) | 0 / 12 (0.00%) | 2 / 146 (1.37%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0          | 1 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0          | 0 / 0           |

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

| <b>Non-serious adverse events</b>                           | Double-blinded Part:<br>Placebo +<br>Gemcitabine +<br>Cisplatin | Safety Run-In Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin | Double-blinded Part:<br>M7824 +<br>Gemcitabine +<br>Cisplatin |
|---|---|--|---|
| Total subjects affected by non-serious adverse events       |   |  |   |
| subjects affected / exposed                                 | 142 / 149 (95.30%)  | 12 / 12 (100.00%)  | 134 / 146 (91.78%)  |
| <b>Vascular disorders</b>                                   |   |  |   |
| Hypertension  |   |  |   |
| subjects affected / exposed                                 | 11 / 149 (7.38%)  | 1 / 12 (8.33%)   | 6 / 146 (4.11%)   |
| occurrences (all)   | 11  | 1  | 6   |
| <b>General disorders and administration site conditions</b> |   |  |   |
| Oedema peripheral   |   |  |   |

|   |                   |                 |                   |
|---|-------------------|-----------------|-------------------|
| subjects affected / exposed                     | 10 / 149 (6.71%)  | 1 / 12 (8.33%)  | 9 / 146 (6.16%)   |
| occurrences (all)                               | 10                | 1               | 9                 |
| Mucosal inflammation                            |                   |                 |                   |
| subjects affected / exposed                     | 4 / 149 (2.68%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)                               | 4                 | 1               | 1                 |
| Malaise   |                   |                 |                   |
| subjects affected / exposed                     | 11 / 149 (7.38%)  | 0 / 12 (0.00%)  | 5 / 146 (3.42%)   |
| occurrences (all)                               | 11                | 0               | 5                 |
| Generalised oedema                              |                   |                 |                   |
| subjects affected / exposed                     | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                               | 0                 | 1               | 0                 |
| Fatigue   |                   |                 |                   |
| subjects affected / exposed                     | 35 / 149 (23.49%) | 4 / 12 (33.33%) | 29 / 146 (19.86%) |
| occurrences (all)                               | 35                | 4               | 29                |
| Asthenia  |                   |                 |                   |
| subjects affected / exposed                     | 18 / 149 (12.08%) | 2 / 12 (16.67%) | 23 / 146 (15.75%) |
| occurrences (all)                               | 18                | 2               | 23                |
| Pyrexia   |                   |                 |                   |
| subjects affected / exposed                     | 19 / 149 (12.75%) | 3 / 12 (25.00%) | 33 / 146 (22.60%) |
| occurrences (all)                               | 19                | 3               | 33                |
| Respiratory, thoracic and mediastinal disorders |                   |                 |                   |
| Pulmonary embolism                              |                   |                 |                   |
| subjects affected / exposed                     | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 2 / 146 (1.37%)   |
| occurrences (all)                               | 1                 | 1               | 2                 |
| Epistaxis                                       |                   |                 |                   |
| subjects affected / exposed                     | 3 / 149 (2.01%)   | 2 / 12 (16.67%) | 19 / 146 (13.01%) |
| occurrences (all)                               | 3                 | 2               | 19                |
| Dyspnoea exertional                             |                   |                 |                   |
| subjects affected / exposed                     | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)                               | 0                 | 1               | 3                 |
| Cough   |                   |                 |                   |
| subjects affected / exposed                     | 9 / 149 (6.04%)   | 3 / 12 (25.00%) | 3 / 146 (2.05%)   |
| occurrences (all)                               | 9                 | 3               | 3                 |
| Psychiatric disorders                           |                   |                 |                   |



|  |                         |                      |                        |
|--|-------------------------|----------------------|------------------------|
| Adjustment disorder<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 149 (0.67%)<br>1    | 1 / 12 (8.33%)<br>1  | 0 / 146 (0.00%)<br>0   |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 6 / 149 (4.03%)<br>6    | 1 / 12 (8.33%)<br>1  | 3 / 146 (2.05%)<br>3   |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 2 / 149 (1.34%)<br>2    | 1 / 12 (8.33%)<br>1  | 12 / 146 (8.22%)<br>12 |
| Investigations   |                         |                      |                        |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 20 / 149 (13.42%)<br>20 | 2 / 12 (16.67%)<br>2 | 13 / 146 (8.90%)<br>13 |
| Amylase increased<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 149 (5.37%)<br>8    | 2 / 12 (16.67%)<br>2 | 4 / 146 (2.74%)<br>4   |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 22 / 149 (14.77%)<br>22 | 2 / 12 (16.67%)<br>2 | 13 / 146 (8.90%)<br>13 |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)              | 4 / 149 (2.68%)<br>4    | 1 / 12 (8.33%)<br>1  | 1 / 146 (0.68%)<br>1   |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 8 / 149 (5.37%)<br>8    | 1 / 12 (8.33%)<br>1  | 7 / 146 (4.79%)<br>7   |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)            | 14 / 149 (9.40%)<br>14  | 0 / 12 (0.00%)<br>0  | 9 / 146 (6.16%)<br>9   |
| Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)           | 7 / 149 (4.70%)<br>7    | 1 / 12 (8.33%)<br>1  | 6 / 146 (4.11%)<br>6   |
| Blood magnesium decreased<br>subjects affected / exposed<br>occurrences (all)            | 3 / 149 (2.01%)<br>3    | 1 / 12 (8.33%)<br>1  | 2 / 146 (1.37%)<br>2   |
| Creatinine renal clearance decreased   |                         |                      |                        |

|  |                   |                 |                   |
|--|-------------------|-----------------|-------------------|
| subjects affected / exposed                    | 9 / 149 (6.04%)   | 1 / 12 (8.33%)  | 4 / 146 (2.74%)   |
| occurrences (all)                              | 9                 | 1               | 4                 |
| Gamma-glutamyltransferase increased            |                   |                 |                   |
| subjects affected / exposed                    | 10 / 149 (6.71%)  | 1 / 12 (8.33%)  | 4 / 146 (2.74%)   |
| occurrences (all)                              | 10                | 1               | 4                 |
| Haemoglobin decreased                          |                   |                 |                   |
| subjects affected / exposed                    | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)                              | 0                 | 1               | 3                 |
| Iron binding capacity total decreased          |                   |                 |                   |
| subjects affected / exposed                    | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                              | 0                 | 1               | 0                 |
| Lipase increased                               |                   |                 |                   |
| subjects affected / exposed                    | 9 / 149 (6.04%)   | 2 / 12 (16.67%) | 5 / 146 (3.42%)   |
| occurrences (all)                              | 9                 | 2               | 5                 |
| Neutrophil count decreased                     |                   |                 |                   |
| subjects affected / exposed                    | 59 / 149 (39.60%) | 5 / 12 (41.67%) | 28 / 146 (19.18%) |
| occurrences (all)                              | 59                | 5               | 28                |
| White blood cell count decreased               |                   |                 |                   |
| subjects affected / exposed                    | 36 / 149 (24.16%) | 3 / 12 (25.00%) | 19 / 146 (13.01%) |
| occurrences (all)                              | 36                | 3               | 19                |
| Platelet count decreased                       |                   |                 |                   |
| subjects affected / exposed                    | 38 / 149 (25.50%) | 3 / 12 (25.00%) | 34 / 146 (23.29%) |
| occurrences (all)                              | 38                | 3               | 34                |
| Injury, poisoning and procedural complications |                   |                 |                   |
| Infusion related reaction                      |                   |                 |                   |
| subjects affected / exposed                    | 3 / 149 (2.01%)   | 1 / 12 (8.33%)  | 6 / 146 (4.11%)   |
| occurrences (all)                              | 3                 | 1               | 6                 |
| Cardiac disorders                              |                   |                 |                   |
| Bradycardia                                    |                   |                 |                   |
| subjects affected / exposed                    | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                              | 0                 | 1               | 0                 |
| Tachycardia                                    |                   |                 |                   |
| subjects affected / exposed                    | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                              | 1                 | 1               | 0                 |
| Nervous system disorders                       |                   |                 |                   |

|                                      |                   |                 |                   |
|--------------------------------------|-------------------|-----------------|-------------------|
| Dizziness                            |                   |                 |                   |
| subjects affected / exposed          | 13 / 149 (8.72%)  | 0 / 12 (0.00%)  | 8 / 146 (5.48%)   |
| occurrences (all)                    | 13                | 0               | 8                 |
| Taste disorder                       |                   |                 |                   |
| subjects affected / exposed          | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                    | 0                 | 1               | 0                 |
| Peripheral sensory neuropathy        |                   |                 |                   |
| subjects affected / exposed          | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 5 / 146 (3.42%)   |
| occurrences (all)                    | 1                 | 1               | 5                 |
| Headache                             |                   |                 |                   |
| subjects affected / exposed          | 13 / 149 (8.72%)  | 0 / 12 (0.00%)  | 12 / 146 (8.22%)  |
| occurrences (all)                    | 13                | 0               | 12                |
| Dysgeusia                            |                   |                 |                   |
| subjects affected / exposed          | 3 / 149 (2.01%)   | 2 / 12 (16.67%) | 6 / 146 (4.11%)   |
| occurrences (all)                    | 3                 | 2               | 6                 |
| Blood and lymphatic system disorders |                   |                 |                   |
| Anaemia                              |                   |                 |                   |
| subjects affected / exposed          | 79 / 149 (53.02%) | 6 / 12 (50.00%) | 78 / 146 (53.42%) |
| occurrences (all)                    | 79                | 6               | 78                |
| Lymphopenia                          |                   |                 |                   |
| subjects affected / exposed          | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)                    | 1                 | 1               | 1                 |
| Leukopenia                           |                   |                 |                   |
| subjects affected / exposed          | 7 / 149 (4.70%)   | 1 / 12 (8.33%)  | 4 / 146 (2.74%)   |
| occurrences (all)                    | 7                 | 1               | 4                 |
| Neutropenia                          |                   |                 |                   |
| subjects affected / exposed          | 40 / 149 (26.85%) | 1 / 12 (8.33%)  | 25 / 146 (17.12%) |
| occurrences (all)                    | 40                | 1               | 25                |
| Thrombocytopenia                     |                   |                 |                   |
| subjects affected / exposed          | 12 / 149 (8.05%)  | 1 / 12 (8.33%)  | 14 / 146 (9.59%)  |
| occurrences (all)                    | 12                | 1               | 14                |
| Ear and labyrinth disorders          |                   |                 |                   |
| Tinnitus                             |                   |                 |                   |
| subjects affected / exposed          | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)                    | 0                 | 1               | 3                 |
| Ear discomfort                       |                   |                 |                   |

|                             |                   |                 |                   |
|-----------------------------|-------------------|-----------------|-------------------|
| subjects affected / exposed | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 0                 | 1               | 0                 |
| Ear congestion              |                   |                 |                   |
| subjects affected / exposed | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 0                 | 1               | 0                 |
| Eye disorders               |                   |                 |                   |
| Eye pain                    |                   |                 |                   |
| subjects affected / exposed | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 1                 | 1               | 0                 |
| Vision blurred              |                   |                 |                   |
| subjects affected / exposed | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 1                 | 1               | 0                 |
| Retinal haemorrhage         |                   |                 |                   |
| subjects affected / exposed | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 0                 | 1               | 0                 |
| Gastrointestinal disorders  |                   |                 |                   |
| Abdominal pain              |                   |                 |                   |
| subjects affected / exposed | 11 / 149 (7.38%)  | 2 / 12 (16.67%) | 13 / 146 (8.90%)  |
| occurrences (all)           | 11                | 2               | 13                |
| Abdominal distension        |                   |                 |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 12 (8.33%)  | 5 / 146 (3.42%)   |
| occurrences (all)           | 3                 | 1               | 5                 |
| Abdominal pain lower        |                   |                 |                   |
| subjects affected / exposed | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 0                 | 1               | 0                 |
| Abdominal pain upper        |                   |                 |                   |
| subjects affected / exposed | 6 / 149 (4.03%)   | 2 / 12 (16.67%) | 5 / 146 (3.42%)   |
| occurrences (all)           | 6                 | 2               | 5                 |
| Diarrhoea                   |                   |                 |                   |
| subjects affected / exposed | 15 / 149 (10.07%) | 3 / 12 (25.00%) | 20 / 146 (13.70%) |
| occurrences (all)           | 15                | 3               | 20                |
| Constipation                |                   |                 |                   |
| subjects affected / exposed | 51 / 149 (34.23%) | 4 / 12 (33.33%) | 40 / 146 (27.40%) |
| occurrences (all)           | 51                | 4               | 40                |
| Ascites                     |                   |                 |                   |

|  |                         |                      |                         |
|--|-------------------------|----------------------|-------------------------|
| subjects affected / exposed<br>occurrences (all)   | 9 / 149 (6.04%)<br>9    | 0 / 12 (0.00%)<br>0  | 1 / 146 (0.68%)<br>1    |
| Aphthous ulcer<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 149 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  | 0 / 146 (0.00%)<br>0    |
| Dyspepsia<br>subjects affected / exposed<br>occurrences (all)  | 10 / 149 (6.71%)<br>10  | 1 / 12 (8.33%)<br>1  | 6 / 146 (4.11%)<br>6    |
| Gingival bleeding<br>subjects affected / exposed<br>occurrences (all)                                  | 0 / 149 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  | 13 / 146 (8.90%)<br>13  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 32 / 149 (21.48%)<br>32 | 1 / 12 (8.33%)<br>1  | 31 / 146 (21.23%)<br>31 |
| Stomatitis<br>subjects affected / exposed<br>occurrences (all)   | 6 / 149 (4.03%)<br>6    | 0 / 12 (0.00%)<br>0  | 16 / 146 (10.96%)<br>16 |
| Rectal haemorrhage<br>subjects affected / exposed<br>occurrences (all)                                 | 1 / 149 (0.67%)<br>1    | 1 / 12 (8.33%)<br>1  | 1 / 146 (0.68%)<br>1    |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 72 / 149 (48.32%)<br>72 | 6 / 12 (50.00%)<br>6 | 64 / 146 (43.84%)<br>64 |
| Hepatobiliary disorders<br>Hyperbilirubinaemia<br>subjects affected / exposed<br>occurrences (all)     | 0 / 149 (0.00%)<br>0    | 1 / 12 (8.33%)<br>1  | 0 / 146 (0.00%)<br>0    |
| Cholangitis<br>subjects affected / exposed<br>occurrences (all)  | 3 / 149 (2.01%)<br>3    | 1 / 12 (8.33%)<br>1  | 2 / 146 (1.37%)<br>2    |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all) | 16 / 149 (10.74%)<br>16 | 0 / 12 (0.00%)<br>0  | 5 / 146 (3.42%)<br>5    |
| Blister  |                         |                      |                         |

|  |                   |                 |                   |
|--|-------------------|-----------------|-------------------|
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                                  | 0                 | 1               | 0                 |
| <b>Dermatitis</b>                                  |                   |                 |                   |
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)                                  | 0                 | 1               | 3                 |
| <b>Erythema multiforme</b>                         |                   |                 |                   |
| subjects affected / exposed                        | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 2 / 146 (1.37%)   |
| occurrences (all)                                  | 1                 | 1               | 2                 |
| <b>Palmar-plantar erythrodysaesthesia syndrome</b> |                   |                 |                   |
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)                                  | 0                 | 1               | 1                 |
| <b>Urticaria</b>                                   |                   |                 |                   |
| subjects affected / exposed                        | 6 / 149 (4.03%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)                                  | 6                 | 1               | 3                 |
| <b>Rash papular</b>                                |                   |                 |                   |
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)                                  | 0                 | 1               | 1                 |
| <b>Rash maculo-papular</b>                         |                   |                 |                   |
| subjects affected / exposed                        | 4 / 149 (2.68%)   | 0 / 12 (0.00%)  | 10 / 146 (6.85%)  |
| occurrences (all)                                  | 4                 | 0               | 10                |
| <b>Rash</b>  |                   |                 |                   |
| subjects affected / exposed                        | 21 / 149 (14.09%) | 6 / 12 (50.00%) | 36 / 146 (24.66%) |
| occurrences (all)                                  | 21                | 6               | 36                |
| <b>Pruritus</b>                                    |                   |                 |                   |
| subjects affected / exposed                        | 14 / 149 (9.40%)  | 4 / 12 (33.33%) | 35 / 146 (23.97%) |
| occurrences (all)                                  | 14                | 4               | 35                |
| <b>Pigmentation disorder</b>                       |                   |                 |                   |
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)                                  | 0                 | 1               | 0                 |
| <b>Skin lesion</b>                                 |                   |                 |                   |
| subjects affected / exposed                        | 0 / 149 (0.00%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)                                  | 0                 | 1               | 1                 |
| <b>Renal and urinary disorders</b>                 |                   |                 |                   |
| Pollakiuria  |                   |                 |                   |

|  |                      |                     |                      |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 2 / 149 (1.34%)<br>2 | 1 / 12 (8.33%)<br>1 | 0 / 146 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders  |                      |                     |                      |
| Back pain  |                      |                     |                      |
| subjects affected / exposed                      | 6 / 149 (4.03%)      | 1 / 12 (8.33%)      | 8 / 146 (5.48%)      |
| occurrences (all)                                | 6                    | 1                   | 8                    |
| Myalgia  |                      |                     |                      |
| subjects affected / exposed                      | 10 / 149 (6.71%)     | 0 / 12 (0.00%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 10                   | 0                   | 0                    |
| Infections and infestations                      |                      |                     |                      |
| Urinary tract infection                          |                      |                     |                      |
| subjects affected / exposed                      | 4 / 149 (2.68%)      | 0 / 12 (0.00%)      | 9 / 146 (6.16%)      |
| occurrences (all)                                | 4                    | 0                   | 9                    |
| Systemic candida                                 |                      |                     |                      |
| subjects affected / exposed                      | 0 / 149 (0.00%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 0                    | 1                   | 0                    |
| Pneumonia  |                      |                     |                      |
| subjects affected / exposed                      | 1 / 149 (0.67%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 1                    | 1                   | 0                    |
| Oral candidiasis                                 |                      |                     |                      |
| subjects affected / exposed                      | 1 / 149 (0.67%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 1                    | 1                   | 0                    |
| Herpes zoster                                    |                      |                     |                      |
| subjects affected / exposed                      | 0 / 149 (0.00%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 0                    | 1                   | 0                    |
| Cystitis   |                      |                     |                      |
| subjects affected / exposed                      | 1 / 149 (0.67%)      | 1 / 12 (8.33%)      | 4 / 146 (2.74%)      |
| occurrences (all)                                | 1                    | 1                   | 4                    |
| Clostridium difficile infection                  |                      |                     |                      |
| subjects affected / exposed                      | 0 / 149 (0.00%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 0                    | 1                   | 0                    |
| Nasopharyngitis                                  |                      |                     |                      |
| subjects affected / exposed                      | 0 / 149 (0.00%)      | 1 / 12 (8.33%)      | 0 / 146 (0.00%)      |
| occurrences (all)                                | 0                    | 1                   | 0                    |
| Metabolism and nutrition disorders               |                      |                     |                      |

|                             |                   |                 |                   |
|-----------------------------|-------------------|-----------------|-------------------|
| Hypercalcaemia              |                   |                 |                   |
| subjects affected / exposed | 4 / 149 (2.68%)   | 1 / 12 (8.33%)  | 3 / 146 (2.05%)   |
| occurrences (all)           | 4                 | 1               | 3                 |
| Diabetes mellitus           |                   |                 |                   |
| subjects affected / exposed | 1 / 149 (0.67%)   | 1 / 12 (8.33%)  | 0 / 146 (0.00%)   |
| occurrences (all)           | 1                 | 1               | 0                 |
| Decreased appetite          |                   |                 |                   |
| subjects affected / exposed | 36 / 149 (24.16%) | 3 / 12 (25.00%) | 30 / 146 (20.55%) |
| occurrences (all)           | 36                | 3               | 30                |
| Hypocalcaemia               |                   |                 |                   |
| subjects affected / exposed | 4 / 149 (2.68%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)           | 4                 | 1               | 1                 |
| Hypomagnesaemia             |                   |                 |                   |
| subjects affected / exposed | 13 / 149 (8.72%)  | 0 / 12 (0.00%)  | 8 / 146 (5.48%)   |
| occurrences (all)           | 13                | 0               | 8                 |
| Hyponatraemia               |                   |                 |                   |
| subjects affected / exposed | 8 / 149 (5.37%)   | 0 / 12 (0.00%)  | 10 / 146 (6.85%)  |
| occurrences (all)           | 8                 | 0               | 10                |
| Hypophosphataemia           |                   |                 |                   |
| subjects affected / exposed | 3 / 149 (2.01%)   | 1 / 12 (8.33%)  | 1 / 146 (0.68%)   |
| occurrences (all)           | 3                 | 1               | 1                 |
| Hypokalaemia                |                   |                 |                   |
| subjects affected / exposed | 10 / 149 (6.71%)  | 1 / 12 (8.33%)  | 7 / 146 (4.79%)   |
| occurrences (all)           | 10                | 1               | 7                 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment  |
|-----------------|--|
| 11 October 2019 | <ul style="list-style-type: none"><li>• To describe a single primary endpoint (overall survival) in the randomized, double-blind part of the study rather than dual primary endpoints.</li><li>• To remove the requirement for initial progressive disease as determined by the Investigator to be verified by an Independent Review Committee (IRC).</li><li>• The analysis of progression-free survival (PFS) and other tumor-based efficacy endpoints was based on Investigator assessment; analysis based on IRC assessment was only performed if the study is not expanded to Phase III.</li><li>• To acknowledge that, for the purposes of marketing authorization in Japan, if the study was not expanded into Phase III, it will not be acceptable as a confirmatory study.</li><li>• To provide additional information on the power to detect differences in efficacy among the different biliary tract cancer anatomical subgroups.</li><li>• To exclude subjects with history of bleeding diathesis and provide further guidance on dose modifications for bleeding events according to National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) severity grade and site of bleeding.</li><li>• To include additional patient-reported outcome measures to enable subjects experience of the study intervention to be further characterized.</li><li>• To allow chemotherapy to be given on Day 15 of a given cycle if administration on Day 1 or Day 8 was not possible.</li></ul> |
| 27 July 2020    | <ul style="list-style-type: none"><li>• Updated maximal number of subjects for Phase II.</li><li>• Updated text to clarify that initial 150 subjects recruited in Phase II were analyzed for an expansion decision into Phase III.</li><li>• Updated a minimum follow-up period at least 19 weeks for the first 150 subjects randomized were included.</li><li>• Updated assumptions of sample size calculation (i.e., number of subjects and time periods).</li><li>• Added the information about the Independent Data Monitoring Committee (IDMC) and Independent Review Committee (IRC) responsibility for Phase II and Phase III study.</li><li>• Added clarification that Independent Review Committee (IRC) used in Phase II only.</li><li>• Updated exclusion criteria 2, 5 and 16.</li><li>• Clarified administration of chemotherapy and dose modification for neutropenia and thrombocytopenia in the case of gemcitabine and/or cisplatin-related adverse drug reactions.</li><li>• Clarified the magnetic resonance imaging (MRI) areas.</li><li>• Removed the information for central imaging read and interpretation for all scans.</li><li>• Added Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1).</li><li>• Clarified that radiological images collected from the remaining 350 subjects must be submitted.</li></ul>   |

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| 20 April 2021 | <ul style="list-style-type: none"> <li>• An additional criterion has been added to the definition of the efficacy analysis set was used for the analysis for decision on the expansion to Phase III sample size.</li> <li>• Futility criterion was introduced for expansion decision and Overall Survival (OS) analysis.</li> <li>• A description was added to provide clarity on the type of study population to be analyzed for efficacy and safety analysis for expansion into Phase III. This clarification would also help IDMC's assessment of efficacy and safety data and to provide their recommendation for expansion into the Phase III.</li> <li>• A note has been added to guide in checking enrollment of the study population.</li> <li>• Further information was added to explain the rationale for selecting antibiotics-naïve subjects for expansion decision.</li> <li>• Edits are done to highlight dose modification of the study intervention in a specific condition.</li> <li>• Inclusion criterion number 2 has been updated.</li> <li>• Exclusion criterion number 5 and 13 has been updated.</li> <li>• Details were added on study treatment administration. Edits were done in this section to indicate dose modification of M7824/placebo to 1200 mg was allowed in the study.</li> </ul> |
| 14 July 2021  | <ul style="list-style-type: none"> <li>• Text was revised to include a summary of the additional criterion for expansion into Phase III.</li> <li>• Exclusion criterion 10 was split into 2 separate bullets without change in content.</li> <li>• Text related to local requirements for dosing of gemcitabine and cisplatin was revised. Links to Sections 6.6.3 and 6.6.4 referring to dose modification instructions for gemcitabine and cisplatin were added.</li> </ul>   |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Data collection and analysis of Pharmacokinetics and Immunogenicity were omitted and not conducted due to business reason.

Notes: