



Clinical trial results:

A non-randomised, open-label, multicenter phase 4 pilot study on the effect and safety of Iluvien® in chronic diabetic macular edema patients considered insufficiently responsive to available therapies with or without intravitreal corticosteroid therapy. (RESPOND)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-003491-23 |
| Trial protocol | PT |
| Global end of trial date | 09 March 2016 |

Results information

| | |
|-----------------------------------|--|
| Result version number | v1 (current) |
| This version publication date | 15 November 2020 |
| First version publication date | 15 November 2020 |
| Summary attachment (see zip file) | Clinical Study Report (Imp_16-7-3 00_Study_Report_RESPOND_20160906.pdf) |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | 4C-2014-06 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02359526 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AIBILI |
| Sponsor organisation address | Azinhaga Santa Comba, Coimbra, Portugal, 3000 |
| Public contact | Sandrina Nunes, AIBILI – Association for Innovation and Biomedical Research on Light and Image, 00351 239480112, sandrina@aibili.pt |
| Scientific contact | Sandrina Nunes, AIBILI – Association for Innovation and Biomedical Research on Light and Image, 00351 239480112, sandrina@aibili.pt |

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 | 29 July 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 09 March 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 March 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect and safety of ILUVIEN in patients with chronic DME insufficiently responsive to prior available therapies with or without prior history of intraocular corticosteroid therapy.

Protection of trial subjects:

This study was designed, implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

The final study protocol, including the substantial amendments and the final version of the subject information and consent form, were reviewed and approved by an Independent Ethics Committee (IEC) prior to inclusion of subjects.

The Investigator ensured that each patient was fully informed about the nature and objective of the study and possible risks associated with participation.

Eligible patients only participated in the study after providing written (witnessed, where required by law or regulation), approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient was informed about the study to the extent possible given his/her understanding. If the patient was capable of doing so, he/she indicated assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent was obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent is documented in the patient source documents. The Sponsor provided to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and considered appropriate for this study.

Background therapy:

The pathogenesis of DME involves several contributing factors including an over-expression of vascular endothelial growth factor (VEGF) and multi-factorial inflammatory processes that lead to the breakdown of the blood-retina barrier and retinal ischemia. Owing to the over expression of VEGF, anti-VEGF therapies are currently used as treatment options in DME. The standard of care and reference therapy for DME (HAS Transparency Commission opinion on Lucentis, 2011) involves the use of laser. In the case that the DME patient still remains insufficiently responsive to laser therapy, subsequent therapy involves on-label treatments such as anti-VEGF therapy and off-label treatment with intravitreal corticosteroids (i.e., referred to herein as current clinical practice). To date, ILUVIEN has not formed part of DME clinical practice and so there is, naturally, limited experience of using ILUVIEN in Portugal. Recently, however, the Portuguese Competent Authority (INFARMED) has conceded marketing authorization and has approved reimbursement for ILUVIEN. Therefore, ILUVIEN will form one of the therapies that can be used by treating physicians in Portugal.

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 29 October 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 12 Months |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Portugal: 12 |
| Worldwide total number of subjects | 12 |
| EEA total number of subjects | 12 |

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) | 8 |
| From 65 to 84 years | 4 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Chronic DME patients considered insufficiently responsive to available therapies (laser, anti-VEGF) with or without intravitreal corticosteroid therapy.

Pre-assignment

Screening details:

Chronic DME patients and considered as insufficiently responsive as defined as having underwent other previous treatments.

Period 1

| | |
|------------------------------|-----------------------------|
| Period 1 title | Baseline (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Non-randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|-----------|------------|
| Arm title | DME Cohort |
|-----------|------------|

Arm description:

Cohort of DM patients

| | |
|--|-------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Iluvien |
| Investigational medicinal product code | |
| Other name | fluocinolone acetonide |
| Pharmaceutical forms | Implant in pre-filled syringe |
| Routes of administration | Intravitreal use |

Dosage and administration details:

The implant is an injectable intraocular sustained-release drug delivery system for FAc preloaded into a one-time use sterile applicator. Each implant contains 0.19 mg of FAc as the active ingredient within a cylindrical polyimide tube 3.5 mm long with an internal diameter of 0.34 mm. Inactive ingredients are polyimide, polyvinyl alcohol (PVA) and silicone adhesive. The polyimide tube and silicone adhesive are impermeable to FAc, while the cured PVA coated end of the tube act as a diffusion port allowing the drug to be released. The implant is to be injected through the pars plana into the vitreous using the applicator.

| | |
|--|-------------------------------|
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| Number of subjects in period 1 | DME Cohort |
|---------------------------------------|------------|
| Started | 12 |
| Baseline | 12 |
| Completed | 12 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Baseline |
|-----------------------|----------|

| |
|------------------------------|
| Reporting group description: |
|------------------------------|

| |
|------------|
| DME cohort |
|------------|

| Reporting group values | Baseline | Total | |
|---------------------------------|----------|-------|--|
| Number of subjects | 12 | 12 | |
| Age categorical | | | |
| Units: Subjects | | | |
| Over 18 years | 12 | 12 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 69.6 | | |
| standard deviation | ± 9.3 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 8 | 8 | |
| BCVA | | | |
| Baseline BCVA | | | |
| Units: Letters | | | |
| arithmetic mean | 48.7 | | |
| standard deviation | ± 10.9 | - | |
| CST | | | |
| Central subfield thickness | | | |
| Units: micrometer | | | |
| arithmetic mean | 650.5 | | |
| standard deviation | ± 140.9 | - | |
| MV | | | |
| Macular volume | | | |
| Units: millimeters ³ | | | |
| arithmetic mean | 11.61 | | |
| standard deviation | ± 2.01 | - | |

Subject analysis sets

| | |
|----------------------------|------------------|
| Subject analysis set title | Study Population |
|----------------------------|------------------|

| | |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

| |
|-----------------------------------|
| Subject analysis set description: |
|-----------------------------------|

| |
|--|
| All included patients will be analyzed |
|--|

| Reporting group values | Study Population | | |
|------------------------|------------------|--|--|
| Number of subjects | 12 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Over 18 years | 12 | | |

| | | | |
|----------------------------|---------|--|--|
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 69.6 | | |
| standard deviation | ± 9.3 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | | |
| Male | 8 | | |
| BCVA | | | |
| Baseline BCVA | | | |
| Units: Letters | | | |
| arithmetic mean | 48.7 | | |
| standard deviation | ± 10.9 | | |
| CST | | | |
| Central subfield thickness | | | |
| Units: micrometer | | | |
| arithmetic mean | 650.5 | | |
| standard deviation | ± 140.9 | | |
| MV | | | |
| Macular volume | | | |
| Units: millimeters^3 | | | |
| arithmetic mean | 11.6 | | |
| standard deviation | ± 2.01 | | |

End points

End points reporting groups

| | |
|--|------------------|
| Reporting group title | DME Cohort |
| Reporting group description: | |
| Cohort of DM patients | |
| Subject analysis set title | Study Population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All included patients will be analyzed | |

Primary: BCVA

| | |
|-----------------------------------|---------|
| End point title | BCVA |
| End point description: | |
| Changes from baseline to month-12 | |
| End point type | Primary |
| End point timeframe: | |
| month-12 | |

| End point values | DME Cohort | Study Population | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: Letters | | | | |
| arithmetic mean (standard deviation) | 52.4 (± 15.1) | 52.4 (± 15.1) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Primary outcomes |
| Statistical analysis description: | |
| The efficacy hypotheses | |
| • H0: there is no change in BCVA from baseline to Month-12 | |
| • H1: there is a change in BCVA from baseline to Month-12 | |
| and | |
| • H0: there is no change in central retinal thickness assessed using SD-OCT from baseline to Month-12 | |
| • H1: there is a change in central retinal thickness assessed using SD-OCT from baseline to Month-12 | |
| were tested using Wilcoxon Signed-Rank test, due the small sample size. | |
| An alpha of 0.05 was considered in all analyses. | |
| Comparison groups | DME Cohort v Study Population |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | = 0.255 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1 |
| Variability estimate | Standard deviation |
| Dispersion value | 10 |

Notes:

[1] - Pilot study. Exploratory analyses.

Primary: CST

| | |
|--|---------|
| End point title | CST |
| End point description: | |
| Change of the Central subfield Thickness from baseline | |
| End point type | Primary |
| End point timeframe: | |
| month-12 | |

| End point values | DME Cohort | Study Population | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: micrometers | | | | |
| arithmetic mean (standard deviation) | 357.7 (± 169.5) | 357.7 (± 169.5) | | |

Statistical analyses

| | |
|--|-------------------------------|
| Statistical analysis title | CST analysis |
| Statistical analysis description: | |
| Changes in CST from baseline to month-12 | |
| Comparison groups | DME Cohort v Study Population |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | = 0.003 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Mean difference (net) |
| Point estimate | 0 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1 |
| Variability estimate | Standard deviation |
| Dispersion value | 100 |

Notes:

[2] - Pilot study. Exploratory analysis

Primary: MV

| | |
|---|---------|
| End point title | MV |
| End point description: Changes of the Macular Volume from baseline to month-12 | |
| End point type | Primary |
| End point timeframe: Month-12 | |

| End point values | DME Cohort | Study Population | | |
|--------------------------------------|-----------------|----------------------|--|--|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 12 | 12 | | |
| Units: millimeters ³ | | | | |
| arithmetic mean (standard deviation) | 9.8 (± 1.9) | 9.8 (± 1.9) | | |

Statistical analyses

| | |
|--|-------------------------------|
| Statistical analysis title | MV analysis |
| Statistical analysis description: Changes from baseline | |
| Comparison groups | DME Cohort v Study Population |
| Number of subjects included in analysis | 24 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.005 |
| Method | Wilcoxon (Mann-Whitney) |
| Parameter estimate | Median difference (net) |
| Point estimate | 0 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -1 |
| upper limit | 1 |
| Variability estimate | Standard deviation |
| Dispersion value | 2 |

Notes:

[3] - Pilot. Exploratory analysis.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

24 months (12 months of study plus 12 months of post study)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | DME Cohort |
|-----------------------|------------|

Reporting group description:

All patients are considered. All received the study IMP.

| Serious adverse events | DME Cohort | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 3 %

| Non-serious adverse events | DME Cohort | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 12 (91.67%) | | |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Keratitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Ocular hypertension | | | |
| subjects affected / exposed | 5 / 12 (41.67%) | | |
| occurrences (all) | 5 | | |
| Vitreous haemorrhage | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The reduced number of patients included in this exploratory study limited the conclusions, namely the statistical significance of results.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/28178701>