



## Clinical trial results:

### A Phase 1/Randomized Phase 2 Study to Evaluate LY2603618 in Combination With Gemcitabine in Patients With Pancreatic Cancer

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2008-006209-17   |
| Trial protocol           | DE SK PL IT      |
| Global end of trial date | 09 December 2013 |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 06 March 2018 |
| First version publication date | 06 March 2018 |

#### Trial information

##### Trial identification

|                       |             |
|-----------------------|-------------|
| Sponsor protocol code | I2I-MC-JMMC |
|-----------------------|-------------|

##### Additional study identifiers

|                                    |                     |
|------------------------------------|---------------------|
| ISRCTN number                      | -                   |
| ClinicalTrials.gov id (NCT number) | NCT00839332         |
| WHO universal trial number (UTN)   | -                   |
| Other trial identifiers            | Trial Number: 12096 |

Notes:

#### Sponsors

|                              |                                                                           |
|------------------------------|---------------------------------------------------------------------------|
| Sponsor organisation name    | Eli Lilly and Company                                                     |
| Sponsor organisation address | Lilly Corporate Center, Indianapolis, IN, United States, 46285            |
| Public contact               | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877CTLilly, |
| Scientific contact           | Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 8772854559, |

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:

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**Results analysis stage**

|                                                      |                  |
|------------------------------------------------------|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 09 December 2013 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 09 December 2013 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

Main objective of the trial:

The purpose of the Phase 1 portion of this study was to determine the dose of LY2603618 that can be safely administered 24 hours after gemcitabine treatment. This dose was then used for the Phase 2 portion of the study. The Phase 2 portion of the study evaluated whether LY2603618, when administered 24 hours after gemcitabine therapy, was an effective treatment for participants with pancreatic cancer

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 26 February 2009 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 73 |
| Country: Number of subjects enrolled | Spain: 35         |
| Country: Number of subjects enrolled | Romania: 3        |
| Country: Number of subjects enrolled | Germany: 26       |
| Country: Number of subjects enrolled | Netherlands: 5    |
| Country: Number of subjects enrolled | Italy: 5          |
| Country: Number of subjects enrolled | Poland: 2         |
| Worldwide total number of subjects   | 149               |
| EEA total number of subjects         | 76                |

Notes:

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**Subjects enrolled per age group**

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |

|                                          |    |
|------------------------------------------|----|
| Infants and toddlers (28 days-23 months) | 0  |
| Children (2-11 years)                    | 0  |
| Adolescents (12-17 years)                | 0  |
| Adults (18-64 years)                     | 80 |
| From 65 to 84 years                      | 68 |
| 85 years and over                        | 1  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

No Text Entered

### Period 1

|                              |                            |
|------------------------------|----------------------------|
| Period 1 title               | Phase 1/2 (overall period) |
| Is this the baseline period? | Yes                        |
| Allocation method            | Randomised - controlled    |
| Blinding used                | Not blinded                |

### Arms

|                              |                                  |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes                              |
| <b>Arm title</b>             | Phase 1: LY2603618 + Gemcitabine |

Arm description:

All participants in Phase 1 received LY2603618 in combination with gemcitabine.

LY2603618: 70 to 250 milligrams/meter squared (mg/m<sup>2</sup>) LY2603618 as a 1-hour continuous intravenous (IV) infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received LY2603618 as part of the dose escalation cohort of Phase 1 (dose of 70, 105, 150, 200, or 250 mg/m<sup>2</sup>) or as part of the expansion cohort of Phase 1 (flat dose of 200 or 230 mg). The flat dose cohorts were conducted in parallel.

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | LY2603618       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

75 to 250 milligrams/meter squared (mg/m<sup>2</sup>) LY2603618 as a 1-hour continuous intravenous (IV) infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression (DP). Participants received LY2603618 as part of the dose escalation cohort (dose of 70, 105, 150, 200, or 250 mg/m<sup>2</sup>) or the expansion cohort (flat dose of 200 mg or 230 mg).

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Gemcitabine     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until DP. Participants received gemcitabine 24 hours prior to LY2603618 administration

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Phase 2: LY2603618 + Gemcitabine |
|------------------|----------------------------------|

Arm description:

LY2603618: 230 mg flat dose LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

Gemcitabine: Participants were administered 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                                        |                 |
|----------------------------------------|-----------------|
| Arm type                               | Experimental    |
| Investigational medicinal product name | LY2603618       |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

230 mg flat dose LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

|                                        |                 |
|----------------------------------------|-----------------|
| Investigational medicinal product name | Gemcitabine     |
| Investigational medicinal product code |                 |
| Other name                             |                 |
| Pharmaceutical forms                   | Infusion        |
| Routes of administration               | Intravenous use |

Dosage and administration details:

1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Phase 2: Gemcitabine |
|------------------|----------------------|

Arm description:

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | Gemcitabine       |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Infusion          |
| Routes of administration               | Intravenous use   |

Dosage and administration details:

1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

| <b>Number of subjects in period 1</b>  | <b>Phase 1: LY2603618 + Gemcitabine</b> | <b>Phase 2: LY2603618 + Gemcitabine</b> | <b>Phase 2: Gemcitabine</b> |
|----------------------------------------|-----------------------------------------|-----------------------------------------|-----------------------------|
| Started                                | 50                                      | 65                                      | 34                          |
| Received at least 1 dose of study drug | 50                                      | 65                                      | 34                          |
| Completed                              | 0                                       | 0                                       | 0                           |
| Not completed                          | 50                                      | 65                                      | 34                          |
| Adverse event, serious fatal           | -                                       | 3                                       | 1                           |
| Consent withdrawn by subject           | 4                                       | 3                                       | 5                           |
| Physician decision                     | 2                                       | 4                                       | 1                           |
| Adverse event, non-fatal               | 6                                       | 8                                       | 6                           |
| Disease Progression                    | 38                                      | 46                                      | 21                          |

|                    |   |   |   |
|--------------------|---|---|---|
| Protocol deviation | - | 1 | - |
|--------------------|---|---|---|

## Baseline characteristics

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1: LY2603618 + Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

All participants in Phase 1 received LY2603618 in combination with gemcitabine.

LY2603618: 70 to 250 milligrams/meter squared (mg/m<sup>2</sup>) LY2603618 as a 1-hour continuous intravenous (IV) infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received LY2603618 as part of the dose escalation cohort of Phase 1 (dose of 70, 105, 150, 200, or 250 mg/m<sup>2</sup>) or as part of the expansion cohort of Phase 1 (flat dose of 200 or 230 mg). The flat dose cohorts were conducted in parallel.

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 2: LY2603618 + Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

LY2603618: 230 mg flat dose LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

Gemcitabine: Participants were administered 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 2: Gemcitabine |
|-----------------------|----------------------|

Reporting group description:

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

| Reporting group values                             | Phase 1: LY2603618 + Gemcitabine | Phase 2: LY2603618 + Gemcitabine | Phase 2: Gemcitabine |
|----------------------------------------------------|----------------------------------|----------------------------------|----------------------|
| Number of subjects                                 | 50                               | 65                               | 34                   |
| Age categorical                                    |                                  |                                  |                      |
| Units: Subjects                                    |                                  |                                  |                      |
| In utero                                           | 0                                | 0                                | 0                    |
| Preterm newborn infants (gestational age < 37 wks) | 0                                | 0                                | 0                    |
| Newborns (0-27 days)                               | 0                                | 0                                | 0                    |
| Infants and toddlers (28 days-23 months)           | 0                                | 0                                | 0                    |
| Children (2-11 years)                              | 0                                | 0                                | 0                    |
| Adolescents (12-17 years)                          | 0                                | 0                                | 0                    |
| Adults (18-64 years)                               | 29                               | 35                               | 16                   |
| From 65-84 years                                   | 21                               | 30                               | 17                   |
| 85 years and over                                  | 0                                | 0                                | 1                    |
| Age Continuous                                     |                                  |                                  |                      |
| Units: years                                       |                                  |                                  |                      |
| arithmetic mean                                    | 59                               | 64.3                             | 64.4                 |
| standard deviation                                 | ± 12.2                           | ± 8.3                            | ± 10.1               |
| Gender, Male/Female                                |                                  |                                  |                      |
| Units:                                             |                                  |                                  |                      |
| Female                                             | 24                               | 23                               | 14                   |

|      |    |    |    |
|------|----|----|----|
| Male | 26 | 42 | 20 |
|------|----|----|----|

|                                                                                                                                                                                                                                                                                |    |    |    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|----|----|
| Race/Ethnicity, Customized<br>Units: Subjects                                                                                                                                                                                                                                  |    |    |    |
| White                                                                                                                                                                                                                                                                          | 46 | 62 | 32 |
| Black or African American                                                                                                                                                                                                                                                      | 1  | 2  | 2  |
| American Indian or Alaska Native                                                                                                                                                                                                                                               | 0  | 1  | 0  |
| Asian                                                                                                                                                                                                                                                                          | 3  | 0  | 0  |
| Region of Enrollment<br>Units: Subjects                                                                                                                                                                                                                                        |    |    |    |
| United States                                                                                                                                                                                                                                                                  | 32 | 27 | 14 |
| Spain                                                                                                                                                                                                                                                                          | 18 | 12 | 5  |
| Romania                                                                                                                                                                                                                                                                        | 0  | 2  | 1  |
| Germany                                                                                                                                                                                                                                                                        | 0  | 17 | 9  |
| Netherlands                                                                                                                                                                                                                                                                    | 0  | 3  | 2  |
| Italy                                                                                                                                                                                                                                                                          | 0  | 3  | 2  |
| Poland                                                                                                                                                                                                                                                                         | 0  | 1  | 1  |
| Initial Pathological Diagnosis<br>Units: Subjects                                                                                                                                                                                                                              |    |    |    |
| Adenocarcinoma, Pancreas                                                                                                                                                                                                                                                       | 10 | 65 | 34 |
| Adenocarcinoma, Colon                                                                                                                                                                                                                                                          | 7  | 0  | 0  |
| Carcinoma, Breast                                                                                                                                                                                                                                                              | 4  | 0  | 0  |
| Carcinoma, Non-Small Cell, Lung NOS                                                                                                                                                                                                                                            | 3  | 0  | 0  |
| Adenocarcinoma, Cervix                                                                                                                                                                                                                                                         | 2  | 0  | 0  |
| Adenocarcinoma, Rectum                                                                                                                                                                                                                                                         | 2  | 0  | 0  |
| Carcinoma, Endometrium                                                                                                                                                                                                                                                         | 2  | 0  | 0  |
| Carcinoma, Infiltrating Ductal, Breast                                                                                                                                                                                                                                         | 2  | 0  | 0  |
| Carcinoma, Renal Cell                                                                                                                                                                                                                                                          | 2  | 0  | 0  |
| Sarcoma, Leiomyosarcoma, Abdomen (Non-Gist)                                                                                                                                                                                                                                    | 2  | 0  | 0  |
| Squamous Cell Carcinoma, Head and Neck                                                                                                                                                                                                                                         | 2  | 0  | 0  |
| Ampulla of Pancreas                                                                                                                                                                                                                                                            | 1  | 0  | 0  |
| Carcinoma, Head and Neck                                                                                                                                                                                                                                                       | 1  | 0  | 0  |
| Carcinoma, Ovarian                                                                                                                                                                                                                                                             | 1  | 0  | 0  |
| Carcinoma, Peritoneal                                                                                                                                                                                                                                                          | 1  | 0  | 0  |
| Carcinoma, Small Cell, Lung                                                                                                                                                                                                                                                    | 1  | 0  | 0  |
| Carcinoma, Transitional Cell, Urothelium                                                                                                                                                                                                                                       | 1  | 0  | 0  |
| Ewing's Sarcoma                                                                                                                                                                                                                                                                | 1  | 0  | 0  |
| Lymphoma, Non-Hodgkin's Lymphoma                                                                                                                                                                                                                                               | 1  | 0  | 0  |
| Mesothelioma, Pleural, Malignant                                                                                                                                                                                                                                               | 1  | 0  | 0  |
| Ovarian Adenocarcinoma                                                                                                                                                                                                                                                         | 1  | 0  | 0  |
| Squamous Cell Carcinoma, Cervix                                                                                                                                                                                                                                                | 1  | 0  | 0  |
| Tumor                                                                                                                                                                                                                                                                          | 1  | 0  | 0  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status                                                                                                                                                                                                                   |    |    |    |
| Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death) as follows: 0 - Fully Active; 1 - Ambulatory, Restricted Strenuous Activity; 2 - Ambulatory, No |    |    |    |

|                                                                                                           |    |    |    |
|-----------------------------------------------------------------------------------------------------------|----|----|----|
| Work Activities; 3 - Partially Confined to Bed, Limited Self Care; 4 - Completely Disabled; and 5 - Dead. |    |    |    |
| Units: Subjects                                                                                           |    |    |    |
| ECOG Status 0                                                                                             | 19 | 28 | 14 |
| ECOG Status 1                                                                                             | 31 | 31 | 17 |
| ECOG Status 2                                                                                             | 0  | 6  | 3  |

|                                                    |       |  |  |
|----------------------------------------------------|-------|--|--|
| <b>Reporting group values</b>                      | Total |  |  |
| Number of subjects                                 | 149   |  |  |
| Age categorical                                    |       |  |  |
| Units: Subjects                                    |       |  |  |
| In utero                                           | 0     |  |  |
| Preterm newborn infants (gestational age < 37 wks) | 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)                               | 80    |  |  |
| From 65-84 years                                   | 68    |  |  |
| 85 years and over                                  | 1     |  |  |
| Age Continuous                                     |       |  |  |
| Units: years                                       |       |  |  |
| arithmetic mean                                    |       |  |  |
| standard deviation                                 | -     |  |  |
| Gender, Male/Female                                |       |  |  |
| Units:                                             |       |  |  |
| Female                                             | 61    |  |  |
| Male                                               | 88    |  |  |
| Race/Ethnicity, Customized                         |       |  |  |
| Units: Subjects                                    |       |  |  |
| White                                              | 140   |  |  |
| Black or African American                          | 5     |  |  |
| American Indian or Alaska Native                   | 1     |  |  |
| Asian                                              | 3     |  |  |
| Region of Enrollment                               |       |  |  |
| Units: Subjects                                    |       |  |  |
| United States                                      | 73    |  |  |
| Spain                                              | 35    |  |  |
| Romania                                            | 3     |  |  |
| Germany                                            | 26    |  |  |
| Netherlands                                        | 5     |  |  |
| Italy                                              | 5     |  |  |
| Poland                                             | 2     |  |  |
| Initial Pathological Diagnosis                     |       |  |  |
| Units: Subjects                                    |       |  |  |
| Adenocarcinoma, Pancreas                           | 109   |  |  |
| Adenocarcinoma, Colon                              | 7     |  |  |
| Carcinoma, Breast                                  | 4     |  |  |
| Carcinoma, Non-Small Cell, Lung NOS                | 3     |  |  |
| Adenocarcinoma, Cervix                             | 2     |  |  |

|                                                                                                                                                                                                                                                                                                                                                                                          |    |  |  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|--|--|
| Adenocarcinoma, Rectum                                                                                                                                                                                                                                                                                                                                                                   | 2  |  |  |
| Carcinoma, Endometrium                                                                                                                                                                                                                                                                                                                                                                   | 2  |  |  |
| Carcinoma, Infiltrating Ductal, Breast                                                                                                                                                                                                                                                                                                                                                   | 2  |  |  |
| Carcinoma, Renal Cell                                                                                                                                                                                                                                                                                                                                                                    | 2  |  |  |
| Sarcoma, Leiomyosarcoma, Abdomen (Non-Gist)                                                                                                                                                                                                                                                                                                                                              | 2  |  |  |
| Squamous Cell Carcinoma, Head and Neck                                                                                                                                                                                                                                                                                                                                                   | 2  |  |  |
| Ampulla of Pancreas                                                                                                                                                                                                                                                                                                                                                                      | 1  |  |  |
| Carcinoma, Head and Neck                                                                                                                                                                                                                                                                                                                                                                 | 1  |  |  |
| Carcinoma, Ovarian                                                                                                                                                                                                                                                                                                                                                                       | 1  |  |  |
| Carcinoma, Peritoneal                                                                                                                                                                                                                                                                                                                                                                    | 1  |  |  |
| Carcinoma, Small Cell, Lung                                                                                                                                                                                                                                                                                                                                                              | 1  |  |  |
| Carcinoma, Transitional Cell, Urothelium                                                                                                                                                                                                                                                                                                                                                 | 1  |  |  |
| Ewing's Sarcoma                                                                                                                                                                                                                                                                                                                                                                          | 1  |  |  |
| Lymphoma, Non-Hodgkin's Lymphoma                                                                                                                                                                                                                                                                                                                                                         | 1  |  |  |
| Mesothelioma, Pleural, Malignant                                                                                                                                                                                                                                                                                                                                                         | 1  |  |  |
| Ovarian Adenocarcinoma                                                                                                                                                                                                                                                                                                                                                                   | 1  |  |  |
| Squamous Cell Carcinoma, Cervix Tumor                                                                                                                                                                                                                                                                                                                                                    | 1  |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status                                                                                                                                                                                                                                                                                                                             |    |  |  |
| Eastern Cooperative Oncology Group (ECOG) Performance Status classifies participants according to their functional impairment. Scores range from 0 (Fully Active) to 5 (Death) as follows: 0 - Fully Active; 1 - Ambulatory, Restricted Strenuous Activity; 2 - Ambulatory, No Work Activities; 3 - Partially Confined to Bed, Limited Self Care; 4 - Completely Disabled; and 5 - Dead. |    |  |  |
| Units: Subjects                                                                                                                                                                                                                                                                                                                                                                          |    |  |  |
| ECOG Status 0                                                                                                                                                                                                                                                                                                                                                                            | 61 |  |  |
| ECOG Status 1                                                                                                                                                                                                                                                                                                                                                                            | 79 |  |  |
| ECOG Status 2                                                                                                                                                                                                                                                                                                                                                                            | 9  |  |  |

## End points

### End points reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 1: LY2603618 + Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

All participants in Phase 1 received LY2603618 in combination with gemcitabine.

LY2603618: 70 to 250 milligrams/meter squared ( $\text{mg}/\text{m}^2$ ) LY2603618 as a 1-hour continuous intravenous (IV) infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received LY2603618 as part of the dose escalation cohort of Phase 1 (dose of 70, 105, 150, 200, or 250  $\text{mg}/\text{m}^2$ ) or as part of the expansion cohort of Phase 1 (flat dose of 200 or 230 mg). The flat dose cohorts were conducted in parallel.

Gemcitabine: 1000  $\text{mg}/\text{m}^2$  gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 2: LY2603618 + Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

LY2603618: 230 mg flat dose LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

Gemcitabine: Participants were administered 1000  $\text{mg}/\text{m}^2$  gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 2: Gemcitabine |
|-----------------------|----------------------|

Reporting group description:

Gemcitabine: 1000  $\text{mg}/\text{m}^2$  gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

### Primary: Phase 1: Determine the recommended Phase 2 dose for LY2603618 when administered after gemcitabine

|                 |                                                                                                                     |
|-----------------|---------------------------------------------------------------------------------------------------------------------|
| End point title | Phase 1: Determine the recommended Phase 2 dose for LY2603618 when administered after gemcitabine <sup>[1][2]</sup> |
|-----------------|---------------------------------------------------------------------------------------------------------------------|

End point description:

The recommended Phase 2 dose for LY2603618 when administered approximately 24 hours after gemcitabine was based on the maximum tolerated dose and achievement of predefined LY2603618 plasma systemic exposures targets (area under the LY2603618 plasma concentration versus time curve from time zero to infinity  $[\text{AUC}(0-\text{inf})] > 21,000$  nanogram\*hour/milliliter  $[\text{ng} \cdot \text{h}/\text{mL}]$  and maximum LY2603618 plasma concentration  $[\text{C}_{\text{max}}] > 2000$  nanograms/milliliter  $[\text{ng}/\text{mL}]$ ). Population analyzed was all phase 1 participants who received at least 1 dose of study drug.

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

End point timeframe:

Baseline through 18 months

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

[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.

Justification: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

|                             |                                        |  |  |  |
|-----------------------------|----------------------------------------|--|--|--|
| <b>End point values</b>     | Phase 1:<br>LY2603618 +<br>Gemcitabine |  |  |  |
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 50                                     |  |  |  |
| Units: milligrams (mg)      |                                        |  |  |  |
| number (not applicable)     | 230                                    |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Primary: Phase 2: Overall Survival (OS)

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Phase 2: Overall Survival (OS) <sup>[3]</sup> |
|-----------------|-----------------------------------------------|

End point description:

Overall survival (OS) time is defined as the time from the date of randomization to the date of death from any cause. For participants not known to have died as of the data cut-off date, OS time was censored at the last contact date the participant was known to be alive prior to the cut-off date. OS was summarized using Kaplan-Meier estimates. Population analyzed was all phase 2 participants who received at least 1 dose of study drug.

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

End point timeframe:

Phase 2: Baseline to date of death

Notes:

[3] - 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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

|                                  |                                        |                         |  |  |
|----------------------------------|----------------------------------------|-------------------------|--|--|
| <b>End point values</b>          | Phase 2:<br>LY2603618 +<br>Gemcitabine | Phase 2:<br>Gemcitabine |  |  |
| Subject group type               | Reporting group                        | Reporting group         |  |  |
| Number of subjects analysed      | 65                                     | 34                      |  |  |
| Units: months                    |                                        |                         |  |  |
| median (confidence interval 95%) | 7.8 (5 to 11.1)                        | 8.3 (5.1 to 14.1)       |  |  |

## Statistical analyses

|                                         |                                                         |
|-----------------------------------------|---------------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1                                  |
| Comparison groups                       | Phase 2: LY2603618 + Gemcitabine v Phase 2: Gemcitabine |
| Number of subjects included in analysis | 99                                                      |
| Analysis specification                  | Pre-specified                                           |
| Analysis type                           | superiority                                             |
| P-value                                 | = 0.333 <sup>[4]</sup>                                  |
| Method                                  | Bayesian Posterior Probability                          |

Notes:

[4] - Inference about survival was made using a Bayesian posterior probability. The combination treatment would have been considered superior to gemcitabine alone if the posterior probability of superiority exceeded 0.8.

## Secondary: Phase 1: Maximum Plasma Concentration (Cmax) of gemcitabine, 2',2'-difluorodeoxyuridine (dFdU), and LY2603618

|                 |                                                                                                                              |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|
| End point title | Phase 1: Maximum Plasma Concentration (Cmax) of gemcitabine, 2',2'-difluorodeoxyuridine (dFdU), and LY2603618 <sup>[5]</sup> |
|-----------------|------------------------------------------------------------------------------------------------------------------------------|

### End point description:

Plasma samples for pharmacokinetic (PK) analysis were collected following IV infusion of each study drug. However, the dose-normalized PK analysis of gemcitabine and dFdU were not reported because the gemcitabine and dFdU plasma concentration data generated for all participants with PK samples collected in this study were withdrawn (invalidated) as a result of the failure of the Incurred Sample Reanalysis (ISR) for both gemcitabine and dFdU. Therefore, only the LY2603618 plasma Cmax values are reported for each LY2603618 dose level on Cycle (C) 1 /Day (D) 1, Cycle 1 /Day 16, and Cycle 2 /Day 2. The number of PK observations (n) used in the analysis is presented for each dose level and time point. Population analyzed was all phase 1 participants who received at least 1 dose of study drug and had sufficient LY2603618 plasma concentration data to enable determination of the LY2603618 Cmax.

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

### End point timeframe:

Phase 1: LY2603618 - Predose and 0, 1, 3, 6, 24, 48, and 72 hours after the end of infusion on C1 /D2, C1 /D16, and C2 /D2. Gemcitabine - Predose and 0, 10, 30, 60, and 120 minutes after the end of infusion on C1 /D1, C1 /D15, and C2 /D1.

### 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: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                                    | Phase 1:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-----------------------------------------------------|----------------------------------------|--|--|--|
| Subject group type                                  | Reporting group                        |  |  |  |
| Number of subjects analysed                         | 50                                     |  |  |  |
| Units: nanograms per milliliter (ng/mL)             |                                        |  |  |  |
| geometric mean (geometric coefficient of variation) |                                        |  |  |  |
| 70 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=2)         | 3530 (± 23)                            |  |  |  |
| 70 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)        | 3360 (± 26)                            |  |  |  |
| 70 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)         | 3100 (± 12)                            |  |  |  |
| 105 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=3)        | 4890 (± 25)                            |  |  |  |
| 105 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)       | 5170 (± 38)                            |  |  |  |
| 105 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)        | 5360 (± 23)                            |  |  |  |
| 150 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=7)        | 4280 (± 29)                            |  |  |  |
| 150 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=6)       | 5040 (± 38)                            |  |  |  |
| 150 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=6)        | 4370 (± 38)                            |  |  |  |
| 200 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=11)       | 4870 (± 63)                            |  |  |  |
| 200 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=8)       | 5360 (± 40)                            |  |  |  |
| 200 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=11)       | 5290 (± 40)                            |  |  |  |
| 250 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=5)        | 7990 (± 25)                            |  |  |  |
| 250 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)       | 7990 (± 6)                             |  |  |  |
| 250 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)        | 5290 (± 35)                            |  |  |  |
| 200 mg (flat dose), Cycle 1 /Day 2 (n=10)           | 3440 (± 65)                            |  |  |  |
| 200 mg (flat dose), Cycle 1 /Day 16 (n=6)           | 3470 (± 61)                            |  |  |  |

|                                           |             |  |  |  |
|-------------------------------------------|-------------|--|--|--|
| 200 mg (flat dose), Cycle 2 /Day 2 (n=8)  | 3640 (± 45) |  |  |  |
| 230 mg (flat dose), Cycle 1 /Day 2 (n=10) | 4820 (± 72) |  |  |  |
| 230 mg (flat dose), Cycle 1 /Day 16 (n=6) | 4980 (± 35) |  |  |  |
| 230 mg (flat dose), Cycle 2 /Day 2 (n=7)  | 3830 (± 26) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Maximum Plasma Concentration (Cmax) of gemcitabine, dFdU, and LY2603618

|                 |                                                                                                 |
|-----------------|-------------------------------------------------------------------------------------------------|
| End point title | Phase 2: Maximum Plasma Concentration (Cmax) of gemcitabine, dFdU, and LY2603618 <sup>[6]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------|

End point description:

Plasma samples for PK analysis were collected following IV infusion of each study drug. However, the dose-normalized PK analysis of gemcitabine and dFdU were not reported because the gemcitabine and dFdU plasma concentration data generated for all participants with PK samples collected in this study were withdrawn (invalidated) as a result of the failure of the Incurred Sample Reanalysis (ISR) for both gemcitabine and dFdU. Therefore, only the LY2603618 plasma Cmax values are reported at the 230 mg LY2603618 dose level on Cycle 1 /Day 1, Cycle 1 /Day 16, and Cycle 2 /Day 2. The number of PK observations (n) used in the analysis is presented for each time point. Population analyzed was all phase 2 participants who received at least 1 dose of study drug and had sufficient LY2603618 plasma concentration data to enable determination of the LY2603618 Cmax.

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

End point timeframe:

Phase 2: LY2603618 - Predose and 0, 1, 3, and 24 hours after the end of infusion on Days 2 and 16 of Cycle 1. Gemcitabine - Predose and 0, 10, 60, and 120 minutes after the end of infusion on Days 1 and 15 of Cycle 1.

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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                                    | Phase 2:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-----------------------------------------------------|----------------------------------------|--|--|--|
| Subject group type                                  | Reporting group                        |  |  |  |
| Number of subjects analysed                         | 62                                     |  |  |  |
| Units: ng/mL                                        |                                        |  |  |  |
| geometric mean (geometric coefficient of variation) |                                        |  |  |  |
| Cycle 1 /Day 2 (n=58)                               | 3170 (± 50)                            |  |  |  |
| Cycle 1 /Day 16 (n=48)                              | 3410 (± 50)                            |  |  |  |
| Cycle 2 /Day 2 (n=2)                                | 2390 (± 54)                            |  |  |  |

## Statistical analyses

**Secondary: Phase 1: Area Under the Plasma Concentration versus Time Curve (AUC) of gemcitabine, dFdU, and LY2603618**

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Phase 1: Area Under the Plasma Concentration versus Time Curve (AUC) of gemcitabine, dFdU, and LY2603618 <sup>[7]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

## End point description:

Plasma samples for PK analysis were collected following IV infusion of each study drug. However, the dose-normalized PK analysis of gemcitabine and dFdU were not reported because the gemcitabine plasma and dFdU concentration data generated for all pts. with PK samples collected in this study were withdrawn (invalidated) as a result of failure of Incurred Sample Reanalysis (ISR) for both gemcitabine and dFdU. Therefore, only study drug plasma AUC from time zero to 24 hours (AUC[0-24]), AUC from time zero to last time point with measurable concentration (AUC[0-tlast]), and AUC from time zero to infinity (AUC[0-inf]) values are reported for each study drug dose level on Cycle1/Day1, Cycle1/Day16, and Cycle2/Day2. The number of PK observations (n) used in the analysis is presented for each dose level and time point. Population analyzed was all phase 1 pts. who received at least 1 dose of study drug and had sufficient study drug plasma concentration to enable calculation of study drug AUC.

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

## End point timeframe:

Phase 1: LY2603618 - Predose and 0, 1, 3, 6, 24, 48, and 72 hours after the end of infusion on C1 /D2, C1 /D16, and C2 /D2. Gemcitabine - Predose and 0, 10, 30, 60, and 120 minutes after the end of infusion on C1 /D1, C1 /D15, and C2 /D1.

## 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: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                                            | Phase 1:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-------------------------------------------------------------|----------------------------------------|--|--|--|
| Subject group type                                          | Reporting group                        |  |  |  |
| Number of subjects analysed                                 | 50                                     |  |  |  |
| Units: nanogram*hour/milliliter<br>(ng*h/mL)                |                                        |  |  |  |
| geometric mean (geometric coefficient<br>of variation)      |                                        |  |  |  |
| AUC(0-24), 70 mg/m <sup>2</sup> , Cycle 1 /Day 2<br>(n=2)   | 21300 (± 24)                           |  |  |  |
| AUC(0-24), 70 mg/m <sup>2</sup> , Cycle 1 /Day<br>16 (n=3)  | 21200 (± 27)                           |  |  |  |
| AUC(0-24), 70 mg/m <sup>2</sup> , Cycle 2 /Day 2<br>(n=3)   | 19900 (± 24)                           |  |  |  |
| AUC(0-24), 105 mg/m <sup>2</sup> , Cycle 1 /Day<br>2 (n=3)  | 40500 (± 23)                           |  |  |  |
| AUC(0-24), 105 mg/m <sup>2</sup> , Cycle 1 /Day<br>16 (n=3) | 50100 (± 32)                           |  |  |  |
| AUC(0-24), 105 mg/m <sup>2</sup> , Cycle 2 /Day<br>2 (n=3)  | 49800 (± 4)                            |  |  |  |
| AUC(0-24), 150 mg/m <sup>2</sup> , Cycle 1 /Day<br>2 (n=7)  | 32200 (± 27)                           |  |  |  |
| AUC(0-24), 150 mg/m <sup>2</sup> , Cycle 1 /Day<br>16 (n=6) | 40000 (± 29)                           |  |  |  |
| AUC(0-24), 150 mg/m <sup>2</sup> , Cycle 2 /Day<br>2 (n=6)  | 31000 (± 42)                           |  |  |  |
| AUC(0-24), 200 mg/m <sup>2</sup> , Cycle 1 /Day<br>2 (n=10) | 40200 (± 42)                           |  |  |  |
| AUC(0-24), 200 mg/m <sup>2</sup> , Cycle 1 /Day<br>16 (n=8) | 39800 (± 36)                           |  |  |  |
| AUC(0-24), 200 mg/m <sup>2</sup> , Cycle 2 /Day<br>2 (n=11) | 44300 (± 39)                           |  |  |  |

|                                                             |               |  |  |  |
|-------------------------------------------------------------|---------------|--|--|--|
| AUC(0-24), 250 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=5)     | 88800 (± 27)  |  |  |  |
| AUC(0-24), 250 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)    | 61000 (± 63)  |  |  |  |
| AUC(0-24), 250 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)     | 40000 (± 112) |  |  |  |
| AUC(0-24), 200 mg (flat), Cycle 1 /Day 2 (n=10)             | 22900 (± 77)  |  |  |  |
| AUC(0-24), 200 mg (flat), Cycle 1 /Day 16 (n=6)             | 28700 (± 63)  |  |  |  |
| AUC(0-24), 200 mg (flat), Cycle 2 /Day 2 (n=8)              | 23800 (± 62)  |  |  |  |
| AUC(0-24), 230 mg (flat), Cycle 1 /Day 2 (n=10)             | 32400 (± 38)  |  |  |  |
| AUC(0-24), 230 mg (flat), Cycle 1 /Day 16 (n=6)             | 32300 (± 22)  |  |  |  |
| AUC(0-24), 230 mg (flat), Cycle 2 /Day 2 (n=7)              | 32500 (± 24)  |  |  |  |
| AUC(0-tlast), 70 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=2)   | 24600 (± 28)  |  |  |  |
| AUC(0-tlast), 70 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)  | 27500 (± 21)  |  |  |  |
| AUC(0-tlast), 70 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)   | 25800 (± 29)  |  |  |  |
| AUC(0-tlast), 105 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=3)  | 65800 (± 53)  |  |  |  |
| AUC(0-tlast), 105 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3) | 75500 (± 46)  |  |  |  |
| AUC(0-tlast), 105 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)  | 79600 (± 19)  |  |  |  |
| AUC(0-tlast), 150 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=7)  | 41600 (± 31)  |  |  |  |
| AUC(0-tlast), 150 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=6) | 52000 (± 38)  |  |  |  |
| AUC(0-tlast), 150 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=6)  | 39800 (± 45)  |  |  |  |
| AUC(0-tlast), 200 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=11) | 44300 (± 85)  |  |  |  |
| AUC(0-tlast), 200 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=8) | 55300 (± 51)  |  |  |  |
| AUC(0-tlast), 200 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=11) | 55600 (± 51)  |  |  |  |
| AUC(0-tlast), 250 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=5)  | 140000 (± 37) |  |  |  |
| AUC(0-tlast), 250 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3) | 98200 (± 139) |  |  |  |
| AUC(0-tlast), 250 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)  | 60400 (± 178) |  |  |  |
| AUC(0-tlast), 200 mg (flat), Cycle 1 /Day 2 (n=10)          | 33100 (± 101) |  |  |  |
| AUC(0-tlast), 200 mg (flat), Cycle 1 /Day 16 (n=6)          | 42600 (± 88)  |  |  |  |
| AUC(0-tlast), 200 mg (flat), Cycle 2 /Day 2 (n=8)           | 32400 (± 85)  |  |  |  |
| AUC(0-tlast), 230 mg (flat), Cycle 1 /Day 2 (n=10)          | 43000 (± 50)  |  |  |  |
| AUC(0-tlast), 230 mg (flat), Cycle 1 /Day 16 (n=6)          | 51900 (± 50)  |  |  |  |
| AUC(0-tlast), 230 mg (flat), Cycle 2 /Day 2 (n=7)           | 45900 (± 26)  |  |  |  |
| AUC(0-inf), 70 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=2)     | 24900 (± 29)  |  |  |  |

|                                                           |                |  |  |  |
|-----------------------------------------------------------|----------------|--|--|--|
| AUC(0-inf), 70 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3)  | 28600 (± 19)   |  |  |  |
| AUC(0-inf), 70 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)   | 27100 (± 31)   |  |  |  |
| AUC(0-inf), 105 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=3)  | 78600 (± 68)   |  |  |  |
| AUC(0-inf), 105 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3) | 79800 (± 51)   |  |  |  |
| AUC(0-inf), 105 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)  | 88800 (± 25)   |  |  |  |
| AUC(0-inf), 150 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=7)  | 42800 (± 33)   |  |  |  |
| AUC(0-inf), 150 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=6) | 54600 (± 43)   |  |  |  |
| AUC(0-inf), 150 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=6)  | 41000 (± 46)   |  |  |  |
| AUC(0-inf), 200 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=10) | 60300 (± 58)   |  |  |  |
| AUC(0-inf), 200 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=8) | 56800 (± 54)   |  |  |  |
| AUC(0-inf), 200 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=11) | 65400 (± 49)   |  |  |  |
| AUC(0-inf), 250 mg/m <sup>2</sup> , Cycle 1 /Day 2 (n=5)  | 153000 (± 41)  |  |  |  |
| AUC(0-inf), 250 mg/m <sup>2</sup> , Cycle 1 /Day 16 (n=3) | 101000 (± 141) |  |  |  |
| AUC(0-inf), 250 mg/m <sup>2</sup> , Cycle 2 /Day 2 (n=3)  | 70500 (± 216)  |  |  |  |
| AUC(0-inf), 200 mg (flat), Cycle 1 /Day 2 (n=10)          | 35200 (± 117)  |  |  |  |
| AUC(0-inf), 200 mg (flat), Cycle 1 /Day 16 (n=6)          | 45700 (± 93)   |  |  |  |
| AUC(0-inf), 200 mg (flat), Cycle 2 /Day 2 (n=8)           | 34400 (± 93)   |  |  |  |
| AUC(0-inf), 230 mg (flat), Cycle 1 /Day 2 (n=10)          | 45200 (± 50)   |  |  |  |
| AUC(0-inf), 230 mg (flat), Cycle 1 /Day 16 (n=6)          | 57700 (± 58)   |  |  |  |
| AUC(0-inf), 230 mg (flat), Cycle 2 /Day 2 (n=7)           | 48000 (± 26)   |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Area Under the Plasma Concentration versus Time Curve (AUC) of gemcitabine, dFdU, and LY2603618

|                 |                                                                                                                         |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|
| End point title | Phase 2: Area Under the Plasma Concentration versus Time Curve (AUC) of gemcitabine, dFdU, and LY2603618 <sup>[8]</sup> |
|-----------------|-------------------------------------------------------------------------------------------------------------------------|

### End point description:

Plasma samples for PK analysis were collected following IV infusion of each study drug. However, the dose-normalized PK analysis of gemcitabine and dFdU were not reported because the gemcitabine and dFdU plasma concentration data generated for all participants with PK samples collected in this study were withdrawn (invalidated) as a result of the failure of the Incurred Sample Reanalysis (ISR) for both gemcitabine and dFdU. Therefore, only the LY2603618 plasma AUC(0-24), AUC(0-tlast), and AUC(0-inf) values are reported for the 230 mg LY2603618 dose on Cycle 1 /Day 1, Cycle 1 /Day 16, and Cycle 2 /Day 2. The number of PK observations (n) used in the analysis is presented for each time point. Population analyzed was all phase 2 participants who received at least 1 dose of study drug and had

sufficient LY2603618 plasma concentration data to enable calculation of the LY2603618 AUC.

|                                                                                                                                                                                                                           |           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| End point type                                                                                                                                                                                                            | Secondary |
| End point timeframe:                                                                                                                                                                                                      |           |
| Phase 2: LY2603618 - Predose and 0, 1, 3, and 24 hours after the end of infusion on Days 2 and 16 of Cycle 1. Gemcitabine - Predose and 0, 10, 60, and 120 minutes after the end of infusion on Days 1 and 15 of Cycle 1. |           |

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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

|                                                     |                                        |  |  |  |
|-----------------------------------------------------|----------------------------------------|--|--|--|
| End point values                                    | Phase 2:<br>LY2603618 +<br>Gemcitabine |  |  |  |
| Subject group type                                  | Reporting group                        |  |  |  |
| Number of subjects analysed                         | 62                                     |  |  |  |
| Units: ng*h/mL                                      |                                        |  |  |  |
| geometric mean (geometric coefficient of variation) |                                        |  |  |  |
| AUC(0-24), Cycle 1 /Day 2 (n=54)                    | 23200 (± 68)                           |  |  |  |
| AUC(0-24), Cycle 1 /Day 16 (n=42)                   | 23700 (± 60)                           |  |  |  |
| AUC(0-24), Cycle 2 /Day 2 (n=2)                     | 19800 (± 63)                           |  |  |  |
| AUC(0-tlast), Cycle 1 /Day 2 (n=58)                 | 22200 (± 73)                           |  |  |  |
| AUC(0-tlast), Cycle 1 /Day 16 (n=48)                | 20800 (± 78)                           |  |  |  |
| AUC(0-tlast), Cycle 2 /Day 2 (n=2)                  | 20100 (± 64)                           |  |  |  |
| AUC(0-inf), Cycle 1 /Day 2 (n=54)                   | 29400 (± 84)                           |  |  |  |
| AUC(0-inf), Cycle 1 /Day 16 (n=42)                  | 29100 (± 74)                           |  |  |  |
| AUC(0-inf), Cycle 2 /Day 2 (n=2)                    | 23300 (± 69)                           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Progression-free Survival (PFS)

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Phase 2: Progression-free Survival (PFS) <sup>[9]</sup> |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                         |
| Progression-free survival (PFS) time was defined as the time from the date of randomization to the first date of progressive disease (symptomatic or objective) or death due to any cause, whichever occurred first. For participants who were not known to have died or progressed as of the data-inclusion cutoff date, PFS time was censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy. PFS was summarized using Kaplan-Meier estimates. Population analyzed was all phase 2 participants who received at least 1 dose of study drug. |                                                         |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Secondary                                               |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                         |
| Phase 2: Baseline to measured progressive disease or date of death from any cause                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                         |

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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                 | Phase 2:<br>LY2603618 +<br>Gemcitabine | Phase 2:<br>Gemcitabine |  |  |
|----------------------------------|----------------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group                        | Reporting group         |  |  |
| Number of subjects analysed      | 65                                     | 34                      |  |  |
| Units: months                    |                                        |                         |  |  |
| median (confidence interval 95%) | 3.5 (2.1 to 3.6)                       | 5.6 (2.6 to 7.6)        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Overall Response Rate

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Phase 2: Overall Response Rate <sup>[10]</sup> |
|-----------------|------------------------------------------------|

End point description:

Overall response rate is the best response of complete response (CR) or partial response (PR) as classified by the investigators according to the Response Evaluation Criteria In Solid Tumors (RECIST v1.1) guidelines. CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of not-target lesions or appearance of new lesions. Overall response rate is calculated as a total number of participants with CR or PR divided by the total number of participants with at least 1 measurable lesion, multiplied by 100. Population analyzed was all phase 2 participants who received at least 1 dose of study drug.

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

End point timeframe:

Phase 2: Baseline to measured progressive disease or date of death from any cause

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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                  | Phase 2:<br>LY2603618 +<br>Gemcitabine | Phase 2:<br>Gemcitabine |  |  |
|-----------------------------------|----------------------------------------|-------------------------|--|--|
| Subject group type                | Reporting group                        | Reporting group         |  |  |
| Number of subjects analysed       | 65                                     | 34                      |  |  |
| Units: percentage of participants |                                        |                         |  |  |
| number (confidence interval 95%)  | 21.5 (12.3 to 33.5)                    | 8.8 (1.9 to 23.7)       |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Clinical Benefit Rate

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Phase 2: Clinical Benefit Rate <sup>[11]</sup> |
|-----------------|------------------------------------------------|

End point description:

Clinical benefit rate is the best response CR, PR, or stable disease (SD) as classified by the investigators according to the RECIST v1.1 guidelines. CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of

target lesions (taking as reference the baseline sum diameter) without progression of not-target lesions or appearance of new lesions. SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since treatment started. Overall response rate is calculated as a total number of participants with CR, PR, or SD divided by the total number of participants with at least 1 measurable lesion, multiplied by 100. Population analyzed was all phase 2 participants who received at least 1 dose of study drug.

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

End point timeframe:

Phase 2: Baseline to measured progressive disease or date of death from any cause

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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                  | Phase 2:<br>LY2603618 +<br>Gemcitabine | Phase 2:<br>Gemcitabine |  |  |
|-----------------------------------|----------------------------------------|-------------------------|--|--|
| Subject group type                | Reporting group                        | Reporting group         |  |  |
| Number of subjects analysed       | 65                                     | 34                      |  |  |
| Units: percentage of participants |                                        |                         |  |  |
| number (confidence interval 95%)  | 55.4 (42.5 to 67.7)                    | 64.7 (46.5 to 80.3)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Duration of Response

|                 |                                               |
|-----------------|-----------------------------------------------|
| End point title | Phase 2: Duration of Response <sup>[12]</sup> |
|-----------------|-----------------------------------------------|

End point description:

Duration of response was defined as the time from the first observation of complete response (CR) or partial response (PR) to the first observation of progressive disease or death from any cause. For participants who were not known to have died as of the data-inclusion cut-off date and who do not have progressive disease, the duration was censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent anticancer therapy (systemic, radiologic, or surgery). Participants were also censored at the last valid assessment prior to missing more than 1 consecutive scheduled assessment. Duration of response was summarized using Kaplan-Meier estimates. Population analyzed was all phase 2 participants who received at least 1 dose of study drug and had a confirmed response (CR or PR).

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

End point timeframe:

Phase 2. Baseline to measured progressive disease or date of death from any cause

Notes:

[12] - 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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                 | Phase 2:<br>LY2603618 +<br>Gemcitabine | Phase 2:<br>Gemcitabine |  |  |
|----------------------------------|----------------------------------------|-------------------------|--|--|
| Subject group type               | Reporting group                        | Reporting group         |  |  |
| Number of subjects analysed      | 14                                     | 3                       |  |  |
| Units: months                    |                                        |                         |  |  |
| median (confidence interval 95%) | 3.5 (1.9 to 5.8)                       | 6 (3.7 to 6.8)          |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 1: Electrocardiogram QTc prolongation

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Phase 1: Electrocardiogram QTc prolongation <sup>[13]</sup> |
|-----------------|-------------------------------------------------------------|

End point description:

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave. Twelve-lead electrocardiogram (ECG) data was used to calculate the corrected QT (QTc) based on Fridericia's formula ( $QTc = QT / RR^{0.33}$ , where RR is the interval between two R waves). For each participant, changes in QTc were calculated by subtracting the reading taken before LY2603618 administration from the reading taken after LY2603618 administration on Days 2 and 16 during Cycle 1. The number of participants in which the change in QTc was  $\leq 30$  milliseconds (msec),  $>30$ -60 msec, or  $>60$  msec is presented by dose group and overall. Population analyzed was all phase 1 participants who received at least 1 dose of study drug and had evaluable ECG data.

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

End point timeframe:

Phase 1: Days 2 and 16 of Cycle 1

Notes:

[13] - 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: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                              | Phase 1:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-----------------------------------------------|----------------------------------------|--|--|--|
| Subject group type                            | Reporting group                        |  |  |  |
| Number of subjects analysed                   | 49                                     |  |  |  |
| Units: participants                           |                                        |  |  |  |
| number (not applicable)                       |                                        |  |  |  |
| 70 mg/m <sup>2</sup> , $\leq 30$ msec (n=3)   | 2                                      |  |  |  |
| 70 mg/m <sup>2</sup> , $>30$ -60 msec (n=3)   | 1                                      |  |  |  |
| 70 mg/m <sup>2</sup> , $>60$ msec (n=3)       | 0                                      |  |  |  |
| 105 mg/m <sup>2</sup> , $\leq 30$ msec (n=3)  | 2                                      |  |  |  |
| 105 mg/m <sup>2</sup> , $>30$ -60 msec (n=3)  | 0                                      |  |  |  |
| 105 mg/m <sup>2</sup> , $>60$ msec (n=3)      | 0                                      |  |  |  |
| 150 mg/m <sup>2</sup> , $\leq 30$ msec (n=7)  | 6                                      |  |  |  |
| 150 mg/m <sup>2</sup> , $>30$ -60 msec (n=7)  | 1                                      |  |  |  |
| 150 mg/m <sup>2</sup> , $>60$ msec (n=7)      | 0                                      |  |  |  |
| 200 mg/m <sup>2</sup> , $\leq 30$ msec (n=11) | 11                                     |  |  |  |
| 200 mg/m <sup>2</sup> , $>30$ -60 msec (n=11) | 0                                      |  |  |  |
| 200 mg/m <sup>2</sup> , $>60$ msec (n=11)     | 0                                      |  |  |  |
| 250 mg/m <sup>2</sup> , $\leq 30$ msec (n=6)  | 6                                      |  |  |  |

|                                           |    |  |  |  |
|-------------------------------------------|----|--|--|--|
| 250 mg/m <sup>2</sup> , >30-60 msec (n=6) | 0  |  |  |  |
| 250 mg/m <sup>2</sup> , >60 msec (n=6)    | 0  |  |  |  |
| 200 mg (flat dose), ≤30 msec (n=10)       | 9  |  |  |  |
| 200 mg (flat dose), >30-60 msec (n=10)    | 1  |  |  |  |
| 200 mg (flat dose), >60 msec (n=10)       | 0  |  |  |  |
| 230 mg (flat dose), ≤30 msec (n=10)       | 8  |  |  |  |
| 230 mg (flat dose), >30-60 msec (n=10)    | 2  |  |  |  |
| 230 mg (flat dose), >60 msec (n=10)       | 0  |  |  |  |
| Total, ≤30 msec                           | 44 |  |  |  |
| Total, >30-60 msec                        | 5  |  |  |  |
| Total, >60 msec                           | 0  |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Phase 2: Electrocardiogram QTc Prolongation

|                 |                                                             |
|-----------------|-------------------------------------------------------------|
| End point title | Phase 2: Electrocardiogram QTc Prolongation <sup>[14]</sup> |
|-----------------|-------------------------------------------------------------|

End point description:

The QT interval is a measure of the time between the start of the Q wave and the end of the T wave. Twelve-lead ECG data was used to calculate QTc based on Fridericia's formula ( $QTc = QT / RR^{0.33}$ , where RR is the interval between two R waves). For each participant, changes in QTc were calculated by subtracting the reading taken before LY2603618 administration from the reading taken after LY2603618 administration on Days 2 and 16 during Cycle 1. The number of participants in which the change in QTc was ≤30 milliseconds (msec), >30-60 msec, or >60 msec is presented. Population analyzed was all phase 2 participants who received at least 1 dose of study drug and had evaluable ECG data.

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

End point timeframe:

Phase 2: Days 2 and 16 of Cycle 1

Notes:

[14] - 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: Statistics are being reported for only phase 2 participants as per the protocol or Statistical Analysis Plan or both.

| End point values            | Phase 2:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-----------------------------|----------------------------------------|--|--|--|
| Subject group type          | Reporting group                        |  |  |  |
| Number of subjects analysed | 60                                     |  |  |  |
| Units: participants         |                                        |  |  |  |
| number (not applicable)     |                                        |  |  |  |
| ≤30 msec                    | 55                                     |  |  |  |
| >30-60 msec                 | 5                                      |  |  |  |
| >60 msec                    | 0                                      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Number of Deaths During the Phase 1 Post-study Period

|                 |                                                                       |
|-----------------|-----------------------------------------------------------------------|
| End point title | Number of Deaths During the Phase 1 Post-study Period <sup>[15]</sup> |
|-----------------|-----------------------------------------------------------------------|

End point description:

The number of participants who died during the post-study period of Phase 1 does not include the outcomes for the 4 participants who died while on treatment during Phase 2 as captured in the Participant Flow Table. A summary of serious and other nonserious adverse events regardless of causality is located in the Reported Adverse Events module. Population analyzed was all phase 1 participants who received at least 1 dose of study drug.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Phase 1: Time of last dose of study drug through the end of the follow-up period

Notes:

[15] - 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: Statistics are being reported for only phase 1 participants as per the protocol or Statistical Analysis Plan or both.

| End point values                                    | Phase 1:<br>LY2603618 +<br>Gemcitabine |  |  |  |
|-----------------------------------------------------|----------------------------------------|--|--|--|
| Subject group type                                  | Reporting group                        |  |  |  |
| Number of subjects analysed                         | 50                                     |  |  |  |
| Units: participants                                 |                                        |  |  |  |
| number (not applicable)                             |                                        |  |  |  |
| Total deaths                                        | 5                                      |  |  |  |
| Deaths within 30 days of last dose of<br>study drug | 4                                      |  |  |  |
| Deaths during the follow-up period                  | 1                                      |  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Entire Study

Adverse event reporting additional description:

I2I-MC-JMMC

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Phase 1 |
|-----------------------|---------|

Reporting group description:

All participants in Phase 1 received LY2603618 in combination with gemcitabine.

LY2603618: 70 to 250 mg/m<sup>2</sup> LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received LY2603618 as part of the dose escalation cohort of Phase 1 (dose of 70, 105, 150, 200, or 250 mg/m<sup>2</sup>) or as part of the expansion cohort of Phase 1 (flat dose of 200 or 230 mg). The flat dose cohorts were conducted in parallel.

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Phase 2: LY2603618 + Gemcitabine |
|-----------------------|----------------------------------|

Reporting group description:

LY2603618: 230 mg flat dose LY2603618 as a 1-hour continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

Gemcitabine: Participants were administered 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression. Participants received gemcitabine 24 hours prior to LY2603618 administration.

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Phase 2: Gemcitabine |
|-----------------------|----------------------|

Reporting group description:

Gemcitabine: 1000 mg/m<sup>2</sup> gemcitabine as a 30-minute continuous IV infusion once per week for 3 weeks, followed by 1 week of rest. This 28-day cycle was repeated for a minimum of 2 cycles and/or until disease progression.

| Serious adverse events                                              | Phase 1          | Phase 2: LY2603618 + Gemcitabine | Phase 2: Gemcitabine |
|---------------------------------------------------------------------|------------------|----------------------------------|----------------------|
| Total subjects affected by serious adverse events                   |                  |                                  |                      |
| subjects affected / exposed                                         | 21 / 50 (42.00%) | 27 / 65 (41.54%)                 | 18 / 34 (52.94%)     |
| number of deaths (all causes)                                       | 0                | 0                                | 0                    |
| number of deaths resulting from adverse events                      | 0                | 0                                | 0                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                                  |                      |
| malignant ascites                                                   |                  |                                  |                      |
| alternative dictionary used: MedDRA 15.1                            |                  |                                  |                      |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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 ovary                             |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed <sup>[1]</sup>      | 0 / 24 (0.00%) | 0 / 23 (0.00%) | 1 / 14 (7.14%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| tumour pain                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Vascular disorders                              |                |                |                |
| deep vein thrombosis                            |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 2 / 50 (4.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 2          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| hypotension                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| peripheral arterial occlusive disease           |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1          | 0 / 0          |
| phlebitis                                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                      |                |                |                |
|------------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                          | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| phlebitis superficial                                |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |
| subjects affected / exposed                          | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| venous thrombosis limb                               |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |
| subjects affected / exposed                          | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| General disorders and administration site conditions |                |                |                |
| device occlusion                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |
| subjects affected / exposed                          | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| fatigue                                              |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |
| subjects affected / exposed                          | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| pyrexia                                              |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |
| subjects affected / exposed                          | 1 / 50 (2.00%) | 3 / 65 (4.62%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all      | 0 / 1          | 1 / 3          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| thrombosis in device                                 |                |                |                |
| alternative dictionary used: MedDRA 15.1             |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| 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 system disorders                         |                |                |                |
| drug hypersensitivity                           |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (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          |
| Respiratory, thoracic and mediastinal disorders |                |                |                |
| acute pulmonary oedema                          |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (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          |
| acute respiratory failure                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| interstitial lung disease                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| pleural effusion                                |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| pneumonitis                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pulmonary embolism                              |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| respiratory failure                             |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| Psychiatric disorders                           |                |                |                |
| confusional state                               |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Investigations                                  |                |                |                |
| c-reactive protein increased                    |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| international normalised ratio increased        |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Injury, poisoning and procedural complications  |                |                |                |
| infusion related reaction                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| Cardiac disorders                               |                |                |                |
| angina pectoris                                 |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| atrial fibrillation                             |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| bundle branch block left                        |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (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          |
| left ventricular dysfunction                    |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (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          |
| myocardial infarction                           |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Nervous system disorders                        |                |                |                |
| cerebrovascular accident                        |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (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          |
| syncope                                         |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Blood and lymphatic system disorders            |                |                |                |
| anaemia                                         |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| disseminated intravascular coagulation          |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| haemolytic uraemic syndrome                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| haemorrhagic anaemia                            |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| neutropenia                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 2 / 50 (4.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| thrombocytopenia                                |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 3 / 50 (6.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 3 / 3          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| thrombotic microangiopathy                      |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| 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                      |                |                |                |
| abdominal pain                                  |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ascites                                         |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| colitis ischaemic                               |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| constipation                                    |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 50 (2.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| diarrhoea                                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| duodenal ulcer perforation                      |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ileus                                           |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ileus paralytic                                 |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| intestinal ischaemia                            |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| intestinal obstruction                          |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 2 / 50 (4.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |

|                                                    |                |                |                |
|----------------------------------------------------|----------------|----------------|----------------|
| nausea                                             |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 2 / 50 (4.00%) | 1 / 65 (1.54%) | 1 / 34 (2.94%) |
| occurrences causally related to<br>treatment / all | 1 / 2          | 0 / 1          | 0 / 1          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pancreatic pseudocyst                              |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pancreatitis                                       |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pancreatitis acute                                 |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 2          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| small intestinal obstruction                       |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all | 0 / 0          | 1 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| vomiting                                           |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |
| subjects affected / exposed                        | 3 / 50 (6.00%) | 1 / 65 (1.54%) | 1 / 34 (2.94%) |
| occurrences causally related to<br>treatment / all | 2 / 3          | 0 / 1          | 1 / 2          |
| deaths causally related to<br>treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Hepatobiliary disorders                            |                |                |                |
| bile duct obstruction                              |                |                |                |
| alternative dictionary used:<br>MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cholangitis                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 3 / 65 (4.62%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 3          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cholecystitis                                   |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cholestasis                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| jaundice                                        |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Renal and urinary disorders                     |                |                |                |
| nephrotic syndrome                              |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| renal failure acute                             |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 3 / 3          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| ureteric stenosis                               |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Musculoskeletal and connective tissue disorders |                |                |                |
| back pain                                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| abdominal sepsis                                |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%) |
| 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                                     |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| bacterial sepsis                                |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| bronchitis                                      |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| cellulitis                                      |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 2 / 50 (4.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| clostridium difficile colitis                   |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| device related infection                        |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |
| escherichia bacteraemia                         |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| pneumonia                                       |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| renal abscess                                   |                |                |                |
| alternative dictionary used: MedDRA 15.1        |                |                |                |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (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          |

|                                                                        |                |                |                |
|------------------------------------------------------------------------|----------------|----------------|----------------|
| sepsis<br>alternative dictionary used:<br>MedDRA 15.1                  |                |                |                |
| subjects affected / exposed                                            | 1 / 50 (2.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all                     | 0 / 1          | 0 / 0          | 0 / 0          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| urinary tract infection<br>alternative dictionary used:<br>MedDRA 15.1 |                |                |                |
| subjects affected / exposed                                            | 0 / 50 (0.00%) | 0 / 65 (0.00%) | 3 / 34 (8.82%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0          | 0 / 0          | 1 / 3          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| Metabolism and nutrition disorders                                     |                |                |                |
| decreased appetite<br>alternative dictionary used:<br>MedDRA 15.1      |                |                |                |
| subjects affected / exposed                                            | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| dehydration<br>alternative dictionary used:<br>MedDRA 15.1             |                |                |                |
| subjects affected / exposed                                            | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 3 / 34 (8.82%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0          | 0 / 1          | 2 / 3          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| hyperkalaemia<br>alternative dictionary used:<br>MedDRA 15.1           |                |                |                |
| subjects affected / exposed                                            | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 0 / 34 (0.00%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0          | 0 / 1          | 0 / 0          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| hyponatraemia<br>alternative dictionary used:<br>MedDRA 15.1           |                |                |                |
| subjects affected / exposed                                            | 0 / 50 (0.00%) | 1 / 65 (1.54%) | 1 / 34 (2.94%) |
| occurrences causally related to<br>treatment / all                     | 0 / 0          | 0 / 1          | 0 / 1          |
| deaths causally related to<br>treatment / all                          | 0 / 0          | 0 / 0          | 0 / 0          |
| hypovolaemia<br>alternative dictionary used:<br>MedDRA 15.1            |                |                |                |

|                                                 |                |                |                |
|-------------------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 50 (0.00%) | 2 / 65 (3.08%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 2          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.

Justification: This event is gender specific, only occurring in male or female participants. The number of participants exposed has been adjusted accordingly.

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

| <b>Non-serious adverse events</b>                                                                                                                                                     | Phase 1                  | Phase 2: LY2603618 + Gemcitabine | Phase 2: Gemcitabine     |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------------------|--------------------------|
| Total subjects affected by non-serious adverse events                                                                                                                                 |                          |                                  |                          |
| subjects affected / exposed                                                                                                                                                           | 48 / 50 (96.00%)         | 64 / 65 (98.46%)                 | 34 / 34 (100.00%)        |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps)<br>tumour pain<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 0 / 50 (0.00%)<br><br>0  | 0 / 65 (0.00%)<br><br>0          | 2 / 34 (5.88%)<br><br>3  |
| Vascular disorders<br>deep vein thrombosis<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 50 (2.00%)<br><br>1  | 4 / 65 (6.15%)<br><br>4          | 3 / 34 (8.82%)<br><br>3  |
| flushing<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                           | 6 / 50 (12.00%)<br><br>8 | 0 / 65 (0.00%)<br><br>0          | 0 / 34 (0.00%)<br><br>0  |
| hypertension<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                       | 1 / 50 (2.00%)<br><br>1  | 3 / 65 (4.62%)<br><br>3          | 3 / 34 (8.82%)<br><br>3  |
| hypotension<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                        | 5 / 50 (10.00%)<br><br>5 | 3 / 65 (4.62%)<br><br>3          | 5 / 34 (14.71%)<br><br>5 |
| thrombophlebitis superficial<br>alternative dictionary used:<br>MedDRA 15.1                                                                                                           |                          |                                  |                          |

|                                                      |                  |                  |                  |
|------------------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                          | 0 / 50 (0.00%)   | 4 / 65 (6.15%)   | 0 / 34 (0.00%)   |
| occurrences (all)                                    | 0                | 4                | 0                |
| General disorders and administration site conditions |                  |                  |                  |
| asthenia                                             |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 4 / 50 (8.00%)   | 10 / 65 (15.38%) | 5 / 34 (14.71%)  |
| occurrences (all)                                    | 5                | 19               | 8                |
| chills                                               |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 5 / 50 (10.00%)  | 9 / 65 (13.85%)  | 2 / 34 (5.88%)   |
| occurrences (all)                                    | 6                | 15               | 2                |
| fatigue                                              |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 31 / 50 (62.00%) | 22 / 65 (33.85%) | 14 / 34 (41.18%) |
| occurrences (all)                                    | 50               | 28               | 19               |
| influenza like illness                               |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 3 / 50 (6.00%)   | 3 / 65 (4.62%)   | 3 / 34 (8.82%)   |
| occurrences (all)                                    | 3                | 8                | 3                |
| infusion site pain                                   |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 5 / 50 (10.00%)  | 0 / 65 (0.00%)   | 1 / 34 (2.94%)   |
| occurrences (all)                                    | 10               | 0                | 4                |
| irritability                                         |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 3 / 50 (6.00%)   | 0 / 65 (0.00%)   | 0 / 34 (0.00%)   |
| occurrences (all)                                    | 3                | 0                | 0                |
| non-cardiac chest pain                               |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |
| subjects affected / exposed                          | 3 / 50 (6.00%)   | 1 / 65 (1.54%)   | 1 / 34 (2.94%)   |
| occurrences (all)                                    | 3                | 1                | 1                |
| oedema peripheral                                    |                  |                  |                  |
| alternative dictionary used: MedDRA 15.1             |                  |                  |                  |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                                                                                                       |                                                                                                                                     |                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| subjects affected / exposed<br>occurrences (all)<br><br>pyrexia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 8 / 50 (16.00%)<br>9<br><br>15 / 50 (30.00%)<br>33                                                                                    | 19 / 65 (29.23%)<br>23<br><br>19 / 65 (29.23%)<br>23                                                                                | 12 / 34 (35.29%)<br>16<br><br>11 / 34 (32.35%)<br>14                                                                             |
| Immune system disorders<br>drug hypersensitivity<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 5 / 50 (10.00%)<br>5                                                                                                                  | 2 / 65 (3.08%)<br>5                                                                                                                 | 0 / 34 (0.00%)<br>0                                                                                                              |
| Respiratory, thoracic and mediastinal disorders<br>cough<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>dysphonia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>dyspnoea<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>dyspnoea exertional<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>epistaxis<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 10 / 50 (20.00%)<br>12<br><br>0 / 50 (0.00%)<br>0<br><br>8 / 50 (16.00%)<br>11<br><br>4 / 50 (8.00%)<br>7<br><br>5 / 50 (10.00%)<br>5 | 7 / 65 (10.77%)<br>7<br><br>2 / 65 (3.08%)<br>2<br><br>12 / 65 (18.46%)<br>13<br><br>2 / 65 (3.08%)<br>2<br><br>1 / 65 (1.54%)<br>2 | 5 / 34 (14.71%)<br>6<br><br>2 / 34 (5.88%)<br>2<br><br>2 / 34 (5.88%)<br>2<br><br>1 / 34 (2.94%)<br>1<br><br>0 / 34 (0.00%)<br>0 |
| Psychiatric disorders                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                       |                                                                                                                                     |                                                                                                                                  |

|                                                                                                                                                         |                        |                        |                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|
| anxiety<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                              | 4 / 50 (8.00%)<br>4    | 0 / 65 (0.00%)<br>0    | 3 / 34 (8.82%)<br>3  |
| confusional state<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 50 (2.00%)<br>1    | 1 / 65 (1.54%)<br>1    | 2 / 34 (5.88%)<br>2  |
| depression<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                           | 6 / 50 (12.00%)<br>7   | 2 / 65 (3.08%)<br>2    | 3 / 34 (8.82%)<br>4  |
| insomnia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                             | 7 / 50 (14.00%)<br>9   | 4 / 65 (6.15%)<br>4    | 6 / 34 (17.65%)<br>8 |
| Investigations<br>alanine aminotransferase increased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 10 / 50 (20.00%)<br>15 | 13 / 65 (20.00%)<br>18 | 6 / 34 (17.65%)<br>6 |
| aspartate aminotransferase increased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                 | 11 / 50 (22.00%)<br>14 | 10 / 65 (15.38%)<br>15 | 5 / 34 (14.71%)<br>5 |
| blood alkaline phosphatase increased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 50 (0.00%)<br>0    | 5 / 65 (7.69%)<br>5    | 3 / 34 (8.82%)<br>3  |
| blood lactate dehydrogenase increased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                | 1 / 50 (2.00%)<br>1    | 2 / 65 (3.08%)<br>2    | 3 / 34 (8.82%)<br>3  |
| gamma-glutamyltransferase increased                                                                                                                     |                        |                        |                      |

|                                                                                                                                                                                |                     |                        |                     |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|------------------------|---------------------|
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                                | 4 / 50 (8.00%)<br>4 | 12 / 65 (18.46%)<br>12 | 3 / 34 (8.82%)<br>3 |
| haemoglobin decreased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                       | 0 / 50 (0.00%)<br>0 | 2 / 65 (3.08%)<br>2    | 2 / 34 (5.88%)<br>3 |
| neutrophil count decreased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                  | 0 / 50 (0.00%)<br>0 | 3 / 65 (4.62%)<br>3    | 2 / 34 (5.88%)<br>6 |
| platelet count decreased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                    | 0 / 50 (0.00%)<br>0 | 7 / 65 (10.77%)<br>11  | 1 / 34 (2.94%)<br>5 |
| weight decreased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                            | 2 / 50 (4.00%)<br>3 | 7 / 65 (10.77%)<br>8   | 3 / 34 (8.82%)<br>3 |
| white blood cell count decreased<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                            | 2 / 50 (4.00%)<br>2 | 2 / 65 (3.08%)<br>4    | 2 / 34 (5.88%)<br>8 |
| Injury, poisoning and procedural complications<br>infusion related reaction<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 50 (6.00%)<br>3 | 1 / 65 (1.54%)<br>1    | 0 / 34 (0.00%)<br>0 |
| procedural pain<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                             | 3 / 50 (6.00%)<br>4 | 0 / 65 (0.00%)<br>0    | 0 / 34 (0.00%)<br>0 |
| Cardiac disorders                                                                                                                                                              |                     |                        |                     |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                        |                                                                                                         |                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| sinus tachycardia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                                                                                                                                                                    | 3 / 50 (6.00%)<br>3                                                                                    | 0 / 65 (0.00%)<br>0                                                                                     | 1 / 34 (2.94%)<br>1                                                                                   |
| Nervous system disorders<br>dizziness<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>dysgeusia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>headache<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>peripheral sensory neuropathy<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 5 / 50 (10.00%)<br>5<br><br>3 / 50 (6.00%)<br>5<br><br>5 / 50 (10.00%)<br>7<br><br>4 / 50 (8.00%)<br>4 | 5 / 65 (7.69%)<br>5<br><br>5 / 65 (7.69%)<br>5<br><br>7 / 65 (10.77%)<br>10<br><br>7 / 65 (10.77%)<br>8 | 4 / 34 (11.76%)<br>4<br><br>2 / 34 (5.88%)<br>2<br><br>2 / 34 (5.88%)<br>2<br><br>2 / 34 (5.88%)<br>4 |
| Blood and lymphatic system disorders<br>anaemia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>leukocytosis<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>leukopenia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)<br><br>lymphopenia                                                                                                       | 23 / 50 (46.00%)<br>29<br><br>3 / 50 (6.00%)<br>3<br><br>4 / 50 (8.00%)<br>5                           | 16 / 65 (24.62%)<br>21<br><br>1 / 65 (1.54%)<br>1<br><br>8 / 65 (12.31%)<br>27                          | 10 / 34 (29.41%)<br>13<br><br>0 / 34 (0.00%)<br>0<br><br>6 / 34 (17.65%)<br>10                        |

|                                                                                                                                                                               |                                   |                                   |                                   |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|-----------------------------------|
| <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                               | <p>5 / 50 (10.00%)</p> <p>6</p>   | <p>4 / 65 (6.15%)</p> <p>7</p>    | <p>4 / 34 (11.76%)</p> <p>4</p>   |
| <p>neutropenia</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                            | <p>16 / 50 (32.00%)</p> <p>26</p> | <p>15 / 65 (23.08%)</p> <p>49</p> | <p>10 / 34 (29.41%)</p> <p>24</p> |
| <p>thrombocytopenia</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                       | <p>23 / 50 (46.00%)</p> <p>46</p> | <p>23 / 65 (35.38%)</p> <p>63</p> | <p>15 / 34 (44.12%)</p> <p>39</p> |
| <p>thrombocytosis</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                         | <p>1 / 50 (2.00%)</p> <p>1</p>    | <p>0 / 65 (0.00%)</p> <p>0</p>    | <p>2 / 34 (5.88%)</p> <p>5</p>    |
| <p>Gastrointestinal disorders</p> <p>abdominal discomfort</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 50 (6.00%)</p> <p>3</p>    | <p>1 / 65 (1.54%)</p> <p>2</p>    | <p>0 / 34 (0.00%)</p> <p>0</p>    |
| <p>abdominal distension</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                   | <p>4 / 50 (8.00%)</p> <p>4</p>    | <p>2 / 65 (3.08%)</p> <p>3</p>    | <p>2 / 34 (5.88%)</p> <p>2</p>    |
| <p>abdominal pain</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                         | <p>12 / 50 (24.00%)</p> <p>12</p> | <p>14 / 65 (21.54%)</p> <p>19</p> | <p>5 / 34 (14.71%)</p> <p>7</p>   |
| <p>abdominal pain upper</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                   | <p>2 / 50 (4.00%)</p> <p>2</p>    | <p>5 / 65 (7.69%)</p> <p>5</p>    | <p>1 / 34 (2.94%)</p> <p>1</p>    |
| <p>anorectal discomfort</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p>                                                                                               |                                   |                                   |                                   |

|                                             |                  |                  |                  |
|---------------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed                 | 0 / 50 (0.00%)   | 0 / 65 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences (all)                           | 0                | 0                | 2                |
| constipation                                |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 17 / 50 (34.00%) | 21 / 65 (32.31%) | 9 / 34 (26.47%)  |
| occurrences (all)                           | 22               | 27               | 10               |
| diarrhoea                                   |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 8 / 50 (16.00%)  | 21 / 65 (32.31%) | 10 / 34 (29.41%) |
| occurrences (all)                           | 10               | 36               | 15               |
| dyspepsia                                   |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 3 / 50 (6.00%)   | 4 / 65 (6.15%)   | 1 / 34 (2.94%)   |
| occurrences (all)                           | 3                | 4                | 1                |
| flatulence                                  |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 1 / 50 (2.00%)   | 4 / 65 (6.15%)   | 0 / 34 (0.00%)   |
| occurrences (all)                           | 1                | 7                | 0                |
| gastritis                                   |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 3 / 50 (6.00%)   | 1 / 65 (1.54%)   | 0 / 34 (0.00%)   |
| occurrences (all)                           | 3                | 1                | 0                |
| haemorrhoids                                |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 2 / 50 (4.00%)   | 0 / 65 (0.00%)   | 2 / 34 (5.88%)   |
| occurrences (all)                           | 2                | 0                | 2                |
| nausea                                      |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 20 / 50 (40.00%) | 27 / 65 (41.54%) | 15 / 34 (44.12%) |
| occurrences (all)                           | 25               | 42               | 21               |
| steatorrhoea                                |                  |                  |                  |
| alternative dictionary used:<br>MedDRA 15.1 |                  |                  |                  |
| subjects affected / exposed                 | 0 / 50 (0.00%)   | 1 / 65 (1.54%)   | 2 / 34 (5.88%)   |
| occurrences (all)                           | 0                | 1                | 2                |

|                                                                                                                                                       |                        |                        |                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|
| stomatitis<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                         | 5 / 50 (10.00%)<br>9   | 13 / 65 (20.00%)<br>14 | 2 / 34 (5.88%)<br>2  |
| vomiting<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                           | 14 / 50 (28.00%)<br>16 | 19 / 65 (29.23%)<br>35 | 4 / 34 (11.76%)<br>5 |
| Hepatobiliary disorders<br>hyperbilirubinaemia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)     | 2 / 50 (4.00%)<br>2    | 2 / 65 (3.08%)<br>2    | 4 / 34 (11.76%)<br>4 |
| Skin and subcutaneous tissue disorders<br>alopecia<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 2 / 50 (4.00%)<br>2    | 7 / 65 (10.77%)<br>8   | 5 / 34 (14.71%)<br>6 |
| decubitus ulcer<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                    | 1 / 50 (2.00%)<br>1    | 4 / 65 (6.15%)<br>4    | 0 / 34 (0.00%)<br>0  |
| dermatitis acneiform<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                               | 4 / 50 (8.00%)<br>5    | 2 / 65 (3.08%)<br>2    | 0 / 34 (0.00%)<br>0  |
| hyperhidrosis<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                      | 3 / 50 (6.00%)<br>3    | 1 / 65 (1.54%)<br>1    | 0 / 34 (0.00%)<br>0  |
| pruritus<br>alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all)                                           | 1 / 50 (2.00%)<br>1    | 4 / 65 (6.15%)<br>6    | 2 / 34 (5.88%)<br>2  |
| Renal and urinary disorders                                                                                                                           |                        |                        |                      |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                               |                                                                                                                                                               |                                                                                                                                                             |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>pollakiuria</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | <p>3 / 50 (6.00%)</p> <p>3</p>                                                                                                                                | <p>0 / 65 (0.00%)</p> <p>0</p>                                                                                                                                | <p>0 / 34 (0.00%)</p> <p>0</p>                                                                                                                              |
| <p>Musculoskeletal and connective tissue disorders</p> <p>arthralgia</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>back pain</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>muscular weakness</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>musculoskeletal chest pain</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>pain in extremity</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 50 (6.00%)</p> <p>3</p> <p>6 / 50 (12.00%)</p> <p>6</p> <p>7 / 50 (14.00%)</p> <p>9</p> <p>3 / 50 (6.00%)</p> <p>3</p> <p>5 / 50 (10.00%)</p> <p>7</p> | <p>1 / 65 (1.54%)</p> <p>1</p> <p>9 / 65 (13.85%)</p> <p>10</p> <p>2 / 65 (3.08%)</p> <p>2</p> <p>0 / 65 (0.00%)</p> <p>0</p> <p>8 / 65 (12.31%)</p> <p>9</p> | <p>0 / 34 (0.00%)</p> <p>0</p> <p>4 / 34 (11.76%)</p> <p>4</p> <p>2 / 34 (5.88%)</p> <p>2</p> <p>2 / 34 (5.88%)</p> <p>2</p> <p>1 / 34 (2.94%)</p> <p>1</p> |
| <p>Infections and infestations</p> <p>oral candidiasis</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>upper respiratory tract infection</p> <p>alternative dictionary used:<br/>MedDRA 15.1</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>urinary tract infection</p>                                                                                                                                                                                                                                                                                                                                                                                            | <p>4 / 50 (8.00%)</p> <p>4</p> <p>3 / 50 (6.00%)</p> <p>4</p>                                                                                                 | <p>1 / 65 (1.54%)</p> <p>2</p> <p>0 / 65 (0.00%)</p> <p>0</p>                                                                                                 | <p>1 / 34 (2.94%)</p> <p>1</p> <p>0 / 34 (0.00%)</p> <p>0</p>                                                                                               |

|                                                                                                 |                        |                        |                      |
|-------------------------------------------------------------------------------------------------|------------------------|------------------------|----------------------|
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 50 (6.00%)<br>3    | 2 / 65 (3.08%)<br>2    | 3 / 34 (8.82%)<br>3  |
| Metabolism and nutrition disorders                                                              |                        |                        |                      |
| decreased appetite                                                                              |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 16 / 50 (32.00%)<br>19 | 21 / 65 (32.31%)<br>22 | 5 / 34 (14.71%)<br>6 |
| dehydration                                                                                     |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 50 (6.00%)<br>4    | 1 / 65 (1.54%)<br>1    | 3 / 34 (8.82%)<br>3  |
| hyperglycaemia                                                                                  |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 3 / 50 (6.00%)<br>8    | 12 / 65 (18.46%)<br>13 | 4 / 34 (11.76%)<br>6 |
| hyperkalaemia                                                                                   |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 0 / 50 (0.00%)<br>0    | 2 / 65 (3.08%)<br>2    | 3 / 34 (8.82%)<br>4  |
| hypoalbuminaemia                                                                                |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>2    | 4 / 65 (6.15%)<br>4    | 3 / 34 (8.82%)<br>3  |
| hypocalcaemia                                                                                   |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 1 / 50 (2.00%)<br>1    | 2 / 65 (3.08%)<br>4    | 6 / 34 (17.65%)<br>6 |
| hypokalaemia                                                                                    |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1<br>subjects affected / exposed<br>occurrences (all) | 4 / 50 (8.00%)<br>4    | 1 / 65 (1.54%)<br>1    | 5 / 34 (14.71%)<br>6 |
| hyponatraemia                                                                                   |                        |                        |                      |
| alternative dictionary used:<br>MedDRA 15.1                                                     |                        |                        |                      |

|                                             |                |                |                 |
|---------------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed                 | 3 / 50 (6.00%) | 6 / 65 (9.23%) | 5 / 34 (14.71%) |
| occurrences (all)                           | 4              | 7              | 5               |
| hypovolaemia                                |                |                |                 |
| alternative dictionary used:<br>MedDRA 15.1 |                |                |                 |
| subjects affected / exposed                 | 4 / 50 (8.00%) | 0 / 65 (0.00%) | 0 / 34 (0.00%)  |
| occurrences (all)                           | 8              | 0              | 0               |
| vitamin d deficiency                        |                |                |                 |
| alternative dictionary used:<br>MedDRA 15.1 |                |                |                 |
| subjects affected / exposed                 | 3 / 50 (6.00%) | 0 / 65 (0.00%) | 1 / 34 (2.94%)  |
| occurrences (all)                           | 3              | 0              | 1               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment                                                                                                                                                                                    |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 22 September 2009 | Amendment (a) clarified dose omissions/reductions during a cycle, declaration of a DLT, and description of the MTD that will be carried into Phase 2. The ECG collection was also clarified. |
| 30 June 2010      | Amendment (b) added 2 additional cohorts of patients (n=20) prior to selecting the recommended Phase 2 dose.                                                                                 |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported