



Clinical trial results:

A randomized, double-blind, placebo-controlled, multi-center study of BYM338 for treatment of cachexia in patients with stage IV non-small cell lung cancer or stage III/IV adenocarcinoma of the pancreas

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2010-024342-30 |
| Trial protocol | GB LT |
| Global end of trial date | 24 April 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 16 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CBYM338X2202 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01433263 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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 | 24 April 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 24 April 2014 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 April 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to assess the preliminary efficacy of a single intravenous i.v. dose of BYM338 in increasing thigh muscle volume (TMV) as assessed by Magnetic Resonance Imaging (MRI) compared to placebo.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 22 August 2011 |
| 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 | United States: 24 |
| Country: Number of subjects enrolled | United Kingdom: 7 |
| Country: Number of subjects enrolled | Switzerland: 10 |
| Country: Number of subjects enrolled | Lithuania: 3 |
| Country: Number of subjects enrolled | Romania: 13 |
| Worldwide total number of subjects | 57 |
| EEA total number of subjects | 23 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |

| | |
|---------------------------|----|
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 57 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Core Phase single dose BYM338 30mg/kg i.v. active or placebo with 8week followup. Followup phase started Week 8 & patients on placebo in the Core Phase were given BYM338 & patients on BYM338 in Core Phase continued to be followed for an additional 8 weeks. Late BYM338 are patients who received Placebo during Core Phase and then BYM338 after Week 8.

Pre-assignment

Screening details:

Core Phase single dose BYM338 30mg/kg i.v. active or placebo with 8week followup. Followup phase started Week 8 & patients on placebo in the Core Phase were given BYM338 & patients on BYM338 in Core Phase continued to be followed for an additional 8 weeks. Late BYM338 are patients who received Placebo during Core Phase and then BYM338 after Week 8.

Period 1

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

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 30mg/kg BYM338 |

Arm description: -

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | BYM338 |
| Investigational medicinal product code | BYM338 |
| Other name | Bimagrumab |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

single dose BYM338 30 mg/kg i.v. lyophilized powder for injection

| | |
|------------------|-------------------------------|
| Arm title | Placebo / late 30mg/kg BYM338 |
|------------------|-------------------------------|

Arm description: -

| | |
|--|--|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to match BYM338 |
| Investigational medicinal product code | BYM338 |
| Other name | Placebo |
| Pharmaceutical forms | Powder and solution for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

single dose Placebo to match BYM338 i.v.

| Number of subjects in period 1 | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 |
|---------------------------------------|----------------|----------------------------------|
| Started | 29 | 28 |
| Completed | 10 | 16 |
| Not completed | 19 | 12 |
| Adverse event, serious fatal | 5 | 3 |
| Consent withdrawn by subject | 10 | 7 |
| Adverse event, non-fatal | 3 | 1 |
| Protocol Deviation | 1 | - |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|-------------------------------|
| Reporting group title | 30mg/kg BYM338 |
| Reporting group description: - | |
| Reporting group title | Placebo / late 30mg/kg BYM338 |
| Reporting group description: - | |

| Reporting group values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | Total |
|---|----------------|-------------------------------|-------|
| Number of subjects | 29 | 28 | 57 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 17 | 14 | 31 |
| From 65-84 years | 12 | 14 | 26 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: years | | | |
| arithmetic mean | 62.8 | 61.5 | |
| standard deviation | ± 10.17 | ± 10.74 | - |
| Gender, Male/Female Units: participants | | | |
| Male | 20 | 22 | 42 |
| Female | 9 | 6 | 15 |

End points

End points reporting groups

| | |
|--------------------------------|-------------------------------|
| Reporting group title | 30mg/kg BYM338 |
| Reporting group description: - | |
| Reporting group title | Placebo / late 30mg/kg BYM338 |
| Reporting group description: - | |

Primary: Percentage Change from Baseline of Thigh Muscle Volume (TMV) by MRI Scan at week 8

| | |
|------------------------|---|
| End point title | Percentage Change from Baseline of Thigh Muscle Volume (TMV) by MRI Scan at week 8 |
| End point description: | Thigh Muscle Volume (TMV) change was evaluated by a responder analysis. Patients whose loss of muscle TMV by MRI was no more than or equal to 2% at Week 8 was considered responders. |
| End point type | Primary |
| End point timeframe: | Baseline, week 8 |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--------------------------------------|-----------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 15 | 22 | | |
| Units: Percentage Change of TMV | | | | |
| arithmetic mean (standard deviation) | 2 (± 8.094) | 0.65 (± 8.239) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | % Change from Baseline of TMV by MRI Scan week 8 |
| Comparison groups | 30mg/kg BYM338 v Placebo / late 30mg/kg BYM338 |
| Number of subjects included in analysis | 37 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.541 |
| Method | ANCOVA |

Secondary: Percentage Change in body weight from baseline at week 7 and week 9

| | |
|------------------------|---|
| End point title | Percentage Change in body weight from baseline at week 7 and week 9 |
| End point description: | Percentage Change in body weight from baseline in kilograms (kg) at week 7 and week 9 |

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 7 and Week 9 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--------------------------------------|-------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 28 | | |
| Units: Percent Change of Weight (kg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 7 (n= 15, 17) | -3.3 (± 5.035) | -0.68 (± 4.457) | | |
| Week 9 (n=14,16) | -1.8 (± 7.131) | -0.32 (± 3.271) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax)

| | |
|--|---|
| End point title | Maximum Observed Serum Concentration (Cmax) |
| End point description: | |
| Blood samples for pharmacokinetic (PK) evaluation were drawn on Day 1 30mg/kg BYM338 (Core) or week 8 Late 30mg/kg BYM338 (when placebo subjects were rolled over to active). PK parameters were calculated from plasma concentration-time data using non-compartmental methods. | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 and Week 8 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--------------------------------------|-------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 14 | | |
| Units: ng/ml | | | | |
| arithmetic mean (standard deviation) | 422 (± 142) | 408 (± 78.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Concentration After Drug Administration (Tmax)

| | |
|--|--|
| End point title | Time to Reach the Maximum Concentration After Drug Administration (Tmax) |
| End point description: Blood samples for pharmacokinetic (PK) evaluation were drawn on Day 1 30mg/kg BYM338 (Core) or week 8 Late 30mg/kg BYM338 (when placebo subjects were rolled over to active). Tmax was directly determined from the raw serum concentration-time data. | |
| End point type | Secondary |
| End point timeframe: Day 1 and Week 8 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|---------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 | 14 | | |
| Units: hr | | | | |
| median (inter-quartile range (Q1-Q3)) | 2.05 (1.83 to 3.92) | 2.22 (2 to 4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in total lean body mass (LBM) by Dual-Energy X-ray Absorptiometry (DXA) compared to placebo: at week 8

| | |
|--|--|
| End point title | Percentage Change from Baseline in total lean body mass (LBM) by Dual-Energy X-ray Absorptiometry (DXA) compared to placebo: at week 8 |
| End point description: total lean body mass (LBM) is measured by dual energy x-ray absorptiometry (DXA). Percent Change = $[(\text{LBM at Visit} - \text{LBM at Baseline}) / \text{LBM at Baseline}] * 100$. | |
| End point type | Secondary |
| End point timeframe: Baseline, Week 8 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--------------------------------------|---------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 22 | | |
| Units: Percentage Change in LBM | | | | |
| arithmetic mean (standard deviation) | 4.97 (\pm 7.537) | 2.41 (\pm 4.625) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) compared to placebo at week 8

| | |
|-----------------|---|
| End point title | Percentage Change from Baseline of Bone Mineral Density (BMD) by Dual-Energy X-ray Absorptiometry (DXA) compared to placebo at week 8 |
|-----------------|---|

End point description:

Bone Mineral Density (BMD) is measured by dual energy x-ray absorptiometry (DXA). Percent Change = $[(\text{BMD at Visit} - \text{BMD at Baseline}) / \text{BMD at Baseline}] * 100$.

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

End point timeframe:

Baseline, Week 8

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--------------------------------------|-------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 | 22 | | |
| Units: Percentage Change in BMD | | | | |
| arithmetic mean (standard deviation) | 0.51 (± 3.712) | 0.14 (± 4.14) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) number of steps taken compared to placebo at week 4 and 7

| | |
|-----------------|--|
| End point title | Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) number of steps taken compared to placebo at week 4 and 7 |
|-----------------|--|

End point description:

Each patient was required to wear the ActivPal™ for a span of 6 days at Week 4 and Week 7 for patient home activity recording. The ActivPal™ was given to patients in clinic to wear for 6 consecutive days. The ActivPAL™ records periods spent sitting, standing and walking, sit-to-stand transitions, step count and rate of stepping (cadence) over a maximum period of 10 days with a fully charged new battery.

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

End point timeframe:

Baseline, Week 4 and Week 7

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|---|-------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 28 | | |
| Units: percentage change in number of steps | | | | |

| | | | | |
|--------------------------------------|---------------------|-------------------|--|--|
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=18, 23) | 917.78 (± 3720.491) | 63.59 (± 130.913) | | |
| Week 7 (n=13, 22) | -17.37 (± 80.35) | 35.8 (± 119.486) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Sedentary taken compared to placebo at week 4 and 7

| | |
|------------------------|--|
| End point title | Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Sedentary taken compared to placebo at week 4 and 7 |
| End point description: | Each patient was required to wear the ActivPal™ for a span of 6 days at Week 4 and Week 7 for patient home activity recording. The ActivPal™ was given to patients in clinic to wear for 6 consecutive days. The ActivPAL™ records periods spent sitting, standing and walking, sit-to-stand transitions, step count and rate of stepping (cadence) over a maximum period of 10 days with a fully charged new battery. |
| End point type | Secondary |
| End point timeframe: | Baseline, Week 4 and Week 7 |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--|--------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 28 | | |
| Units: percentage change in time (minutes) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=18, 23) | -0.05 (± 10.049) | 52.25 (± 207.403) | | |
| Week 7 (n=13, 22) | 107.85 (± 280.791) | 60.25 (± 222.366) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Standing compared to placebo at week 4 and 7

| | |
|------------------------|--|
| End point title | Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Standing compared to placebo at week 4 and 7 |
| End point description: | Each patient was required to wear the ActivPal™ for a span of 6 days at Week 4 and Week 7 for patient home activity recording. The ActivPal™ was given to patients in clinic to wear for 6 consecutive days. |

The ActivPAL™ records periods spent sitting, standing and walking, sit-to-stand transitions, step count and rate of stepping (cadence) over a maximum period of 10 days with a fully charged new battery.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4 and Week 7 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--|---------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 28 | | |
| Units: percentage change in time (minutes) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=18, 23) | 1.82 (± 78.364) | 38.17 (± 111.361) | | |
| Week 7 (n=13, 22) | 41.9 (± 251.291) | 23.76 (± 99.268) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Stepping compared to placebo at week 4 and 7

| | |
|-----------------|--|
| End point title | Percentage Change from Baseline of physical activity levels (using the ActivPAL™ device) Time Stepping compared to placebo at week 4 and 7 |
|-----------------|--|

End point description:

Each patient was required to wear the ActivPal™ for a span of 6 days at Week 4 and Week 7 for patient home activity recording. The ActivPal™ was given to patients in clinic to wear for 6 consecutive days. The ActivPAL™ records periods spent sitting, standing and walking, sit-to-stand transitions, step count and rate of stepping (cadence) over a maximum period of 10 days with a fully charged new battery.

| | |
|-----------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Week 4 and Week 7 | |

| End point values | 30mg/kg BYM338 | Placebo / late 30mg/kg BYM338 | | |
|--|-------------------------|-------------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 27 | 28 | | |
| Units: percentage change in time (minutes) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=18, 22) | 1446.69 (± 6011.324) | 85.3 (± 159.949) | | |
| Week 7 (n=13, 21) | -31.64 (± 67.18) | 33.39 (± 129.218) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Core - 30 mg/kg BYM338 |
|-----------------------|------------------------|

Reporting group description:

Core - 30 mg/kg BYM338

| | |
|-----------------------|----------------|
| Reporting group title | Core - Placebo |
|-----------------------|----------------|

Reporting group description:

Core - Placebo

| | |
|-----------------------|-----------------------------|
| Reporting group title | Follow-up - 30 mg/kg BYM338 |
|-----------------------|-----------------------------|

Reporting group description:

Follow-up - 30 mg/kg BYM338

| | |
|-----------------------|---------------------|
| Reporting group title | Follow-up - Placebo |
|-----------------------|---------------------|

Reporting group description:

Follow-up - Placebo

| | |
|-----------------------|---------------------------------|
| Reporting group title | Follow-up - 30mg/kg BYM338 Late |
|-----------------------|---------------------------------|

Reporting group description:

Follow-up - 30mg/kg BYM338 Late

| Serious adverse events | Core - 30 mg/kg BYM338 | Core - Placebo | Follow-up - 30 mg/kg BYM338 |
|---|------------------------|-----------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 29 (62.07%) | 4 / 28 (14.29%) | 7 / 19 (36.84%) |
| number of deaths (all causes) | 6 | 1 | 4 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Malignant neoplasm progression | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 6 / 29 (20.69%) | 0 / 28 (0.00%) | 3 / 19 (15.79%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 2 |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Disease progression | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (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 |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Hemiparesis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Syncope | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| 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 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ascites | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Gastric haemorrhage | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary dilatation | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (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 |
| Cholestasis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 failure | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 | | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Infection | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella infection | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Pneumonia | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 | | | |
| Dehydration | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 0 / 19 (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 |

| Serious adverse events | Follow-up - Placebo | Follow-up - 30mg/kg BYM338 Late | |
|---|---------------------|---------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 7 / 21 (33.33%) | |
| number of deaths (all causes) | 0 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |

| | | | |
|---|---------------|----------------|--|
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lung neoplasm malignant | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malignant neoplasm progression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Metastases to central nervous system | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatic carcinoma | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angiopathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral ischaemia | | | |

| | | | |
|--|---------------|----------------|--|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disease progression | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|----------------|--|
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebral infarction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|----------------|--|
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile bone marrow aplasia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Obstruction gastric | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary dilatation | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholestasis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---------------|----------------|--|
| Klebsiella infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella sepsis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |

| | | | |
|---|---------------|----------------|--|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Core - 30 mg/kg BYM338 | Core - Placebo | Follow-up - 30 mg/kg BYM338 |
|---|---------------------------|------------------|--------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 29 (65.52%) | 19 / 28 (67.86%) | 12 / 19 (63.16%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign neoplasm | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Hot flush | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 28 (10.71%) | 1 / 19 (5.26%) |
| occurrences (all) | 3 | 7 | 1 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 29 (20.69%) | 3 / 28 (10.71%) | 4 / 19 (21.05%) |
| occurrences (all) | 6 | 4 | 4 |
| Asthenia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 0 | 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 2 / 28 (7.14%) | 0 / 19 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | |
|-------------------------------------|----------------|----------------|----------------|
| Cough | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Nasal congestion | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 2 / 28 (7.14%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 1 | 1 |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Rales | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Wheezing | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Investigations | | | |
| Amylase increased | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood bilirubin increased | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Gamma-glutamyltransferase increased | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 28 (3.57%) 1 | 1 / 19 (5.26%) 1 |
| Liver function test abnormal subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 3 | 0 / 28 (0.00%) 0 | 2 / 19 (10.53%) 2 |
| Injury, poisoning and procedural complications | | | |
| Craniocerebral injury subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Fall subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Laceration subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Nervous system disorders | | | |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 0 / 28 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Headache subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 19 (0.00%) 0 |
| Hepatic encephalopathy subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Myoclonus subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Neuropathy peripheral subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 1 / 28 (3.57%) 2 | 0 / 19 (0.00%) 0 |
| Tremor | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 29 (13.79%) | 6 / 28 (21.43%) | 2 / 19 (10.53%) |
| occurrences (all) | 4 | 6 | 2 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 3 / 28 (10.71%) | 2 / 19 (10.53%) |
| occurrences (all) | 3 | 6 | 2 |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 1 / 28 (3.57%) | 1 / 19 (5.26%) |
| occurrences (all) | 4 | 2 | 1 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 28 (7.14%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 2 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 3 / 28 (10.71%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 3 | 0 |
| Ascites | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 1 | 1 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 3 / 28 (10.71%) | 1 / 19 (5.26%) |
| occurrences (all) | 5 | 3 | 1 |
| Constipation | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 29 (17.24%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Stomatitis | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 3 / 28 (10.71%) 3 | 2 / 19 (10.53%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 4 | 1 / 28 (3.57%) 1 | 0 / 19 (0.00%) 0 |
| Hepatobiliary disorders Jaundice subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Skin and subcutaneous tissue disorders Erythema subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 0 / 28 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Rash subjects affected / exposed occurrences (all) | 1 / 29 (3.45%) 1 | 2 / 28 (7.14%) 2 | 0 / 19 (0.00%) 0 |
| Swelling face subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Renal and urinary disorders Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Bladder irritation subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 2 | 1 / 19 (5.26%) 1 |
| Flank pain subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Muscle spasms subjects affected / exposed occurrences (all) | 2 / 29 (6.90%) 2 | 1 / 28 (3.57%) 1 | 0 / 19 (0.00%) 0 |

| | | | |
|---|----------------------|---------------------|----------------------|
| Pain in extremity subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 28 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Rhabdomyolysis subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Infections and infestations | | | |
| Gingival infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Candida infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 2 / 28 (7.14%) 2 | 0 / 19 (0.00%) 0 |
| Herpes zoster subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 2 / 19 (10.53%) 2 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Septic shock subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Wound infection staphylococcal subjects affected / exposed occurrences (all) | 0 / 29 (0.00%) 0 | 0 / 28 (0.00%) 0 | 1 / 19 (5.26%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 3 / 29 (10.34%) 3 | 0 / 28 (0.00%) 0 | 0 / 19 (0.00%) 0 |
| Dehydration subjects affected / exposed occurrences (all) | 4 / 29 (13.79%) 4 | 1 / 28 (3.57%) 2 | 0 / 19 (0.00%) 0 |
| Hypoalbuminaemia | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 2 / 28 (7.14%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 29 (3.45%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 1 | 0 | 1 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Hyponatraemia | | | |
| subjects affected / exposed | 3 / 29 (10.34%) | 1 / 28 (3.57%) | 0 / 19 (0.00%) |
| occurrences (all) | 3 | 1 | 0 |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 29 (0.00%) | 0 / 28 (0.00%) | 1 / 19 (5.26%) |
| occurrences (all) | 0 | 0 | 1 |
| Malnutrition | | | |
| subjects affected / exposed | 2 / 29 (6.90%) | 1 / 28 (3.57%) | 1 / 19 (5.26%) |
| occurrences (all) | 2 | 1 | 1 |

| Non-serious adverse events | Follow-up - Placebo | Follow-up - 30mg/kg BYM338 Late | |
|---|---------------------|------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 3 (66.67%) | 13 / 21 (61.90%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Benign neoplasm | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| General disorders and administration site conditions | | | |

| | | | |
|--|---------------------|---------------------|--|
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 21 (4.76%) 1 | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 21 (4.76%) 2 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Nasal congestion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Epistaxis subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Pleural effusion subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Pneumonia aspiration subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Rales subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Wheezing | | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Investigations Amylase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Blood bilirubin increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 1 / 21 (4.76%) 1 | |
| Liver function test abnormal subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Injury, poisoning and procedural complications Craniocerebral injury subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Fall subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Laceration subjects affected / exposed occurrences (all) | 0 / 3 (0.00%) 0 | 0 / 21 (0.00%) 0 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 1 / 3 (33.33%) 1 | 1 / 21 (4.76%) 1 | |

| | | | |
|--------------------------------------|----------------|-----------------|--|
| Headache | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Hepatic encephalopathy | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 3 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 3 / 21 (14.29%) | |
| occurrences (all) | 1 | 4 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 3 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 2 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Ascites | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Dysphagia | | | |

| | | | |
|--|----------------|-----------------|--|
| subjects affected / exposed | 1 / 3 (33.33%) | 1 / 21 (4.76%) | |
| occurrences (all) | 1 | 1 | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 5 / 21 (23.81%) | |
| occurrences (all) | 0 | 7 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 21 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 2 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 2 / 21 (9.52%) | |
| occurrences (all) | 0 | 3 | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema | | | |
| subjects affected / exposed | 1 / 3 (33.33%) | 0 / 21 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Swelling face | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Bladder irritation | | | |

| | | | |
|---|---------------|----------------|--|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Gingival infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Candida infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Septic shock | | | |

| | | | |
|------------------------------------|---------------|----------------|--|
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Wound infection staphylococcal | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 1 / 21 (4.76%) | |
| occurrences (all) | 0 | 1 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lactic acidosis | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 3 (0.00%) | 0 / 21 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 June 2011 | Amendment 1 : Revision of Study Design: The study will consist of a Core period, an Open Label Follow-up period, and a Vital Status follow-up period. The Core period will be unchanged with a single dose of BYM338 or placebo at Visit 3. Total duration of the Core period will be 8 weeks. The open-label Extension period will be removed. An eight week open-label treatment/Follow up period will be added: At Visit 8, week 11 a single dose of BYM338 will be offered to all patients who received placebo at Visit 3. Patients who received active drug at Visit 3 will be followed for an additional 8 weeks (total of 16 weeks), but will NOT receive any additional doses of BYM338. Revision of the following Inclusion #3 & 4 and Exclusion #2, 3, 4, 6 Criteria Inclusion #3: Eliminate requirement for 4 weeks of stable 2nd line chemotherapy for pancreatic cancer. Patients must be tolerating chemotherapy with respect to nausea/vomiting and dietary intake before starting study drug, without specifying a time frame. Inclusion #4: Define "simple starvation." Add a provision to include: In patients with 2+ or greater pitting edema of the legs, documented weight loss > 2% over 4 weeks, not due to diuretic therapy, is acceptable for inclusion. Exclusion #2: Clarify radiation that is excluded for 4 weeks refers only to radiation of the soft tissues of the chest, abdomen, or brain. Exclusion #3: Add "uncontrolled pain" after steatorrhea. Exclusion #4: Add "uncontrolled" in front of exocrine pancreas dysfunction. Exclusion #6: Delete including major depression. Delete Food Frequency Questionnaire (FFQ) and food diary; replace with 2-day Food Record. Delete requirement of MRI of primary tumor. CT will be allowed for primary tumor progression imaging. MRI will remain the method used for measuring TMV. Add: Tumor progression will be followed using RECIST criteria. Safety labs (hematology, coagulations, chemistry) will be measured by local laboratories, |
| 25 July 2011 | Amendment 2 : The protocol is being amended to address comments from a Health Authority in addition to updating the text for a serious adverse event, provide clarifications and correct minor issues. Revision of Serious Adverse Event text: The text in amendment 1 stated the SAE occurred 4 weeks after dosing. The text has been updated after the investigator updated the SAE report. The Human Pharmacokinetic data was updated to reflect data from a recent Pharmacokinetic analysis. Inclusion of "maintenance therapy" was added to inclusion criteria #3. At some centers, patients are maintained on a chemotherapeutic regimen if they demonstrate partial response or stable disease; to allow such patients to participate in this study, we are amending the protocol to include this approach as "maintenance (chemo) therapy". Inclusion criteria #5, "unintentional" added before weight loss Visit window for week 8 post dose is +/- 7 days to allow for more flexibility. |
| 06 December 2011 | Amendment 3: The purpose of this amendment is to: 1. Incorporate additional monitoring measures based on Adverse events observed with a compound with a related mechanism of action (supine and standing blood pressure and more specific physical examination) 2. Extend the timeframe for required use of highly effective contraception for women of child-bearing potential to 14 weeks from the previously mandated 8 weeks after stopping treatment, based on a new half-life calculation 3. Correct minor inconsistencies in the document and update information, i.e. serious adverse event information updated. |

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| 07 March 2012 | Amendment 4: The purpose of this amendment is to: To provide clarity on inclusion criteria for lines of chemotherapy for NSCLC and pancreatic patients, based on feedback from active investigators. Available chemotherapeutic agents have been used in different combination and in varying orders depending on the judgement of treating oncologist and tumor response. As a result of longer survival of cancer patients there is a need for a more prolonged and aggressive use of chemtherapeutic agents occasionally known as 3rd or 4th line of therapy In addition, cancer cachexia has been usually manifested in advanced cases with 3rd or 4th line of therapies. In order to capture the appropriate population for this study with the proper weight loss and expected survival, related inclusion criteria have been revised. Correct the timeframe for capturing Serious Adverse Events (SAE's) from 60 days post dose to 30 days post End of Study (EOS) visit. Remove the blood draw for pharmacogenomics at screening. Clarify windows for the study visits to allow for increased flexibility for the sites. Correct inconsistencies in the document and update information, i.e. Serious Adverse Event information updated. |
| 25 September 2012 | Amendment 5: The primary purpose of this amendment is to introduce an internal Data Monitoring Committee (DMC) separate from the BYM338 project team, which is being implemented in all new and ongoing phase 1 and 2a studies with BYM338. This DMC is being introduced at the request of the US FDA because of the new mode of action of BYM338, for which the safety profile is not fully characterized, and because of safety concerns observed by FDA with a non-Novartis molecule with a similar mode of action. |
| 30 July 2013 | Amendment 6: The purpose of this amendment is to address the administrative inconsistencies and to allow for additional interim analyses for decision-making purposes if needed. |
| 10 March 2014 | Amendment 7: In the original protocol, the review of previous concomitant medications was limited to 8 weeks prior to the start of the study. However, it has been recognized that knowledge of concomitant medication administration (e.g., chemotherapy) given > 8 weeks prior to study start provides a fuller context from which to interpret responses to treatment in this study. Therefore the protocol is being amended to allow for collection of information on concomitant medications from the time of diagnosis of the current disease stage. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported