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: milimeters^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:	
AI 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 standard deviation	 69.6 ± 9.3		
Gender categorical Units: Subjects			
Female Male	4 8		
BCVA			
Baseline BCVA			
Units: Letters arithmetic mean standard deviation	 48.7 ± 10.9		
CST			
Central subfield thickness			
Units: micrometer arithmetic mean standard deviation	 650.5 ± 140.9		
MV			
Macular volume			
Units: milimeters^3 arithmetic mean standard deviation	 11.6 ± 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: Al 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 form 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 form 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: milimeters^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