



## Clinical trial results:

### A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE III STUDY OF THE EFFICACY AND SAFETY OF HERCULES PLUS TAXANE VERSUS HERCEPTIN® PLUS TAXANE AS FIRST LINE THERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

#### Summary

|                          |                            |
|--------------------------|----------------------------|
| EudraCT number           | 2011-001965-42             |
| Trial protocol           | DE HU BG CZ SK LV ES GR AT |
| Global end of trial date | 03 August 2018             |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 01 January 2020 |
| First version publication date | 01 January 2020 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | MYL-Her-3001 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02472964 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Mylan GmbH  |
| Sponsor organisation address | Thurgauerstrasse 40, Zurich, Switzerland, 8050  |
| Public contact               | Senior Clinical Project Manager, Gail Tribble, Mylan Inc.<br>1000 Mylan Boulevard<br>Canonsburg, PA, 15317<br>USA, 1 7244856124 , gail.tribble@mylan.com                  |
| Scientific contact           | Deputy General Manager Clinical, Tazeen Aamena Idris, Mylan Pharmaceuticals Private Limited<br>Plot No.1-60/35/A, 500032 Hyderabad, India,<br>TazeenAamena.Idris@mylan.in |

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Final          |
| Date of interim/final analysis                       | 03 August 2018 |
| Is this the analysis of the primary completion data? | No             |
| Global end of trial reached?                         | Yes            |
| Global end of trial date                             | 03 August 2018 |
| Was the trial ended prematurely?                     | No             |

Notes:

## General information about the trial

Main objective of the trial:

Part 1: To compare the independently assessed best overall response rate (ORR) (according to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 criteria) at Week 24 with MYL-14020 plus taxane versus Herceptin® plus taxane in patients who have not received previous first line treatment for HER2+ MBC.

Part 2: To continue to evaluate the safety and tolerability profile of MYL-14020 and Herceptin® given as a single agent. And to compare the immunogenicity of MYL-14020 and Herceptin® by examining clinical immunogenic response.

To compare the clinical activity at Week 48 between treatment arms by measuring PFS, OS and duration of response (DR), and OS at 36 months or after 240 deaths, whichever occurs first, as observed from the time of randomization of the last patient.

Protection of trial subjects:

Monitoring of adverse events and serious adverse events. Regularly scheduled IDMC review.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 16 July 2012 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                         |
|--------------------------------------|-------------------------|
| Country: Number of subjects enrolled | Bulgaria: 2             |
| Country: Number of subjects enrolled | Poland: 19              |
| Country: Number of subjects enrolled | Slovakia: 3             |
| Country: Number of subjects enrolled | Czech Republic: 2       |
| Country: Number of subjects enrolled | Hungary: 14             |
| Country: Number of subjects enrolled | Latvia: 6               |
| Country: Number of subjects enrolled | Romania: 8              |
| Country: Number of subjects enrolled | Russian Federation: 151 |
| Country: Number of subjects enrolled | Philippines: 51         |
| Country: Number of subjects enrolled | Serbia: 5               |
| Country: Number of subjects enrolled | South Africa: 15        |
| Country: Number of subjects enrolled | Thailand: 47            |
| Country: Number of subjects enrolled | Ukraine: 55             |

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Chile: 5    |
| Country: Number of subjects enrolled | Georgia: 62 |
| Country: Number of subjects enrolled | India: 55   |
| Worldwide total number of subjects   | 500         |
| EEA total number of subjects         | 54          |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 415 |
| From 65 to 84 years                       | 85  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

500 subjects enrolled at 95 sites across Eastern Europe, Russia, Asia Pacific, Africa and South America. The intent-to-treat (ITT1) population of 458 was used to determine Primary Outcome of Overall Response Rate.

### Pre-assignment

Screening details:

The primary efficacy analysis was derived from ITT1 population 230 (MYL-1401O) + 228 (Herceptin) = 458. Safety analysis was derived from the Safety Population 247 (MYL-1401O) + 246 (Herceptin) = 493. Total Randomized population 249 (MYL-1401O) + 251 (Herceptin) = 500.

### Period 1

|                              |   |
|------------------------------|---|
| Period 1 title               | Part I (up to week 24)  |
| Is this the baseline period? | Yes   |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

### Arms

|                              |                     |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes                 |
| <b>Arm title</b>             | Herceptin® + Taxane |

Arm description:

Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m<sup>2</sup> weekly intravenously or docetaxel 75 mg/m<sup>2</sup> intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint.

|  |  |
|--|--|
| Arm type                               | Active comparator                                |
| Investigational medicinal product name | Trastuzumab                                      |
| Investigational medicinal product code | Herceptin®                                       |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for infusion |
| Routes of administration               | Intravenous use                                  |

Dosage and administration details:

Trastuzumab 8mg/kg IV over 90 minutes x 1 then Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

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

Dosage and administration details:

Paclitaxel 80mg/m<sup>2</sup> IV over 60 minutes weekly.

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

Dosage and administration details:

Docetaxel 75mg/m<sup>2</sup> IV over 60 minutes on day 1 of a 3 week cycle

|                  |                    |
|------------------|--------------------|
| <b>Arm title</b> | MYL-1401O + Taxane |
|------------------|--------------------|

Arm description:

Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m<sup>2</sup> weekly intravenously or docetaxel 75 mg/m<sup>2</sup>

intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | MYL-1401O  |
| Investigational medicinal product code | trastuzumab  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

Dosage and administration details:

MYL-1401O 8mg/kg IV over 90 minutes x 1 then MYL-1401O Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

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

Dosage and administration details:

Paclitaxel 80mg/m<sup>2</sup> IV over 60 minutes weekly.

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

Dosage and administration details:

Docetaxel 75mg/m<sup>2</sup> IV over 60 minutes on day 1 of a 3 week cycle

| <b>Number of subjects in period 1</b> | <b>Herceptin® + Taxane</b> | <b>MYL-1401O + Taxane</b> |
|---------------------------------------|----------------------------|---------------------------|
| Started                               | 251                        | 249                       |
| Protocol Amendment 2                  | 228                        | 230                       |
| Completed                             | 171                        | 185                       |
| Not completed                         | 80                         | 64                        |
| Adverse event, serious fatal          | 3                          | 6                         |
| Physician decision                    | 5                          | 1                         |
| Consent withdrawn by subject          | 9                          | 2                         |
| Disease progression                   | 58                         | 49                        |
| unknown                               | 2                          | 1                         |
| Adverse event, non-fatal              | 2                          | 4                         |
| Death before treatment start          | 1                          | -                         |
| Lost to follow-up                     | -                          | 1                         |

**Period 2**

|                              |   |
|------------------------------|---|
| Period 2 title               | Part 2 (Week 24-week 48)                                      |
| Is this the baseline period? | No  |
| Allocation method            | Randomised - controlled                                       |
| Blinding used                | Double blind  |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst, Carer, Assessor |

**Arms**

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | Herceptin® |

## Arm description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal .

|  |  |
|--|--|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Herceptin®   |
| Investigational medicinal product code | trastuzumab  |
| Other name                             |  |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

## Dosage and administration details:

Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

|                  |           |
|------------------|-----------|
| <b>Arm title</b> | Myl-1401O |
|------------------|-----------|

## Arm description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal.

|  |  |
|--|--|
| Arm type                               | Experimental   |
| Investigational medicinal product name | MYL-1401O  |
| Investigational medicinal product code | trastuzumab  |
| Other name                             | Hercules   |
| Pharmaceutical forms                   | Powder for concentrate for solution for injection/infusion |
| Routes of administration               | Intravenous use  |

## Dosage and administration details:

MYL-1401O Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

| <b>Number of subjects in period 2<sup>[1]</sup></b> | Herceptin® | Myl-1401O |
|---|------------|-----------|
| Started   | 163        | 179       |
| Completed   | 98         | 116       |
| Not completed                                       | 65         | 63        |
| Adverse event, serious fatal                        | -          | 1         |
| Physician decision                                  | 1          | 1         |
| Consent withdrawn by subject                        | 3          | 1         |
| Disease progression                                 | 52         | 56        |
| Adverse event, non-fatal                            | 4          | 2         |
| Other   | 3          | -         |
| Lost to follow-up                                   | 2          | 1         |

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

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Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: A total of 14 patients who completed Part 1 of the study did not enter Part 2 (MYL-1401O 6 patients, Herceptin 8 patients).

Reasons for not entering Part 2 monotherapy were disease progression (MYL-1401O 4 patients/Herceptin 4 patients), withdrawal of consent (2/1), death (0/1), AE not due to disease progression (0/1), no reason (0/1).

## Baseline characteristics

### Reporting groups

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Herceptin® + Taxane |
|-----------------------|---------------------|

Reporting group description:

Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint.

|                       |                    |
|-----------------------|--------------------|
| Reporting group title | MYL-1401O + Taxane |
|-----------------------|--------------------|

Reporting group description:

Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.

| Reporting group values  | Herceptin® + Taxane | MYL-1401O + Taxane | Total |
|---|---------------------|--------------------|-------|
| Number of subjects  | 251                 | 249                | 500   |
| Age categorical   |                     |                    |       |
| The primary efficacy endpoint analysis was conducted in the intention to treat (ITT1) population ( only those patients randomized after the second amendment of the protocol) |                     |                    |       |
| Units: Subjects   |                     |                    |       |
| 18-49 years   | 93                  | 80                 | 173   |
| >= 50 years   | 158                 | 169                | 327   |
| Gender categorical  |                     |                    |       |
| Units: Subjects   |                     |                    |       |
| Female  | 251                 | 249                | 500   |
| Male  | 0                   | 0                  | 0     |



## End points

### End points reporting groups

|  |                     |
|--|---------------------|
| Reporting group title  | Herceptin® + Taxane |
| Reporting group description:<br>Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint. |                     |
| Reporting group title  | MYL-1401O + Taxane  |
| Reporting group description:<br>Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.               |                     |
| Reporting group title  | Herceptin®          |
| Reporting group description:<br>Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal .   |                     |
| Reporting group title  | Myl-1401O           |
| Reporting group description:<br>Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal.   |                     |

### Primary: Compare Best Overall Response Rate (ORR) (According to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 Criteria) at Week 24 of MYL-1401O Plus Taxane Versus Herceptin® Plus Taxane in the ITT1 Population

|   |  |
|---|--|
| End point title   | Compare Best Overall Response Rate (ORR) (According to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 Criteria) at Week 24 of MYL-14010 Plus Taxane Versus Herceptin® Plus Taxane in the ITT1 Population |
| End point description:<br>Tumor measurements were performed by centralized blinded reviewers using RECIST 1.1 criteria. Per RECIST 1.1: Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm.Partial Response (PR): >/= 30% decrease sum of the diameters of target lesions from baseline sum diameters. Progressive Disease (PD): </= 20% increase in the sum of the diameters of target lesions, from the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression.<br>Stable Disease (SD): Neither sufficient decrease or increase. Evaluation of Non-Target Lesions Complete Response (CR): Disappearance of all non-target lesions. Non-complete Response/Non-Progressive Disease: Persistence of one or more non-target lesions. Progressive Disease (PD): Substantial, unequivocal progression of existing non-target lesions. |  |
| End point type  | Primary  |
| End point timeframe:<br>from time of First treatment to week 24   |  |

| End point values            | Herceptin® + Taxane | MYL-1401O + Taxane |  |  |
|-----------------------------|---------------------|--------------------|--|--|
| Subject group type          | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed | 228 <sup>[1]</sup>  | 230 <sup>[2]</sup> |  |  |
| Units: participants         |                     |                    |  |  |
| Complete Response           | 0                   | 3                  |  |  |
| Partial Response            | 146                 | 157                |  |  |

|                     |    |    |  |  |
|---------------------|----|----|--|--|
| Stable Disease      | 49 | 48 |  |  |
| Progressive Disease | 20 | 9  |  |  |
| Not Evaluable       | 13 | 13 |  |  |

Notes:

[1] - ITT1

[2] - ITT1

## Statistical analyses

| Statistical analysis title | Difference of Best ORR* at week 24 |
|----------------------------|------------------------------------|
|----------------------------|------------------------------------|

Statistical analysis description:

\*ORR = Overall Response Rate

The following hypotheses were set up with the EMA's equivalence margin of (-15%, 15%):

H0: (RT - RC ≤ -15%) or (RT - RC ≥ 15%)

H1: -15% < (RT - RC) < 15%,

where, RT and RC were the best ORR of test (MYL-14010) and control (Herceptin®), respectively.

A two-sided 95% CI for the difference of the best ORRs at Week 24 was calculated. Equivalence was declared if the CI was completely within the equivalence range of (-15%, 15%)

|   |  |
|---|--|
| Comparison groups                       | Herceptin® + Taxane v MYL-14010 + Taxane |
| Number of subjects included in analysis | 458                                      |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | equivalence                              |
| Parameter estimate                      | Risk difference (RD)                     |
| Point estimate                          | 5.5                                      |
| Confidence interval                     |  |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | -3.08                                    |
| upper limit                             | 14.04                                    |

## Secondary: PFS (Progression-Free-Survival) at week 48

|                 |  |
|-----------------|--|
| End point title | PFS (Progression-Free-Survival) at week 48 |
|-----------------|--|

End point description:

To compare the clinical activity at Week 48 between treatment arms by measuring PFS, as observed from the time of randomization.

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

End point timeframe:

week 48

| End point values                 | Herceptin® + Taxane  | MYL-14010 + Taxane   |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed      | 228                  | 230                  |  |  |
| Units: Months                    |                      |                      |  |  |
| median (confidence interval 95%) | 11.1 (8.60 to 11.20) | 11.1 (8.81 to 11.20) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: DR (duration of response) at week 48

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | DR (duration of response) at week 48 |
|-----------------|--------------------------------------|

End point description:

To compare the clinical activity at Week 48 between treatment arms by measuring duration of response (DR), as observed from the time of randomization.

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

End point timeframe:

48 weeks

| End point values                 | Herceptin® + Taxane | MYL-1401O + Taxane |  |  |
|----------------------------------|---------------------|--------------------|--|--|
| Subject group type               | Reporting group     | Reporting group    |  |  |
| Number of subjects analysed      | 228 <sup>[3]</sup>  | 230 <sup>[4]</sup> |  |  |
| Units: months                    |                     |                    |  |  |
| median (confidence interval 95%) | 9.7 (7.68 to 9.87)  | 9.7 (7.38 to 9.89) |  |  |

Notes:

[3] - number of patients with data available: 182

[4] - number of patients with data available: 191

## Statistical analyses

No statistical analyses for this end point

### Secondary: OS (Overall Survival) at month 36

|                 |                                   |
|-----------------|-----------------------------------|
| End point title | OS (Overall Survival) at month 36 |
|-----------------|-----------------------------------|

End point description:

To compare the clinical activity between treatment arms by measuring OS at 36 months as observed from the time of randomization of the last patient.

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

End point timeframe:

36 months

| End point values                 | Herceptin® + Taxane   | MYL-1401O + Taxane    |  |  |
|----------------------------------|-----------------------|-----------------------|--|--|
| Subject group type               | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed      | 228                   | 230                   |  |  |
| Units: months                    |                       |                       |  |  |
| median (confidence interval 95%) | 30.2 (25.00 to 39.86) | 35.0 (26.75 to 39.88) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: TTP (Time to Tumor Progression) at week 48

|  |  |
|--|--|
| End point title  | TTP (Time to Tumor Progression) at week 48 |
| End point description:<br>To compare the clinical activity at Week 48 between treatment arms by measuring TTP, as observed from the time of randomization. |  |
| End point type   | Secondary                                  |
| End point timeframe:<br>week 48  |  |

| End point values                 | Herceptin® + Taxane  | MYL-1401O + Taxane   |  |  |
|----------------------------------|----------------------|----------------------|--|--|
| Subject group type               | Reporting group      | Reporting group      |  |  |
| Number of subjects analysed      | 228                  | 230                  |  |  |
| Units: months                    |                      |                      |  |  |
| median (confidence interval 95%) | 11.1 (8.88 to 11.20) | 11.1 (8.83 to 11.20) |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Active AE reporting period is from first dose until 28 days (+/- 7 days) after last administered dose of IMP per patient. SAEs should be reported any time after the active reporting period when SAE is considered related to study drug.

Adverse event reporting additional description:

Investigator is responsible for detection and documentation of events meeting the criteria of an AE/SAE. At each visit, the patient will be allowed time to report any issues since the last evaluation.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Herceptin® + Taxane (up to wk 24) |
|-----------------------|-----------------------------------|

Reporting group description:

Part 1: Herceptin® (trastuzumab) intravenously+ paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint. Timeframe: up to week 24

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | MYL-1401O + Taxane (up to wk 24) |
|-----------------------|----------------------------------|

Reporting group description:

Part 1: MYL-1401O intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint. Timeframe: up to week 24

|                       |                                    |
|-----------------------|------------------------------------|
| Reporting group title | Herceptin® (wk 25 up to 36 months) |
|-----------------------|------------------------------------|

Reporting group description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal. Timeframe: week 25 up to 36 months

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | MYL-1401O (wk 25 up to 36 months) |
|-----------------------|-----------------------------------|

Reporting group description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal. Timeframe: week 25 up to 36 months

| Serious adverse events  | Herceptin® + Taxane (up to wk 24) | MYL-1401O + Taxane (up to wk 24) | Herceptin® (wk 25 up to 36 months) |
|---|-----------------------------------|----------------------------------|------------------------------------|
| Total subjects affected by serious adverse events                   |                                   |                                  |                                    |
| subjects affected / exposed   | 90 / 246 (36.59%)                 | 95 / 247 (38.46%)                | 10 / 164 (6.10%)                   |
| number of deaths (all causes)                                       | 4                                 | 4                                | 0                                  |
| number of deaths resulting from adverse events                      |                                   |                                  |                                    |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                                  |                                    |
| Lymphangiosis carcinomatosa   |                                   |                                  |                                    |
| subjects affected / exposed   | 1 / 246 (0.41%)                   | 0 / 247 (0.00%)                  | 0 / 164 (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                              |
| Hepatocellular carcinoma  |                                   |                                  |                                    |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 1 / 164 (0.61%) |
| 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                                   |                 |                 |                 |
| Accelerated hypertension                             |                 |                 |                 |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Deep vein thrombosis                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Peripheral ischaemia                                 |                 |                 |                 |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Thrombophlebitis superficial                         |                 |                 |                 |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           | 0 / 0           |
| General disorders and administration site conditions |                 |                 |                 |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0           |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Hyperthermia   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |

|   |   |                 |                 |
|---|---|-----------------|-----------------|
| Malaise   |   |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)                             | 1 / 247 (0.40%) | 0 / 164 (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           |
| Multi-organ disorder                            | Additional description: Multi-organ failure |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)                             | 1 / 247 (0.40%) | 0 / 164 (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           |
| Pyrexia   |   |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%)                             | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2                                       | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           | 0 / 0           |
| Immune system disorders                         |   |                 |                 |
| Anaphylactic reaction                           |   |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)                             | 2 / 247 (0.81%) | 0 / 164 (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           |
| Drug hypersensitivity                           |   |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)                             | 1 / 247 (0.40%) | 0 / 164 (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           |
| Hypersensitivity                                |   |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%)                             | 0 / 247 (0.00%) | 0 / 164 (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           |
| Respiratory, thoracic and mediastinal disorders |   |                 |                 |
| Dyspnoea  |   |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)                             | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0                                       | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           | 0 / 0           |
| Pleural effusion                                |   |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%)                             | 1 / 247 (0.40%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1                                       | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0                                       | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Pneumonitis                                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 247 (0.40%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumothorax spontaneous                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Pulmonary embolism                              |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Pulmonary haemorrhage                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Respiratory failure                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 247 (0.81%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 1 / 1           | 1 / 2           | 0 / 0           |
| Psychiatric disorders                           |                 |                 |                 |
| Anxiety   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Investigations                                  |                 |                 |                 |
| Blood uric acid increased                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 247 (0.40%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Ejection fraction decreased                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| White blood cell count decreased<br>subjects affected / exposed | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Injury, poisoning and procedural<br>complications               |                 |                 |                 |
| Femur fracture  |                 |                 |                 |
| subjects affected / exposed                                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Infusion related reaction                                       |                 |                 |                 |
| subjects affected / exposed                                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to<br>treatment / all              | 1 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |
| Cardiac disorders   |                 |                 |                 |
| Acute myocardial infarction                                     |                 |                 |                 |
| subjects affected / exposed                                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Cardiac failure   |                 |                 |                 |
| subjects affected / exposed                                     | 0 / 246 (0.00%) | 2 / 247 (0.81%) | 0 / 164 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 1 / 2           | 0 / 0           |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 1           | 0 / 0           |
| Carditis  |                 |                 |                 |
| subjects affected / exposed                                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |
| Nervous system disorders  |                 |                 |                 |
| Cerebral infarction   |                 |                 |                 |
| subjects affected / exposed                                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to<br>treatment / all              | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to<br>treatment / all                   | 0 / 0           | 0 / 0           | 0 / 0           |
| Headache  |                 |                 |                 |

|   |                   |                   |                 |
|---|-------------------|-------------------|-----------------|
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 247 (0.00%)   | 0 / 164 (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           |
| Transient ischaemic attack                      |                   |                   |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)   | 1 / 247 (0.40%)   | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0           |
| Blood and lymphatic system disorders            |                   |                   |                 |
| Febrile neutropenia                             |                   |                   |                 |
| subjects affected / exposed                     | 10 / 246 (4.07%)  | 11 / 247 (4.45%)  | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 13            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0           |
| Leukopenia                                      |                   |                   |                 |
| subjects affected / exposed                     | 12 / 246 (4.88%)  | 5 / 247 (2.02%)   | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 13            | 0 / 5             | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0           |
| Neutropenia                                     |                   |                   |                 |
| subjects affected / exposed                     | 62 / 246 (25.20%) | 68 / 247 (27.53%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 78            | 0 / 92            | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0           |
| Pancytopenia                                    |                   |                   |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)   | 1 / 247 (0.40%)   | 0 / 164 (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           |
| Thrombocytopenia                                |                   |                   |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 247 (0.00%)   | 0 / 164 (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           |
| Anaemia   |                   |                   |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%)   | 0 / 247 (0.00%)   | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 0             | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             | 0 / 0           |
| Lymphopenia                                     |                   |                   |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Gastrointestinal disorders                      |                 |                 |                 |
| Abdominal pain                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Anal fissure                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Diarrhoea                                       |                 |                 |                 |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 3 / 247 (1.21%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Duodenal ulcer perforation                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Gastritis                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Gastrointestinal toxicity                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nausea  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 247 (0.81%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Rectal perforation                              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 247 (0.40%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 1 / 2           | 1 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Haemorrhoids                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholecystitis chronic                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Cholelithiasis                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Hepatic failure                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 247 (0.40%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           | 0 / 0           |
| Bile duct stone                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Renal and urinary disorders                     |                 |                 |                 |
| Acute kidney injury                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Musculoskeletal and connective tissue           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| disorders                                       |                 |                 |                 |
| Pathological fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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                     |                 |                 |                 |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Gastroenteritis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 3 / 247 (1.21%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Influenza                                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Mastitis  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Paronychia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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                                       |                 |                 |                 |
| subjects affected / exposed                     | 5 / 246 (2.03%) | 4 / 247 (1.62%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 1 / 5           | 0 / 4           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Rectal abscess                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Renal abscess                                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| Septic shock                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Tubo-ovarian abscess                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 0 / 247 (0.00%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Upper respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Urinary tract infection                         |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 247 (0.81%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Urosepsis                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 0 / 164 (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           |
| Wound infection                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Hypernatraemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Hyperuricaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 247 (0.81%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypokalaemia                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 247 (0.40%) | 1 / 164 (0.61%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hyponatraemia                                   |                 |                 |                 |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 247 (0.00%) | 0 / 164 (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           |
| Tumour lysis syndrome                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 247 (0.00%) | 0 / 164 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| <b>Serious adverse events</b>                                       | MYL-1401O (wk 25 up to 36 months) |  |  |
| Total subjects affected by serious adverse events                   |                                   |  |  |
| subjects affected / exposed   | 10 / 179 (5.59%)                  |  |  |
| number of deaths (all causes)                                       | 2                                 |  |  |
| number of deaths resulting from adverse events                      |                                   |  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |  |  |
| Lymphangiosis carcinomatosa   |                                   |  |  |
| subjects affected / exposed   | 0 / 179 (0.00%)                   |  |  |
| occurrences causally related to treatment / all                     | 0 / 0                             |  |  |
| deaths causally related to treatment / all                          | 0 / 0                             |  |  |
| Hepatocellular carcinoma  |                                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Vascular disorders                                   |                 |  |  |
| Accelerated hypertension                             |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Deep vein thrombosis                                 |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Peripheral ischaemia                                 |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Thrombophlebitis superficial                         |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| General disorders and administration site conditions |                 |  |  |
| Death  |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Fatigue  |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |
| Hyperthermia   |                 |  |  |
| subjects affected / exposed                          | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all      | 0 / 0           |  |  |
| deaths causally related to treatment / all           | 0 / 0           |  |  |



|   |   |  |  |
|---|---|--|--|
| Malaise   |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Multi-organ disorder                            | Additional description: Multi-organ failure |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Pyrexia   |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Immune system disorders                         |   |  |  |
| Anaphylactic reaction                           |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Drug hypersensitivity                           |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Hypersensitivity                                |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |
| Respiratory, thoracic and mediastinal disorders |   |  |  |
| Dyspnoea  |   |  |  |
| subjects affected / exposed                     | 2 / 179 (1.12%)                             |  |  |
| occurrences causally related to treatment / all | 1 / 2                                       |  |  |
| deaths causally related to treatment / all      | 0 / 1                                       |  |  |
| Pleural effusion                                |   |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%)                             |  |  |
| occurrences causally related to treatment / all | 0 / 0                                       |  |  |
| deaths causally related to treatment / all      | 0 / 0                                       |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Pneumonitis                                     |                 |  |  |
| subjects affected / exposed                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumothorax spontaneous                        |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary embolism                              |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pulmonary haemorrhage                           |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Respiratory failure                             |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Psychiatric disorders                           |                 |  |  |
| Anxiety   |                 |  |  |
| subjects affected / exposed                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Investigations                                  |                 |  |  |
| Blood uric acid increased                       |                 |  |  |
| subjects affected / exposed                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Ejection fraction decreased                     |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| White blood cell count decreased<br>subjects affected / exposed | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Injury, poisoning and procedural<br>complications               |                 |  |  |
| Femur fracture  |                 |  |  |
| subjects affected / exposed                                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Infusion related reaction                                       |                 |  |  |
| subjects affected / exposed                                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Cardiac disorders   |                 |  |  |
| Acute myocardial infarction                                     |                 |  |  |
| subjects affected / exposed                                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Cardiac failure   |                 |  |  |
| subjects affected / exposed                                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Carditis  |                 |  |  |
| subjects affected / exposed                                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 1           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 1           |  |  |
| Nervous system disorders  |                 |  |  |
| Cerebral infarction   |                 |  |  |
| subjects affected / exposed                                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to<br>treatment / all              | 0 / 0           |  |  |
| deaths causally related to<br>treatment / all                   | 0 / 0           |  |  |
| Headache  |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Transient ischaemic attack                      |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Blood and lymphatic system disorders            |                 |  |  |
| Febrile neutropenia                             |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Leukopenia                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Neutropenia                                     |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pancytopenia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Thrombocytopenia                                |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anaemia   |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Lymphopenia                                     |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal disorders                      |                 |  |  |
| Abdominal pain                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Anal fissure                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Diarrhoea                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Duodenal ulcer perforation                      |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastritis                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastrointestinal toxicity                       |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Nausea  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal perforation                              |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Vomiting  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Haemorrhoids                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatobiliary disorders                         |                 |  |  |
| Cholecystitis chronic                           |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Cholelithiasis                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hepatic failure                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Bile duct stone                                 |                 |  |  |
| subjects affected / exposed                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Renal and urinary disorders                     |                 |  |  |
| Acute kidney injury                             |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Musculoskeletal and connective tissue           |                 |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| disorders                                       |                 |  |  |
| Pathological fracture                           |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Infections and infestations                     |                 |  |  |
| Bronchitis                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Gastroenteritis                                 |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Influenza                                       |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Mastitis  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Paronychia                                      |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Pneumonia                                       |                 |  |  |
| subjects affected / exposed                     | 2 / 179 (1.12%) |  |  |
| occurrences causally related to treatment / all | 0 / 2           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Rectal abscess                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

|   |                 |  |  |  |
|---|-----------------|--|--|--|
| Renal abscess                                   |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Sepsis  |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Septic shock                                    |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Tubo-ovarian abscess                            |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Upper respiratory tract infection               |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Urinary tract infection                         |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Urosepsis                                       |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Wound infection                                 |                 |  |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |  |
| Metabolism and nutrition disorders              |                 |  |  |  |



|   |                 |  |  |
|---|-----------------|--|--|
| Hypernatraemia                                  |                 |  |  |
| subjects affected / exposed                     | 1 / 179 (0.56%) |  |  |
| occurrences causally related to treatment / all | 0 / 1           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyperuricaemia                                  |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hypokalaemia                                    |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Hyponatraemia                                   |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |
| Tumour lysis syndrome                           |                 |  |  |
| subjects affected / exposed                     | 0 / 179 (0.00%) |  |  |
| occurrences causally related to treatment / all | 0 / 0           |  |  |
| deaths causally related to treatment / all      | 0 / 0           |  |  |

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

| <b>Non-serious adverse events</b>                     | Herceptin® + Taxane (up to wk 24) | MYL-14010 + Taxane (up to wk 24) | Herceptin® (wk 25 up to 36 months) |
|---|-----------------------------------|----------------------------------|------------------------------------|
| Total subjects affected by non-serious adverse events |                                   |                                  |                                    |
| subjects affected / exposed                           | 231 / 246 (93.90%)                | 235 / 247 (95.14%)               | 119 / 164 (72.56%)                 |
| Investigations  |                                   |                                  |                                    |
| Alanine aminotransferase increased                    |                                   |                                  |                                    |
| subjects affected / exposed                           | 21 / 246 (8.54%)                  | 18 / 247 (7.29%)                 | 7 / 164 (4.27%)                    |
| occurrences (all)                                     | 36                                | 26                               | 12                                 |
| Aspartate aminotransferase increased                  |                                   |                                  |                                    |
| subjects affected / exposed                           | 22 / 246 (8.94%)                  | 13 / 247 (5.26%)                 | 7 / 164 (4.27%)                    |
| occurrences (all)                                     | 38                                | 20                               | 10                                 |
| Ejection fraction decreased                           |                                   |                                  |                                    |

|  |  |  |  |
|--|--|--|--|
| subjects affected / exposed<br>occurrences (all)   | 3 / 246 (1.22%)<br>3   | 5 / 247 (2.02%)<br>6   | 6 / 164 (3.66%)<br>8   |
| Injury, poisoning and procedural complications<br>Infusion related reaction<br>subjects affected / exposed<br>occurrences (all)  | 10 / 246 (4.07%)<br>18   | 17 / 247 (6.88%)<br>30   | 1 / 164 (0.61%)<br>1   |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 8 / 246 (3.25%)<br>10  | 7 / 247 (2.83%)<br>7   | 9 / 164 (5.49%)<br>25  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 14 / 246 (5.69%)<br>18<br><br>28 / 246 (11.38%)<br>43<br><br>34 / 246 (13.82%)<br>39   | 15 / 247 (6.07%)<br>15<br><br>28 / 247 (11.34%)<br>36<br><br>29 / 247 (11.74%)<br>38   | 23 / 164 (14.02%)<br>31<br><br>9 / 164 (5.49%)<br>10<br><br>2 / 164 (1.22%)<br>2 |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 40 / 246 (16.26%)<br>66<br><br>40 / 246 (16.26%)<br>57<br><br>79 / 246 (32.11%)<br>114 | 40 / 247 (16.19%)<br>76<br><br>40 / 247 (16.19%)<br>62<br><br>90 / 247 (36.44%)<br>133 | 17 / 164 (10.37%)<br>39<br><br>4 / 164 (2.44%)<br>5<br><br>6 / 164 (3.66%)<br>9  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral   | 32 / 246 (13.01%)<br>58  | 28 / 247 (11.34%)<br>61  | 7 / 164 (4.27%)<br>7   |

|   |                           |                           |                      |
|---|---------------------------|---------------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                  | 28 / 246 (11.38%)<br>38   | 35 / 247 (14.17%)<br>53   | 4 / 164 (2.44%)<br>4 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)       | 28 / 246 (11.38%)<br>33   | 21 / 247 (8.50%)<br>27    | 4 / 164 (2.44%)<br>4 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)      | 40 / 246 (16.26%)<br>78   | 54 / 247 (21.86%)<br>123  | 7 / 164 (4.27%)<br>8 |
| Gastrointestinal disorders  |                           |                           |                      |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)     | 49 / 246 (19.92%)<br>69   | 49 / 247 (19.84%)<br>80   | 2 / 164 (1.22%)<br>4 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)        | 34 / 246 (13.82%)<br>60   | 48 / 247 (19.43%)<br>79   | 6 / 164 (3.66%)<br>6 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)      | 17 / 246 (6.91%)<br>22    | 25 / 247 (10.12%)<br>41   | 6 / 164 (3.66%)<br>6 |
| Respiratory, thoracic and mediastinal disorders                   |                           |                           |                      |
| Cough<br>subjects affected / exposed<br>occurrences (all)         | 16 / 246 (6.50%)<br>17    | 14 / 247 (5.67%)<br>16    | 3 / 164 (1.83%)<br>5 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)      | 17 / 246 (6.91%)<br>22    | 13 / 247 (5.26%)<br>15    | 2 / 164 (1.22%)<br>2 |
| Skin and subcutaneous tissue disorders                            |                           |                           |                      |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)      | 135 / 246 (54.88%)<br>162 | 142 / 247 (57.49%)<br>175 | 5 / 164 (3.05%)<br>5 |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all) | 20 / 246 (8.13%)<br>21    | 17 / 247 (6.88%)<br>18    | 0 / 164 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)          | 23 / 246 (9.35%)<br>41    | 21 / 247 (8.50%)<br>26    | 4 / 164 (2.44%)<br>5 |
| Musculoskeletal and connective tissue disorders                   |                           |                           |                      |

|                                    |                  |                   |                 |
|------------------------------------|------------------|-------------------|-----------------|
| Arthralgia                         |                  |                   |                 |
| subjects affected / exposed        | 11 / 246 (4.47%) | 30 / 247 (12.15%) | 3 / 164 (1.83%) |
| occurrences (all)                  | 17               | 46                | 3               |
| Bone pain                          |                  |                   |                 |
| subjects affected / exposed        | 13 / 246 (5.28%) | 17 / 247 (6.88%)  | 3 / 164 (1.83%) |
| occurrences (all)                  | 23               | 21                | 3               |
| Myalgia                            |                  |                   |                 |
| subjects affected / exposed        | 23 / 246 (9.35%) | 23 / 247 (9.31%)  | 4 / 164 (2.44%) |
| occurrences (all)                  | 39               | 45                | 4               |
| Infections and infestations        |                  |                   |                 |
| Upper respiratory tract infection  |                  |                   |                 |
| subjects affected / exposed        | 4 / 246 (1.63%)  | 14 / 247 (5.67%)  | 4 / 164 (2.44%) |
| occurrences (all)                  | 6                | 14                | 4               |
| Urinary tract infection            |                  |                   |                 |
| subjects affected / exposed        | 16 / 246 (6.50%) | 20 / 247 (8.10%)  | 5 / 164 (3.05%) |
| occurrences (all)                  | 26               | 30                | 7               |
| Metabolism and nutrition disorders |                  |                   |                 |
| Hyperglycaemia                     |                  |                   |                 |
| subjects affected / exposed        | 19 / 246 (7.72%) | 13 / 247 (5.26%)  | 7 / 164 (4.27%) |
| occurrences (all)                  | 29               | 15                | 39              |
| Decreased appetite                 |                  |                   |                 |
| subjects affected / exposed        | 24 / 246 (9.76%) | 21 / 247 (8.50%)  | 5 / 164 (3.05%) |
| occurrences (all)                  | 44               | 56                | 7               |

|   |                                   |  |  |
|---|-----------------------------------|--|--|
| <b>Non-serious adverse events</b>                     | MYL-1401O (wk 25 up to 36 months) |  |  |
| Total subjects affected by non-serious adverse events |                                   |  |  |
| subjects affected / exposed                           | 121 / 179 (67.60%)                |  |  |
| Investigations  |                                   |  |  |
| Alanine aminotransferase increased                    |                                   |  |  |
| subjects affected / exposed                           | 11 / 179 (6.15%)                  |  |  |
| occurrences (all)                                     | 17                                |  |  |
| Aspartate aminotransferase increased                  |                                   |  |  |
| subjects affected / exposed                           | 9 / 179 (5.03%)                   |  |  |
| occurrences (all)                                     | 13                                |  |  |
| Ejection fraction decreased                           |                                   |  |  |

|  |   |  |  |
|--|---|--|--|
| subjects affected / exposed<br>occurrences (all)   | 10 / 179 (5.59%)<br>13  |  |  |
| Injury, poisoning and procedural complications<br>Infusion related reaction<br>subjects affected / exposed<br>occurrences (all)  | 0 / 179 (0.00%)<br>0  |  |  |
| Vascular disorders<br>Hypertension<br>subjects affected / exposed<br>occurrences (all)   | 12 / 179 (6.70%)<br>17  |  |  |
| Nervous system disorders<br>Headache<br>subjects affected / exposed<br>occurrences (all)<br><br>Neuropathy peripheral<br>subjects affected / exposed<br>occurrences (all)<br><br>Peripheral sensory neuropathy<br>subjects affected / exposed<br>occurrences (all) | 19 / 179 (10.61%)<br>25<br><br>5 / 179 (2.79%)<br>5<br><br>5 / 179 (2.79%)<br>6 |  |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)<br><br>Leukopenia<br>subjects affected / exposed<br>occurrences (all)<br><br>Neutropenia<br>subjects affected / exposed<br>occurrences (all)                   | 6 / 179 (3.35%)<br>9<br><br>2 / 179 (1.12%)<br>3<br><br>2 / 179 (1.12%)<br>4    |  |  |
| General disorders and administration site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)<br><br>Oedema peripheral   | 9 / 179 (5.03%)<br>11   |  |  |

|   |                        |  |  |
|---|------------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                  | 2 / 179 (1.12%)<br>2   |  |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)       | 6 / 179 (3.35%)<br>6   |  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)      | 7 / 179 (3.91%)<br>7   |  |  |
| Gastrointestinal disorders  |                        |  |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)     | 8 / 179 (4.47%)<br>13  |  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)        | 8 / 179 (4.47%)<br>10  |  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)      | 10 / 179 (5.59%)<br>11 |  |  |
| Respiratory, thoracic and mediastinal disorders                   |                        |  |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)         | 9 / 179 (5.03%)<br>12  |  |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)      | 6 / 179 (3.35%)<br>8   |  |  |
| Skin and subcutaneous tissue disorders                            |                        |  |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)      | 7 / 179 (3.91%)<br>7   |  |  |
| Nail disorder<br>subjects affected / exposed<br>occurrences (all) | 1 / 179 (0.56%)<br>1   |  |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)          | 6 / 179 (3.35%)<br>6   |  |  |
| Musculoskeletal and connective tissue disorders                   |                        |  |  |

|  |                        |  |  |
|--|------------------------|--|--|
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)   | 9 / 179 (5.03%)<br>12  |  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)  | 4 / 179 (2.23%)<br>4   |  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)  | 7 / 179 (3.91%)<br>10  |  |  |
| Infections and infestations<br>Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 10 / 179 (5.59%)<br>12 |  |  |
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)  | 6 / 179 (3.35%)<br>14  |  |  |
| Metabolism and nutrition disorders<br>Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)             | 5 / 179 (2.79%)<br>9   |  |  |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)   | 4 / 179 (2.23%)<br>4   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 05 September 2013 | Amendment 2 addressed the following: <ul style="list-style-type: none"><li>- Incorporate the current standards of care practices for treatment of metastatic breast cancer (MBC);</li><li>- Address delays related to the centrally performed IHC testing for patient randomization by switching the laboratory vendor to Phenopath Laboratories to avoid continued protocol violations;</li><li>- Remove the requirement of the central safety laboratory and move solely to local laboratory testing for safety labs for treatment decisions;</li><li>- Adjust and control for the global variances in MBC patients through appropriate stratification at randomization;</li><li>- Provide an adaptable study design allowing an interim sample size estimation to ensure a sufficiently statistically powered clinical trial; and</li><li>- Address the need for subject treatment until disease progression (i.e., Identified as a continuation study outlined in Amendment 1).</li></ul> |
| 10 April 2015     | Amendment 6: The goal of this protocol amendment was to <ul style="list-style-type: none"><li>1) reflect updates in the current SmPC of Herceptin®</li><li>2) modify some operational procedures that allow appropriate management of the trial and</li><li>3) update the Data Analysis and Statistical Methods section to reflect updates made to the SAP.</li></ul> Additionally, content of the document "Errata" dated 21 November 2013, has been incorporated in this amended global protocol.   |
| 03 March 2017     | Amendment 7: The goal of this protocol amendment was to <ul style="list-style-type: none"><li>1) include the analysis for best ORR difference and to describe the associated statistical assumptions as indicated in the statistical analysis plan; and</li><li>2) modify select operational procedures that allow appropriate management of the trial.</li></ul> Additionally, content of the document "Errata," dated 21 November 2013, has been incorporated in this amended global protocol.  |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption  | Restart date      |
|--------------|---|-------------------|
| 23 July 2013 | Following careful evaluation and review of the current study protocol and the need to address scientific advice from both, the U.S. Food & Drug Administration and the European Medicines Agency, Mylan has decided to put a temporary hold on site initiations and patient screening (patients currently in screening with a signed consent form will be allowed to proceed to randomization, if eligible) into the Her-3001 clinical trial effective immediately until the amendment to the protocol is approved and the study has been re-initiated. | 13 September 2013 |

Notes:

### Limitations and caveats



None reported