



## Clinical trial results:

### A Multicentre Prospective Open-label Randomised Clinical Trial Comparing the Efficacy of Fixed versus PRN dosing of 700 g Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) in patients with refractory diabetic macular oedema

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2012-003661-17   |
| Trial protocol           | GB               |
| Global end of trial date | 10 November 2014 |

#### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 23 August 2018  |
| First version publication date    | 23 August 2018  |
| Summary attachment (see zip file) | Study Summary (OZDRY study report final.pdf)<br>Trial Results (SIVS1007_Final_Analysis.pdf) |

#### Trial information

##### Trial identification

|                       |                                     |
|-----------------------|-------------------------------------|
| Sponsor protocol code | Protocol SS01 Version 7.0 dated 07- |
|-----------------------|-------------------------------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01892163 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Moorfields Eye Hospital  |
| Sponsor organisation address | 162 City Road, London, United Kingdom, EC1V 2PD  |
| Public contact               | Prof. Sobha Sivaprasad, Moorfields Eye Hospital,<br>sobha.sivaprasad@moorfields.nhs.uk |
| Scientific contact           | Prof. Sobha Sivaprasad, Moorfields Eye Hospital,<br>sobha.sivaprasad@moorfields.nhs.uk |

Notes:

##### Paediatric regulatory details

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

Notes:

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**Results analysis stage**

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|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 06 November 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 10 November 2014 |
| Was the trial ended prematurely?                     | No               |

Notes:

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**General information about the trial**

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Main objective of the trial:

To compare the clinical effectiveness and safety of 5-monthly fixed dosing versus pro-re-nata (PRN) Ozurdex treatment in patients with refractory diabetic macular oedema (DMO).

Protection of trial subjects:

AE and SAE were reported at any point in the study. All AEs and SAEs were discussed at the DMC. The DMC reviewed the accruing trial data and on-going safety issues. There were no safety issues, but if there were any issues that needed further action, these would have been escalated to the Trial Steering Committee who would have then decided whether the study continues, terminates or if any substantial changes to the protocol were required.

There was a one week and 8 weeks visit after the baseline and all subsequent Ozurdex injections in both treatment arms. If there was any safety concern in the opinion of the investigator, patients were assessed at an optional post-injection assessment visit.

If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects, including those already being treated, should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

If any urgent safety measures are taken the PI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures

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Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 05 February 2013 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 100 |
| Worldwide total number of subjects   | 100                 |
| EEA total number of subjects         | 100                 |

Notes:

| <b>Subjects enrolled per age group</b>    |    |
|---|----|
| In utero                                  | 0  |
| Preterm newborn - gestational age < 37 wk | 0  |
| Newborns (0-27 days)                      | 0  |
| Infants and toddlers (28 days-23 months)  | 0  |
| Children (2-11 years)                     | 0  |
| Adolescents (12-17 years)                 | 0  |
| Adults (18-64 years)                      | 45 |
| From 65 to 84 years                       | 53 |
| 85 years and over                         | 2  |

## Subject disposition

### Recruitment

Recruitment details:

A total of 100 patients were enrolled from February 2013 to November 2014 and randomized to study treatment across 5 sites. All recruited patients received the baseline Ozurdex injection and 49/50 (98%) in the fixed arm and 48/50 (96%) in the PRN arm completed the study providing primary outcome data (ITT).

### Pre-assignment

Screening details:

Eligible patients were at least 18 years old with diabetes, BCVA letter score 73 to 34, OCT >300 µm in the central subfield (CST) despite treatment. Exclusion was macular ischemia, previous treatment for DME with steroids in the last 6 months; anti-VEGF therapy in the last one month or macular laser in 3 months, active PDR and substantial cataract

### Pre-assignment period milestones

|                              |                    |
|------------------------------|--------------------|
| Number of subjects started   | 138 <sup>[1]</sup> |
| Number of subjects completed | 100                |

### Pre-assignment subject non-completion reasons

|                            |                                    |
|----------------------------|------------------------------------|
| Reason: Number of subjects | not meeting inclusion criteria: 29 |
| Reason: Number of subjects | declined to participate: 6         |
| Reason: Number of subjects | not known: 3                       |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: 138 patients were screened, 100 patients were enrolled and completed, 38 patients were not enrolled.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Trial (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Single blind                   |
| Roles blinded                | Assessor <sup>[2]</sup>        |

Blinding implementation details:

Primary outcome assessors (optometrists and OCT technicians) were masked to treatment allocation. The patients and clinicians who administered the study treatment and those who performed the safety evaluations were not masked to the treatment arms. The subjects were advised at enrolment that they must not discuss the study arm they were in with the OCT or Visual Acuity examiner.

### Arms

|                              |       |
|------------------------------|-------|
| Are arms mutually exclusive? | Yes   |
| Arm title                    | Fixed |

Arm description:

In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points  
Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation

|          |                  |
|----------|------------------|
| Arm type | intervention arm |
|----------|------------------|

|  |  |
|--|--|
| Investigational medicinal product name | 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) |
| Investigational medicinal product code |  |
| Other name                             | OZURDEX  |
| Pharmaceutical forms                   | Intravitreal implant in applicator                                       |
| Routes of administration               | Intravitreal use   |

**Dosage and administration details:**

The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of dexamethasone, made of a polylacticglycolic acid (PLGA) matrix. It received its market authorisation (EU/1/10/638/001) on 27th July 2010 as Ozurdex 700 micrograms intravitreal implant in applicator.

All patients received baseline Ozurdex injection. Intravitreal Ozurdex injections were performed under local anaesthesia and post-injection topical antibiotics were used. Further Ozurdex injections in each arm were performed according to protocol-defined retreatment criteria. In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points. In addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms.

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | PRN dosing arm |
|------------------|----------------|

**Arm description:**

In the standard arm (PRN), participants were seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participants in standard arm were re-treated at any point, the next visit was after 4 months.

Re-treatment with Ozurdex was indicated if the CST on OCT exceeded 300 µm and the intraocular pressure (IOP) was ≤ 25 mmHg. If the IOP was between 26 and 30mmHg, topical anti-glaucoma eye drops were given before treatment with Ozurdex at the same sitting. If the IOP recorded was 30 mmHg or more, anti-glaucoma eye drops were given and the patient was reviewed a week later and Ozurdex was injected only if the IOP had reduced to less than 30mmHg. Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation.

|  |  |
|--|--|
| Arm type                               | standard   |
| Investigational medicinal product name | 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) |
| Investigational medicinal product code |  |
| Other name                             | OZURDEX  |
| Pharmaceutical forms                   | Intravitreal implant in applicator                                       |
| Routes of administration               | Intravitreal use   |

**Dosage and administration details:**

The Ozurdex (Allergan Inc.) drug delivery system is a sustained-release formulation for posterior-segment delivery of dexamethasone, made of a polylacticglycolic acid (PLGA) matrix. It received its market authorisation (EU/1/10/638/001) on 27th July 2010 as Ozurdex 700 micrograms intravitreal implant in applicator.

All patients received baseline Ozurdex injection. Intravitreal Ozurdex injections were performed under local anaesthesia and post-injection topical antibiotics were used. Further Ozurdex injections in each arm were performed according to protocol-defined retreatment criteria. In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points. In addition, safety visits were done at 1 and 8 weeks after any Ozurdex injection in either treatment arms.

|  |  |
|--|--|
| Investigational medicinal product name | 700 µg Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) |
| Investigational medicinal product code |  |
| Other name                             | Ozurdex  |
| Pharmaceutical forms                   | Intravitreal implant in applicator                                       |
| Routes of administration               | Intravitreal use   |

**Dosage and administration details:**

In the intervention arm (fixed dosing) mandated dose of intravitreal Ozurdex is given at baseline, 5 and 10 months.

In the standard (PRN dosing), re-treatment with Ozurdex is given after the baseline injection if retreatment criteria are met provided the interval between two consecutive injections should exceed 16 weeks. Re-treatment with Ozurdex is indicated in this arm if the following criteria are met:

|  |   |
|--|---|
| Investigational medicinal product name | Dexamethasone Posterior Segment Drug Delivery System (DEX PS DDS) |
| Investigational medicinal product code |   |
| Other name                             | Ozurdex   |
| Pharmaceutical forms                   | Intravitreal implant in applicator                                |
| Routes of administration               | Intravitreal use  |

**Dosage and administration details:**

Both treatment arms will receive intravitreal Ozurdex 700µg at all treatment time-points

In the intervention arm (fixed dosing) mandated dose of intravitreal Ozurdex is given at baseline, 5 and 10 months.

In the standard (PRN dosing), re-treatment with Ozurdex is given after the baseline injection if retreatment criteria are met provided the interval between two consecutive injections should exceed 16 weeks. Re-treatment with Ozurdex is indicated in this arm if the following criteria are met:

**Notes:**

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The trial was single blinded (the optometrists and OCT technicians were blinded to treatment allocation. The patients and clinicians who administered the study treatment and those who performed the safety evaluations were not blinded to the treatment arms).

| <b>Number of subjects in period 1</b> | Fixed | PRN dosing arm |
|---------------------------------------|-------|----------------|
| Started                               | 50    | 50             |
| Completed                             | 49    | 48             |
| Not completed                         | 1     | 2              |
| death                                 | 1     | 1              |
| non compliant                         | -     | 1              |

## Baseline characteristics

### Reporting groups

|                       |       |
|-----------------------|-------|
| Reporting group title | Fixed |
|-----------------------|-------|

Reporting group description:

In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points

Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation

|                       |                |
|-----------------------|----------------|
| Reporting group title | PRN dosing arm |
|-----------------------|----------------|

Reporting group description:

In the standard arm (PRN), participants were seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participants in standard arm were re-treated at any point, the next visit was after 4 months.

Re-treatment with Ozurdex was indicated if the CST on OCT exceeded 300 µm and the intraocular pressure (IOP) was ≤ 25 mmHg. If the IOP was between 26 and 30mmHg, topical anti-glaucoma eye drops were given before treatment with Ozurdex at the same sitting. If the IOP recorded was 30 mmHg or more, anti-glaucoma eye drops were given and the patient was reviewed a week later and Ozurdex was injected only if the IOP had reduced to less than 30mmHg. Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation.

| Reporting group values                                | Fixed   | PRN dosing arm | Total |
|---|---------|----------------|-------|
| Number of subjects                                    | 50      | 50             | 100   |
| Age categorical<br>Units: Subjects                    |         |                |       |
| In utero  |         |                | 0     |
| Preterm newborn infants<br>(gestational age < 37 wks) |         |                | 0     |
| Newborns (0-27 days)                                  |         |                | 0     |
| Infants and toddlers (28 days-23 months)              |         |                | 0     |
| Children (2-11 years)                                 |         |                | 0     |
| Adolescents (12-17 years)                             |         |                | 0     |
| Adults (18-64 years)                                  |         |                | 0     |
| From 65-84 years                                      |         |                | 0     |
| 85 years and over                                     |         |                | 0     |
| Age continuous<br>Units: years                        |         |                |       |
| arithmetic mean                                       | 63.8    | 65.4           | -     |
| standard deviation                                    | ± 11.1  | ± 9.8          | -     |
| Gender categorical<br>Units: Subjects                 |         |                |       |
| Female  | 10      | 16             | 26    |
| Male  | 40      | 34             | 74    |
| Best Corrected Visual Acuity<br>Units: ETDRS letters  |         |                |       |
| arithmetic mean                                       | 57.5    | 61.2           | -     |
| standard deviation                                    | ± 9.5   | ± 8.6          | -     |
| OCT Central subfield thickness<br>Units: microns      |         |                |       |
| arithmetic mean                                       | 472.4   | 467.9          | -     |
| standard deviation                                    | ± 113.5 | ± 126.4        | -     |





## End points

### End points reporting groups

|  |                |
|--|----------------|
| Reporting group title  | Fixed          |
| Reporting group description:   |                |
| In the intervention arm (fixed dosing), mandated intravitreal Ozurdex was given at baseline, 5 and 10 months if the criteria for deferred treatment were not met at those time-points<br>Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation   |                |
| Reporting group title  | PRN dosing arm |
| Reporting group description:   |                |
| In the standard arm (PRN), participants were seen at baseline, 4 months and then monthly to assess the need for re-treatment. If the participants in standard arm were re-treated at any point, the next visit was after 4 months.<br>Re-treatment with Ozurdex was indicated if the CST on OCT exceeded 300 µm and the intraocular pressure (IOP) was ≤ 25 mmHg. If the IOP was between 26 and 30mmHg, topical anti-glaucoma eye drops were given before treatment with Ozurdex at the same sitting. If the IOP recorded was 30 mmHg or more, anti-glaucoma eye drops were given and the patient was reviewed a week later and Ozurdex was injected only if the IOP had reduced to less than 30mmHg. Ozurdex treatment was deferred if the BCVA was better than 83 letters or the IOP was 30 mmHg or more while on Ozurdex therapy or there was evidence of intraocular infection or severe inflammation. |                |

### Primary: BCVA at 12 months ITT analysis

|                        |                                |
|------------------------|--------------------------------|
| End point title        | BCVA at 12 months ITT analysis |
| End point description: |                                |
| End point type         | Primary                        |
| End point timeframe:   |                                |
| 12 months              |                                |

| End point values                     | Fixed           | PRN dosing arm  |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 49              | 48              |  |  |
| Units: ETDRS letters                 |                 |                 |  |  |
| arithmetic mean (standard deviation) | 57.8 (± 18.5)   | 61.4 (± 14)     |  |  |

### Statistical analyses

|  |                           |
|--|---------------------------|
| Statistical analysis title   | Primary endpoint analysis |
| Statistical analysis description:  |                           |
| The primary outcome is the difference in mean change in baseline best corrected ETDRS visual acuity (BCVA) letter score at 12 months between the two study arms, after adjusting for baseline BCVA and study site. |                           |
| Comparison groups  | Fixed v PRN dosing arm    |

|   |                                |
|---|--------------------------------|
| Number of subjects included in analysis | 97                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority                |
| P-value                                 | < 0.05                         |
| Method                                  | descriptive                    |
| Parameter estimate                      | Mean difference (final values) |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 1-sided                        |
| Variability estimate                    | Standard deviation             |

### Secondary: Change in central retinal thickness on OCT at 12 months

|                        |   |
|------------------------|---|
| End point title        | Change in central retinal thickness on OCT at 12 months |
| End point description: |   |
| End point type         | Secondary   |
| End point timeframe:   |   |
| 12 months              |   |

| End point values                     | Fixed            | PRN dosing arm  |  |  |
|--------------------------------------|------------------|-----------------|--|--|
| Subject group type                   | Reporting group  | Reporting group |  |  |
| Number of subjects analysed          | 47               | 47              |  |  |
| Units: microns                       |                  |                 |  |  |
| arithmetic mean (standard deviation) | -179.9 (± 172.4) | -90.1 (± 96.2)  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: No of injections per patient

|                        |                              |
|------------------------|------------------------------|
| End point title        | No of injections per patient |
| End point description: |                              |
| End point type         | Secondary                    |
| End point timeframe:   |                              |
| 12 months              |                              |

|                                      |                 |                 |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| <b>End point values</b>              | Fixed           | PRN dosing arm  |  |  |
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 50              | 50              |  |  |
| Units: number                        |                 |                 |  |  |
| arithmetic mean (standard deviation) | 2.86 (± 0.45)   | 2.6 (± 0.7)     |  |  |

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

February 2013 to November 2014

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

### Dictionary used

|                 |                     |
|-----------------|---------------------|
| Dictionary name | not used dictionary |
|-----------------|---------------------|

|                    |   |
|--------------------|---|
| Dictionary version | 0 |
|--------------------|---|

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Fixed dose arm |
|-----------------------|----------------|

Reporting group description: -

|                       |              |
|-----------------------|--------------|
| Reporting group title | PRN dose arm |
|-----------------------|--------------|

Reporting group description: -

| Serious adverse events                               | Fixed dose arm  | PRN dose arm     |  |
|--|-----------------|------------------|--|
| Total subjects affected by serious adverse events    |                 |                  |  |
| subjects affected / exposed                          | 9 / 50 (18.00%) | 10 / 50 (20.00%) |  |
| number of deaths (all causes)                        | 1               | 1                |  |
| number of deaths resulting from adverse events       | 0               | 0                |  |
| General disorders and administration site conditions |                 |                  |  |
| Death  |                 |                  |  |
| subjects affected / exposed                          | 1 / 50 (2.00%)  | 1 / 50 (2.00%)   |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 1            |  |
| Others general                                       |                 |                  |  |
| subjects affected / exposed                          | 5 / 50 (10.00%) | 3 / 50 (6.00%)   |  |
| occurrences causally related to treatment / all      | 0 / 5           | 0 / 3            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Eye disorders  |                 |                  |  |
| Retinal detachment                                   |                 |                  |  |
| subjects affected / exposed                          | 1 / 50 (2.00%)  | 0 / 50 (0.00%)   |  |
| occurrences causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0            |  |
| Cataract surgery in study eye                        |                 |                  |  |

|   |                |                |  |
|---|----------------|----------------|--|
| subjects affected / exposed                     | 1 / 50 (2.00%) | 4 / 50 (8.00%) |  |
| occurrences causally related to treatment / all | 1 / 1          | 4 / 4          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Endophthalmitis                                 |                |                |  |
| subjects affected / exposed                     | 0 / 50 (0.00%) | 1 / 50 (2.00%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |
| Other ocular                                    |                |                |  |
| subjects affected / exposed                     | 1 / 50 (2.00%) | 1 / 50 (2.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          |  |

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

| <b>Non-serious adverse events</b>                     | Fixed dose arm    | PRN dose arm      |  |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 50 / 50 (100.00%) | 50 / 50 (100.00%) |  |
| General disorders and administration site conditions  |                   |                   |  |
| All Ocular  |                   |                   |  |
| subjects affected / exposed                           | 50 / 50 (100.00%) | 50 / 50 (100.00%) |  |
| occurrences (all)                                     | 136               | 123               |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

|   |
|---|
| 12 month cut off of the study favouring Fixed dose patients, as they had injections at 10 months - so better 12 month results, than PRN<br>Non-inferiority margin of 5 letters might be considered large by some<br>The sample size is a limitation |
|---|

Notes: