



## Clinical trial results:

**A randomized, double-blinded, regimen controlled, phase II, multicenter study to assess the efficacy and safety of two different vismodegib regimens in patients with multiple basal cell carcinomas**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2012-003305-10    |
| Trial protocol           | AT DE NL IT ES FR |
| Global end of trial date |                   |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1           |
| This version publication date  | 13 July 2016 |
| First version publication date | 13 July 2016 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | MO28295 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01815840 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070  |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                |
|--|----------------|
| Analysis stage                                       | Interim        |
| Date of interim/final analysis                       | 27 August 2015 |
| Is this the analysis of the primary completion data? | Yes            |
| Primary completion date                              | 27 August 2015 |
| Global end of trial reached?                         | No             |

Notes:

## General information about the trial

Main objective of the trial:

This randomized, double-blind, regimen-controlled, phase II, multicenter study assessed the efficacy and safety of two different vismodegib regimens in subjects with multiple basal cell carcinoma. Subjects received vismodegib 150 mg orally once daily either in an intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo (Arm A) or as 24 weeks induction followed by an intermittent schedule of 8 weeks placebo followed by 8 weeks vismodegib (Arm B). Anticipated time on study treatment was 72 weeks.

Protection of trial subjects:

All study subjects were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

|   |               |
|---|---------------|
| Actual start date of recruitment                          | 30 April 2013 |
| 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 | Netherlands: 10       |
| Country: Number of subjects enrolled | Spain: 23             |
| Country: Number of subjects enrolled | Austria: 12           |
| Country: Number of subjects enrolled | France: 38            |
| Country: Number of subjects enrolled | Germany: 39           |
| Country: Number of subjects enrolled | Italy: 27             |
| Country: Number of subjects enrolled | Canada: 15            |
| Country: Number of subjects enrolled | Mexico: 8             |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | United States: 48     |
| Worldwide total number of subjects   | 229                   |
| EEA total number of subjects         | 149                   |

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)                     | 127 |
| From 65 to 84 years                      | 94  |
| 85 years and over                        | 8   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

229 subjects were enrolled in 10 countries.

### 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          |

### Arms

|                              |     |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

|                  |                                  |
|------------------|----------------------------------|
| <b>Arm title</b> | Vismodegib Intermittent Schedule |
|------------------|----------------------------------|

Arm description:

Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Vismodegib   |
| Investigational medicinal product code |              |
| Other name                             | Erivedge®    |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Vismodegib 150 mg hard gelatin capsule orally once daily

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Vismodegib Placebo |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Capsule            |
| Routes of administration               | Oral use           |

Dosage and administration details:

Vismodegib placebo orally once daily

|                  |  |
|------------------|--|
| <b>Arm title</b> | Vismodegib Induction Followed by Intermittent Schedule |
|------------------|--|

Arm description:

Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | Vismodegib   |
| Investigational medicinal product code |              |
| Other name                             | Erivedge®    |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

Vismodegib 150 mg hard gelatin capsule orally once daily

|  |                    |
|--|--------------------|
| Investigational medicinal product name | Vismodegib Placebo |
| Investigational medicinal product code |                    |
| Other name                             |                    |

|                          |          |
|--------------------------|----------|
| Pharmaceutical forms     | Capsule  |
| Routes of administration | Oral use |

Dosage and administration details:

Vismodegib placebo orally once daily

| Number of subjects in period 1 | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |
|--------------------------------|----------------------------------|--|
|                                |                                  |  |
| Started                        | 116                              | 113  |
| Completed                      | 0                                | 0  |
| Not completed                  | 116                              | 113  |
| Still on study                 | 73                               | 64   |
| Disease progression            | 1                                | -  |
| Adverse event, non-fatal       | 8                                | 14   |
| Death                          | 2                                | 2  |
| Refused treatment              | 3                                | 1  |
| Investigator decision          | 1                                | 3  |
| Lost to follow-up              | 1                                | 2  |
| Withdrew consent               | 26                               | 26   |
| Missing                        | 1                                | 1  |

## Baseline characteristics

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Vismodegib Intermittent Schedule |
|-----------------------|----------------------------------|

Reporting group description:

Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

|                       |  |
|-----------------------|--|
| Reporting group title | Vismodegib Induction Followed by Intermittent Schedule |
|-----------------------|--|

Reporting group description:

Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

| Reporting group values             | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule | Total |
|------------------------------------|----------------------------------|--|-------|
| Number of subjects                 | 116                              | 113  | 229   |
| Age categorical<br>Units: Subjects |                                  |  |       |

|   |                 |                 |     |
|---|-----------------|-----------------|-----|
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation | 61.1<br>± 13.94 | 59.9<br>± 15.35 | -   |
| Gender categorical<br>Units: Subjects                                   |                 |                 |     |
| Female  | 35              | 25              | 60  |
| Male  | 81              | 88              | 169 |

## End points

### End points reporting groups

|   |  |
|---|--|
| Reporting group title   | Vismodegib Intermittent Schedule                       |
| Reporting group description:<br>Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up |  |
| Reporting group title   | Vismodegib Induction Followed by Intermittent Schedule |
| Reporting group description:<br>Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up                      |  |

### Primary: Percent Reduction From Baseline in the Number of Clinically Evident Basal Cell Carcinomas at Week 73 (After 72 Weeks of Treatment)

|  |  |
|--|--|
| End point title  | Percent Reduction From Baseline in the Number of Clinically Evident Basal Cell Carcinomas at Week 73 (After 72 Weeks of Treatment) |
| End point description:<br>The total number of clinically evident basal cell carcinomas = the total number of target and/or non-target lesions present in individual subjects.<br><br>Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis. The last observation carried forward method was used. |  |
| End point type   | Primary  |
| End point timeframe:<br>Baseline; Week 73  |  |

| End point values                     | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type                   | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed          | 114                              | 113  |  |  |
| Units: percent change                |                                  |  |  |  |
| arithmetic mean (standard deviation) | 62.7 (± 52.02)                   | 54 (± 55.68)   |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | Difference in mean relative reduction   |
| Statistical analysis description:<br>The mean difference in the mean relative reduction between treatment arms, along with the corresponding 95% confidence interval, was estimated by fitting an ANCOVA model with treatment as main effect and the following covariates: number of basal cell carcinomas at baseline, geographical region, immunosuppression status, confirmed basal cell carcinoma nevus syndrome. Asymptotic confidence intervals are presented for the difference between treatment arms. |   |
| Comparison groups  | Vismodegib Intermittent Schedule v Vismodegib Induction Followed by Intermittent Schedule |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 227                            |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | other                          |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | -8.9                           |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -23                            |
| upper limit                             | 5.2                            |

### Secondary: Percentage of Subjects Who Discontinued Study Treatment Due to Tolerability Issues

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Who Discontinued Study Treatment Due to Tolerability Issues |
|-----------------|--|

End point description:

The percentage of subjects who discontinued study treatment (due either to adverse event, refusal of treatment, or withdrawal of consent) was summarized by treatment group.

Intent-to-Treat Analysis Population, defined as all randomized subjects.

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

End point timeframe:

Baseline to Week 73

| End point values                 | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|----------------------------------|----------------------------------|--|--|--|
| Subject group type               | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed      | 116                              | 113  |  |  |
| Units: percentage of subjects    |                                  |  |  |  |
| number (confidence interval 95%) |                                  |  |  |  |
| Overall                          | 37.1 (28.3 to 46.5)              | 40.7 (31.6 to 50.4)                                    |  |  |
| Adverse Events                   | 19.8 (13 to 28.3)                | 26.5 (18.7 to 35.7)                                    |  |  |
| Refused Treatment                | 6 (2.5 to 12)                    | 2.7 (0.6 to 7.6)                                       |  |  |
| Withdrew Consent                 | 11.2 (6.1 to 18.4)               | 11.5 (6.3 to 18.9)                                     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Reduction From Baseline in Total Size of Three Target Basal Cell Carcinoma Lesions in Individual Subjects at Week 73



|  |  |
|--|--|
| End point title  | Percent Reduction From Baseline in Total Size of Three Target Basal Cell Carcinoma Lesions in Individual Subjects at Week 73 |
| End point description:<br>The three target basal cell carcinoma lesions = the three largest visible lesions, at least 5 mm in the longest diameter, in individual subjects.<br><br>Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline; Week 73  |  |

| End point values                     | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type                   | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed          | 94                               | 85   |  |  |
| Units: percent change                |                                  |  |  |  |
| arithmetic mean (standard deviation) | 82.9 (± 27.01)                   | 68.8 (± 52.81)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With at Least 50% Reduction in the Number of Basal Cell Carcinomas at Week 73

|  |  |
|--|--|
| End point title  | Percentage of Subjects With at Least 50% Reduction in the Number of Basal Cell Carcinomas at Week 73 |
| End point description:<br>Intent-to-Treat Analysis Population, defined as all randomized subjects. |  |
| End point type   | Secondary  |
| End point timeframe:<br>Baseline; Week 73  |  |

| End point values              | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|-------------------------------|----------------------------------|--|--|--|
| Subject group type            | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed   | 116                              | 113  |  |  |
| Units: percentage of subjects |                                  |  |  |  |
| number (not applicable)       | 65.5                             | 50.4   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage of Subjects With New Basal Cell Carcinomas at Week 73

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With New Basal Cell Carcinomas at Week 73 |
|-----------------|--|

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 73

| End point values              | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|-------------------------------|----------------------------------|--|--|--|
| Subject group type            | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed   | 94                               | 86   |  |  |
| Units: percentage of subjects |                                  |  |  |  |
| number (not applicable)       |                                  |  |  |  |
| No new lesions                | 76.6                             | 74.4   |  |  |
| 1 new lesion                  | 10.6                             | 11.6   |  |  |
| 2 new lesions                 | 5.3                              | 5.8  |  |  |
| 3 new lesions                 | 5.3                              | 2.3  |  |  |
| >3 new lesions                | 2.1                              | 5.8  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 85 (12 Weeks Following End of Treatment) (Recurrence Rate)

|                 |   |
|-----------------|---|
| End point title | Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 85 (12 Weeks Following End of Treatment) (Recurrence Rate) |
|-----------------|---|

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 85

| End point values                     | Vismodegib<br>Intermittent<br>Schedule | Vismodegib<br>Induction<br>Followed by<br>Intermittent<br>Schedule |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group  |  |  |
| Number of subjects analysed          | 77                                     | 69   |  |  |
| Units: percent change                |  |  |  |  |
| arithmetic mean (standard deviation) | 29.1 (± 34.47)                         | 36.6 (± 37.91)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 97 (24 Weeks Following End of Treatment) (Recurrence Rate)

|                 |   |
|-----------------|---|
| End point title | Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 97 (24 Weeks Following End of Treatment) (Recurrence Rate) |
|-----------------|---|

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 97

| End point values                     | Vismodegib<br>Intermittent<br>Schedule | Vismodegib<br>Induction<br>Followed by<br>Intermittent<br>Schedule |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group  |  |  |
| Number of subjects analysed          | 51                                     | 44   |  |  |
| Units: percent change                |  |  |  |  |
| arithmetic mean (standard deviation) | 28.4 (± 29.58)                         | 38.1 (± 36.5)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change in Total Number of Basal Cell Carcinomas Relative to

**Baseline at Week 125 (52 Weeks Following End of Treatment) (Recurrence Rate)**

|                 |  |
|-----------------|--|
| End point title | Percent Change in Total Number of Basal Cell Carcinomas Relative to Baseline at Week 125 (52 Weeks Following End of Treatment) (Recurrence Rate) |
|-----------------|--|

End point description:

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 125

| End point values                     | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type                   | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed          | 36                               | 26   |  |  |
| Units: percent change                |                                  |  |  |  |
| arithmetic mean (standard deviation) | 35.5 (± 37.19)                   | 46.2 (± 37.55)   |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Percentage of Subjects Experiencing Any Adverse Event**

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Experiencing Any Adverse Event |
|-----------------|---|

End point description:

Safety Analysis Population: Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) who received at least one dose of study treatment.

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

End point timeframe:

Up to 125 weeks

| End point values              | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|-------------------------------|----------------------------------|--|--|--|
| Subject group type            | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed   | 114                              | 113  |  |  |
| Units: percentage of subjects |                                  |  |  |  |
| number (not applicable)       | 99.1                             | 97.3   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in the Skindex-16 Symptom Domain Score at Week 73

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in the Skindex-16 Symptom Domain Score at Week 73 |
|-----------------|--|

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their symptoms, and their answers were combined into a composite Symptom Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 73

| End point values                     | Vismodegib<br>Intermittent<br>Schedule | Vismodegib<br>Induction<br>Followed by<br>Intermittent<br>Schedule |  |  |
|--------------------------------------|--|--|--|--|
| Subject group type                   | Reporting group                        | Reporting group  |  |  |
| Number of subjects analysed          | 87                                     | 77   |  |  |
| Units: percent change                |  |  |  |  |
| arithmetic mean (standard deviation) | -14.9 (±<br>25.75)                     | -12.7 (±<br>24.25)   |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in the Skindex-16 Emotion Domain Score at Week 73

|                 |  |
|-----------------|--|
| End point title | Percent Change From Baseline in the Skindex-16 Emotion Domain Score at Week 73 |
|-----------------|--|

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their emotional state, and their answers were combined into a composite Emotion Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 73

| End point values                     | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type                   | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed          | 87                               | 77   |  |  |
| Units: percent change                |                                  |  |  |  |
| arithmetic mean (standard deviation) | -27.4 (± 27.71)                  | -28.9 (± 28.53)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Percent Change From Baseline in the Skindex-16 Function Domain Score at Week 73

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline in the Skindex-16 Function Domain Score at Week 73 |
|-----------------|---|

End point description:

The Skindex-16 is a patient-reported outcome health questionnaire. Subjects were asked about their ability to function, and answers were combined into a composite Function Domain Score. Scores range from 0 ("never bothered") to 100 ("always bothered").

Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) with available data were included in the analysis.

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

End point timeframe:

Baseline; Week 73

| End point values                     | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |  |
|--------------------------------------|----------------------------------|--|--|--|
| Subject group type                   | Reporting group                  | Reporting group  |  |  |
| Number of subjects analysed          | 87                               | 77   |  |  |
| Units: percent change                |                                  |  |  |  |
| arithmetic mean (standard deviation) | -9.5 (± 20.59)                   | -10.3 (± 26.32)  |  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to 125 weeks

Adverse event reporting additional description:

Safety Analysis Population: Subjects in the Intent-to-Treat Analysis Population (defined as all randomized subjects) who received at least one dose of study treatment.

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

### Dictionary used

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

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

### Reporting groups

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Vismodegib Intermittent Schedule |
|-----------------------|----------------------------------|

Reporting group description:

Vismodegib intermittent schedule of 12 weeks vismodegib followed by 8 weeks placebo, repeated 3 times with a final course of vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

|                       |  |
|-----------------------|--|
| Reporting group title | Vismodegib Induction Followed by Intermittent Schedule |
|-----------------------|--|

Reporting group description:

Vismodegib beginning with 24 weeks induction followed by intermittent schedule 8 weeks placebo, 8 weeks vismodegib (total 72 weeks), followed by 52 weeks treatment-free follow up

| Serious adverse events  | Vismodegib Intermittent Schedule | Vismodegib Induction Followed by Intermittent Schedule |  |
|---|----------------------------------|--|--|
| Total subjects affected by serious adverse events                   |                                  |  |  |
| subjects affected / exposed   | 22 / 114 (19.30%)                | 19 / 113 (16.81%)                                      |  |
| number of deaths (all causes)                                       | 2                                | 2  |  |
| number of deaths resulting from adverse events                      | 1                                | 0  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                  |  |  |
| Squamous cell carcinoma   |                                  |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                  | 2 / 113 (1.77%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1                            | 0 / 2  |  |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0  |  |
| Metastatic squamous cell carcinoma                                  |                                  |  |  |
| subjects affected / exposed   | 1 / 114 (0.88%)                  | 0 / 113 (0.00%)  |  |
| occurrences causally related to treatment / all                     | 0 / 1                            | 0 / 0  |  |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0  |  |
| Spindle cell sarcoma  |                                  |  |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                      |                 |                 |  |
| subjects affected / exposed                          | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Immune system disorders                              |                 |                 |  |
| Primary amyloidosis                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |  |
| Pulmonary embolism                                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 1 / 1           | 0 / 1           |  |
| Acute respiratory failure                            |                 |                 |  |
| subjects affected / exposed                          | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease                |                 |                 |  |
| subjects affected / exposed                          | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                                |                 |                 |  |
| Depression   |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Personality change                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Hepatic enzyme increased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| International normalised ratio increased        |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Ankle fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Limb injury                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thermal burn                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Congenital cerebral cyst                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy  |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorder                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post herpetic neuralgia                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tremor  |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudolymphoma                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric perforation                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Acute hepatic failure                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Xanthelasma                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute kidney injury                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Calculus urinary                                |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| <b>Musculoskeletal and connective tissue disorders</b> |                 |                 |  |
| Arthralgia   |                 |                 |  |
| subjects affected / exposed                            | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all        | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| Back pain  |                 |                 |  |
| subjects affected / exposed                            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| <b>Infections and infestations</b>                     |                 |                 |  |
| Pneumonia  |                 |                 |  |
| subjects affected / exposed                            | 3 / 114 (2.63%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 1           | 0 / 0           |  |
| Abscess limb   |                 |                 |  |
| subjects affected / exposed                            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| Cellulitis   |                 |                 |  |
| subjects affected / exposed                            | 1 / 114 (0.88%) | 0 / 113 (0.00%) |  |
| occurrences causally related to treatment / all        | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| Diverticulitis   |                 |                 |  |
| subjects affected / exposed                            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |
| Gastrointestinal infection                             |                 |                 |  |
| subjects affected / exposed                            | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all        | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all             | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Kidney infection                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis acute                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 114 (0.00%) | 1 / 113 (0.88%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Vismodegib<br>Intermittent<br>Schedule | Vismodegib<br>Induction Followed<br>by Intermittent<br>Schedule |  |
|---|--|---|--|
| Total subjects affected by non-serious adverse events |  |   |  |
| subjects affected / exposed                           | 107 / 114 (93.86%)                     | 108 / 113 (95.58%)  |  |
| Investigations  |  |   |  |
| Weight decreased                                      |  |   |  |
| subjects affected / exposed                           | 24 / 114 (21.05%)                      | 21 / 113 (18.58%)   |  |
| occurrences (all)                                     | 32                                     | 22  |  |
| Blood creatine phosphokinase increased                |  |   |  |

|  |                          |                          |  |
|--|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                       | 11 / 114 (9.65%)<br>14   | 15 / 113 (13.27%)<br>24  |  |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 7 / 114 (6.14%)<br>8     | 5 / 113 (4.42%)<br>5     |  |
| Nervous system disorders   |                          |                          |  |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)                          | 75 / 114 (65.79%)<br>117 | 75 / 113 (66.37%)<br>108 |  |
| Ageusia<br>subjects affected / exposed<br>occurrences (all)                            | 14 / 114 (12.28%)<br>17  | 13 / 113 (11.50%)<br>17  |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                           | 11 / 114 (9.65%)<br>11   | 12 / 113 (10.62%)<br>12  |  |
| General disorders and administration<br>site conditions                                |                          |                          |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                            | 24 / 114 (21.05%)<br>30  | 26 / 113 (23.01%)<br>31  |  |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                           | 15 / 114 (13.16%)<br>27  | 20 / 113 (17.70%)<br>30  |  |
| Gastrointestinal disorders   |                          |                          |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                          | 20 / 114 (17.54%)<br>33  | 18 / 113 (15.93%)<br>22  |  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                             | 23 / 114 (20.18%)<br>31  | 14 / 113 (12.39%)<br>25  |  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                     | 8 / 114 (7.02%)<br>10    | 9 / 113 (7.96%)<br>9     |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)                       | 9 / 114 (7.89%)<br>10    | 6 / 113 (5.31%)<br>8     |  |
| Abdominal pain upper   |                          |                          |  |

|   |                          |                          |  |
|---|--------------------------|--------------------------|--|
| subjects affected / exposed<br>occurrences (all)                      | 9 / 114 (7.89%)<br>12    | 5 / 113 (4.42%)<br>6     |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)          | 7 / 114 (6.14%)<br>8     | 4 / 113 (3.54%)<br>4     |  |
| Skin and subcutaneous tissue disorders                                |                          |                          |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)          | 72 / 114 (63.16%)<br>98  | 73 / 113 (64.60%)<br>93  |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)          | 8 / 114 (7.02%)<br>11    | 11 / 113 (9.73%)<br>12   |  |
| Actinic keratosis<br>subjects affected / exposed<br>occurrences (all) | 10 / 114 (8.77%)<br>12   | 8 / 113 (7.08%)<br>11    |  |
| Musculoskeletal and connective tissue disorders                       |                          |                          |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)     | 83 / 114 (72.81%)<br>187 | 93 / 113 (82.30%)<br>190 |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)        | 18 / 114 (15.79%)<br>23  | 16 / 113 (14.16%)<br>24  |  |
| Myalgia<br>subjects affected / exposed<br>occurrences (all)           | 18 / 114 (15.79%)<br>28  | 12 / 113 (10.62%)<br>14  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)         | 7 / 114 (6.14%)<br>8     | 6 / 113 (5.31%)<br>7     |  |
| Infections and infestations   |                          |                          |  |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)   | 6 / 114 (5.26%)<br>9     | 12 / 113 (10.62%)<br>15  |  |
| Folliculitis<br>subjects affected / exposed<br>occurrences (all)      | 9 / 114 (7.89%)<br>12    | 7 / 113 (6.19%)<br>9     |  |
| Bronchitis  |                          |                          |  |



|  |                         |                         |  |
|--|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 5 / 114 (4.39%)<br>5    | 7 / 113 (6.19%)<br>9    |  |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 7 / 114 (6.14%)<br>12   | 5 / 113 (4.42%)<br>6    |  |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 21 / 114 (18.42%)<br>32 | 17 / 113 (15.04%)<br>21 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date        | Amendment   |
|-------------|---|
| 28 May 2013 | Changes included: additional guidance on amenorrhea/irregular menses; additional laboratory testing to include creatine kinase to further investigate muscle spasm events; additional guidance on Vismodegib in seminal fluid to ensure male subjects did not donate sperm during treatment and for 2 months after treatment; updated eligibility criteria to exclude 1) subjects known or suspected to abuse alcohol and 2) with known rare hereditary disturbance of galactose metabolism; amended drug interaction language to reflect updated core documents regarding possible interactions with metabolize ethinyl estradiol contraceptive steroids; alteration to statistical analysis measure of precision. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported