

**Clinical trial results:****Phase II clinical trial investigating the use of epigallocatechin-3-gallate (Veregen) in the treatment of vulval intraepithelial neoplasia****Summary**

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-003107-19 |
| Trial protocol | GB |
| Global end of trial date | 08 January 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 January 2020 |
| First version publication date | 22 January 2020 |

Trial information**Trial identification**

| | |
|-----------------------|---------|
| Sponsor protocol code | 13-0288 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|--------------------------|
| ISRCTN number | ISRCTN98495886 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | CRCTU CAS number: VU2001 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Birmingham |
| Sponsor organisation address | Vincent Drive, Birmingham, United Kingdom, B15 2TT |
| Public contact | Baljit Kaur, Cancer Research UK Clinical Trials Unit, +44 01214143793, b.kaur@bham.ac.uk |
| Scientific contact | Baljit Kaur, Cancer Research UK Clinical Trials Unit, +44 01214143793, b.kaur@bham.ac.uk |
| Sponsor organisation name | Sandwell and West Birmingham Hospitals NHS Trust |
| Sponsor organisation address | Dudley Road, Birmingham, United Kingdom, B18 7QH |
| Public contact | Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net |
| Scientific contact | Jocelyn Bell, Sandwell and West Birmingham Hospitals NHS Trust, +44 01215074811, jocelyn.bell@nhs.net |

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 | 16 December 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 January 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 08 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this clinical trial is to determine whether topical application of EGCG (Veregen) can lead to histological resolution of usual type vulval intraepithelial neoplasia (uVIN) when assessed at 32 weeks following the start of treatment. This is done by comparing tissue biopsies taken before and after Veregen treatment.

Protection of trial subjects:

Mild local skin reactions, including erythema, pruritus, irritation (mostly burning), pain and oedema at the site of application are very common in patients using Veregen to treat genital warts, especially initially, and are likely to be the same in this cohort. Patients will be instructed to use simple analgesia or topical lignocaine an hour before or after treatment. If more severe, there are dose modification directions in the protocol - the number of applications can be reduced to two or one per day or stopped completely. Contraindications listed in the SmPC have been taken into account in the exclusion criteria - participants should not be or become pregnant, breastfeed, take immunosuppressives or be allergic to Veregen or its excipients. Patients who are under clinical suspicion of vulval cancer will have a biopsy for investigative purposes, and can still use the treatment if they wish. Once the diagnosis has been confirmed, they will stop the study treatment immediately for their standard cancer care to begin.

Background therapy:

Research has shown that a compound found in green tea can "switch on" genes which are silenced in cancer. Clinical studies have shown that this compound (EGCG; also known as Veregen) is a safe and effective treatment for vulval warts which are caused by a virus called human papillomavirus (HPV); certain strains of this virus also cause VIN and vulval cancer. This drug has also been shown to prevent the progression of precancerous changes in the mouth, another disease associated with HPV infection. We believe that Veregen could relieve both the symptoms experienced by women with VIN and reduce their risk of progressing to cancer.

Evidence for comparator:

Tumour suppressor genes (TSG) can be silenced during carcinogenesis by DNA promoter methylation and polycomb mediated gene repression. Aberrant TSG methylation has been shown not only in primary VSCC but also in uVIN, suggesting that these changes may occur early during the natural history of the disease. As epigenetic gene silencing is potentially reversible, there is great interest in the development of new therapeutic strategies using epigenetic modulators. Although the prototype inhibitors of DNA methylation, 5-azacytidine, and 5-aza-2'-deoxycytidine have been shown to be efficacious in the treatment of myelodysplastic syndrome (MDS), these agents were found to be ineffective when first used in solid tumours. While it is now thought that this lack of activity was related to the use of too high doses, limited number of days of drug exposure and assessment of response after only one cycle, these drugs also cause significant myelosuppression and are unstable in solution. It could also be argued that epigenetic therapies have failed in solid tumours because they have only been evaluated in patients with advanced disease. Such tumours may have lost epigenetic dependence due to genetic instability. It would follow from this that the use of epigenetic therapies is more likely to be successful in the treatment of early/pre-neoplastic conditions, for example, MDS and possibly uVIN. In vitro studies have

shown that EGCG, can reverse epigenetic silencing and reactivate gene expression in a range of SCC cell lines including one derived from a vulval cancer. Although not as potent a demethylating agent as 5-aza-2'-deoxycytidine, EGCG offers potentially sustained and longer-term exposures with lower toxicity. As uVIN is often characterised by the asynchronous appearance of dysplastic epithelium at multiple sites, the topical application of an effective treatment would offer the benefit of long-term control of a disease otherwise requiring multiple surgical interventions.

| | |
|---|-----------------|
| Actual start date of recruitment | 13 October 2014 |
| 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 Kingdom: 26 |
| Worldwide total number of subjects | 26 |
| EEA total number of subjects | 26 |

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) | 21 |
| From 65 to 84 years | 5 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 26 patients were recruited from one UK centre between 13-Oct-2014 and 10-May-2017. The target number of patients to recruit was 56, which was not achieved.

Pre-assignment

Screening details:

Potential patients were identified via the vulval clinic in City Hospital, Birmingham. Patients with a clinical diagnosis of uVIN were informed about the trial and, if histological diagnosis for uVIN was positive, patients would be offered the opportunity to give informed consent. Eligibility would then be determined before enrolling patients.

Period 1

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

Blinding implementation details:

In order to maintain this blind, study medication was labelled with a unique number (Treatment Pack Number) which was then assigned to a patient. Each patient treatment allocation was kept in an Emergency Code Break Envelope inside a locked safe, one based in City Hospital Pharmacy and the other in CRCTU. Unblinding could only be performed for medical reasons. The Chief Investigator or co-investigator were required to give approval before an unblinding was undertaken.

Arms

| | |
|--|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Veregen 10% ointment |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Veregen 10% ointment |
| Investigational medicinal product code | |
| Other name | EGCG; epigallocatechin-3-gallate |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Patients will be required to apply the ointment three times a day for a maximum duration of 16 weeks. They are advised to apply a small amount of Veregen 10% ointment to each lesion using the fingers, dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the lesions. This should be applied only to affected areas; any application into the vagina, urethra or anus must be avoided.

| | |
|--|----------------------------------|
| Arm title | Veregen-matched placebo |
| Arm description: - | |
| Arm type | Placebo |
| Investigational medicinal product name | Veregen-matched placebo ointment |
| Investigational medicinal product code | |
| Other name | Placebo |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

Patients will be required to apply the ointment three times a day for a maximum duration of 16 weeks.

They will be advised to apply a small amount of Veregen-matched placebo to each lesion using the fingers, dabbing it on to ensure complete coverage and leaving a thin layer of the ointment on the lesions. This should be applied only to affected areas; any application into the vagina, urethra or anus must be avoided.

| Number of subjects in period 1 | Veregen 10% ointment | Veregen-matched placebo |
|---------------------------------------|-------------------------|----------------------------|
| Started | 13 | 13 |
| Completed | 13 | 13 |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|-------------------------|
| Reporting group title | Veregen 10% ointment |
| Reporting group description: - | |
| Reporting group title | Veregen-matched placebo |
| Reporting group description: - | |

| Reporting group values | Veregen 10% ointment | Veregen-matched placebo | Total |
|--|----------------------|-------------------------|-------|
| Number of subjects | 13 | 13 | 26 |
| 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) | 10 | 11 | 21 |
| From 65-84 years | 3 | 2 | 5 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 52.62 | 49.4 | |
| standard deviation | ± 12 | ± 13.2 | - |
| Gender categorical | | | |
| Only females were eligible for entry into this trial | | | |
| Units: Subjects | | | |
| Female | 13 | 13 | 26 |
| Male | 0 | 0 | 0 |
| Ethnicity | | | |
| Units: Subjects | | | |
| White-British | 13 | 13 | 26 |
| Smoking Status | | | |
| Units: Subjects | | | |
| Current | 6 | 9 | 15 |
| Never | 1 | 1 | 2 |
| Previous | 6 | 3 | 9 |
| First VIN episode? | | | |
| Units: Subjects | | | |
| Yes | 0 | 1 | 1 |
| No | 13 | 12 | 25 |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | 161.75 | 163.11 | |
| standard deviation | ± 7.4 | ± 5.6 | - |
| Weight | | | |

| | | | |
|--|-----------------|-----------------|---|
| Units: kg arithmetic mean standard deviation | 72.03 ± 11.8 | 86.47 ± 31.9 | - |
| Time: first clinical diagnosis to randomisation Units: years arithmetic mean standard deviation | 8.9 ± 6 | 12.66 ± 10.1 | - |
| Time: first histological diagnosis to randomisation Units: years arithmetic mean standard deviation | 8.5 ± 6.7 | 12.85 ± 10.5 | - |
| Time: first symptom to randomisation Units: years arithmetic mean standard deviation | 10.19 ± 5.9 | 14.43 ± 10.2 | - |
| Time: start of current VIN to randomisation Units: months arithmetic mean standard deviation | 15.33 ± 16 | 30.22 ± 44 | - |

End points

End points reporting groups

| | |
|--------------------------------|-------------------------|
| Reporting group title | Veregen 10% ointment |
| Reporting group description: - | |
| Reporting group title | Veregen-matched placebo |
| Reporting group description: - | |

Primary: Best histological response

| | |
|------------------------|--|
| End point title | Best histological response |
| End point description: | Best histological response observed across the 32 weeks, as established by blinded pathology review, will be used in this assessment. "Responder" defined as a patient who has achieved histological resolution at any point across the 32 weeks and "Non-Responder" defined as a patient who has not achieved histological resolution at any point during the 32 weeks. Histological resolution being defined as the absence of uVIN or invasive disease. |
| End point type | Primary |
| End point timeframe: | 32 weeks from start date of trial treatment |

| End point values | Veregen 10% ointment | Veregen-matched placebo | | |
|-----------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: subjects | | | | |
| Responder | 3 | 3 | | |
| Non-responder | 6 | 7 | | |
| No response data | 4 | 3 | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Not Applicable |
| Statistical analysis description: | The primary end point of best histological response over 32 weeks required descriptive analysis only. |
| Comparison groups | Veregen 10% ointment v Veregen-matched placebo |
| Number of subjects included in analysis | 26 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0 ^[1] |
| Method | Not applicable |
| Parameter estimate | Descriptive analysis |

Notes:

[1] - p-value is not applicable to this descriptive data set

Secondary: Clinical resolution

| | |
|-----------------|---------------------|
| End point title | Clinical resolution |
|-----------------|---------------------|

End point description:

Best clinical response over the 52 weeks as measured by difference in current lesion size measurement and baseline lesion size. Refer to appendix 1 of EPIVIN protocol for Clinical Response Definitions.

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

End point timeframe:

Up to 52 weeks from start date of trial treatment

| End point values | Veregen 10% ointment | Veregen-matched placebo | | |
|-----------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: subjects | | | | |
| Complete Response | 5 | 3 | | |
| Partial Response | 8 | 2 | | |
| Stable Disease | 0 | 6 | | |
| Progressive Disease | 0 | 0 | | |
| No Response Data | 0 | 2 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of cumulative treatment

| | |
|-----------------|------------------------------------|
| End point title | Assessment of cumulative treatment |
|-----------------|------------------------------------|

End point description:

Summary statistics will be provided for percentage administered of full treatment, taking into account both dose reductions and interruptions.

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

End point timeframe:

Up to 16 weeks; end of treatment.

| End point values | Veregen 10% ointment | Veregen-matched placebo | | |
|--------------------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: Percentage Administered | | | | |
| arithmetic mean (standard deviation) | 69.94 (± 28.50) | 86.43 (± 16.30) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Histological resolution at 16 weeks

| | |
|-----------------|-------------------------------------|
| End point title | Histological resolution at 16 weeks |
|-----------------|-------------------------------------|

End point description:

Best histological response observed up to 16 weeks, as established by blinded pathology review, will be used in this assessment. "Responder" defined as a patient who has achieved histological resolution at any point across the 16 weeks and "Non-Responder" defined as a patient who has not achieved histological resolution at any point during the 16 weeks. Histological resolution being defined as the absence of uVIN or invasive disease.

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

End point timeframe:

16 weeks from start of treatment

| End point values | Veregen 10% ointment | Veregen-matched placebo | | |
|-----------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 13 | 13 | | |
| Units: Subjects | | | | |
| Responder | 2 | 3 | | |
| Non-responder | 7 | 7 | | |
| No response data | 4 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Details of all Adverse Events will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

Adverse event reporting additional description:

Adverse events are collected on a case report form at each visit and returned to the Trial Office. Serious Adverse Events are reported immediately (within 24 hours of becoming aware) by the investigator who sends a signed SAE form to the Trial Office. All SAE's must be reported whether it is thought to be related to trial treatment or not.

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

Dictionary used

| | |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

| | |
|--------------------|---|
| Dictionary version | 4 |
|--------------------|---|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Veregen arm |
|-----------------------|-------------|

Reporting group description:

Patients randomised to receive Veregen 10% treatment

| | |
|-----------------------|-------------|
| Reporting group title | Placebo arm |
|-----------------------|-------------|

Reporting group description:

Patients randomised to receive Veregen-matched placebo treatment

| Serious adverse events | Veregen arm | Placebo arm | |
|---|----------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | Veregen arm | Placebo arm | |
|---|-------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 13 (100.00%) | 12 / 13 (92.31%) | |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------|-----------------|--|
| bleeding | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 3 / 13 (23.08%) | |
| occurrences (all) | 2 | 5 | |
| Localised Swelling | | | |
| subjects affected / exposed | 2 / 13 (15.38%) | 0 / 13 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Localised oedema | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Malaise | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain | | | |
| subjects affected / exposed | 11 / 13 (84.62%) | 7 / 13 (53.85%) | |
| occurrences (all) | 22 | 19 | |
| General disorders and administration site conditions - Other, specify | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 13 (7.69%) | |
| occurrences (all) | 1 | 1 | |
| Reproductive system and breast disorders | | | |
| Vaginal discharge | | | |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 13 (7.69%) | |
| occurrences (all) | 0 | 4 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| cough | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Laryngeal Hemorrhage | | | |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 13 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|------------------------|-----------------------|--|
| Erythema multiforme subjects affected / exposed occurrences (all) | 8 / 13 (61.54%) 9 | 2 / 13 (15.38%) 7 | |
| Burning sensation subjects affected / exposed occurrences (all) | 8 / 13 (61.54%) 11 | 4 / 13 (30.77%) 5 | |
| exfoliation subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 4 | 0 / 13 (0.00%) 0 | |
| Pruritus subjects affected / exposed occurrences (all) | 10 / 13 (76.92%) 26 | 9 / 13 (69.23%) 27 | |
| Rash acneiform subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 1 / 13 (7.69%) 1 | |
| skin ulceration subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 4 | 1 / 13 (7.69%) 2 | |
| sore around area subjects affected / exposed occurrences (all) | 11 / 13 (84.62%) 18 | 4 / 13 (30.77%) 5 | |
| tingling subjects affected / exposed occurrences (all) | 0 / 13 (0.00%) 0 | 2 / 13 (15.38%) 3 | |
| Skin and subcutaneous tissue disorders - Other, specify subjects affected / exposed occurrences (all) | 2 / 13 (15.38%) 3 | 4 / 13 (30.77%) 4 | |
| Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 13 (7.69%) 1 | 0 / 13 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 01 July 2015 | <ul style="list-style-type: none">• Clarification of the fraction of biopsy that will be reviewed• Removal of RECIST method to assess clinical response• Appendix 1 amended to reflect change in Clinical Evaluation• Removal of colour photography requirement• Addition of stratification variable• Clarification of the definition of histological resolution• Clarification of timing of screening biopsy• Removal of Record of Birth Control at week 32 follow up assessment• Added review of concomitant medication in for weeks 4, 8 and 16• Clarification of the definitions of Patient Withdrawal• Clarification of secondary endpoints• Added description of placebo• Highlighted that sample collection is mandatory• Described use of the HBRC for baseline biopsy |
| 14 September 2015 | <ul style="list-style-type: none">• Amendment to eligibility criteria, clarification of terms used in histological diagnosis of uVIN or VIN3 and exclusion of patients with severe liver dysfunction or chronic liver disease• Updated concomitant medication advice• Removed need to permanently stop trial treatment if more than 6 continuous days missed Other non-substantial modifications: <ul style="list-style-type: none">• Updated Data Monitoring Committee scheduled meeting dates• Removal of Professor Ciaran Woodman's name from signature page and clarification of his role in the trial• Correction of typographical errors |
| 05 February 2016 | Recruitment halt in order to relabel IMP. Protocol updated accordingly. |
| 15 July 2016 | <ul style="list-style-type: none">• Clarification of primary and secondary outcome measures• Modification of "intention to treat" rule• Modification of evaluation of response criteria• Updated Trial Management Group personnel details• Proportion of biopsies for independent review increased |
| 30 November 2016 | Clarification of evaluation of response criteria |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

| | | |
|-----------------|--|-------------------|
| 12 January 2016 | Placebo IMP was due to expire however stability data was produced by Medigene AG to support extension of placebo IMP from February 2016 to January 2018. IMP was relabelled accordingly and recruitment was then able to resume. | 07 April 2016 |
| 12 May 2016 | Active IMP was due to expire however stability data was produced by Medigene AG to support extension of the Active IMP from August 2016 to June 2019. IMP was relabelled accordingly and recruitment was then able to resume. | 23 September 2016 |

Notes:

Limitations and caveats

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

The trial failed to recruit to its specified target of 56 patients. Analysis of outcomes was therefore underpowered.

Notes: