Clinical trial results:
Iluvit – An investigator initiated monocentric pilot study to investigate inflammation parameters and growth factors in the vitreous during a cortisone long-term therapy with Iluvien® in patients with chronic diabetic macular edema

Summary

EudraCT number	2016-004488-38
Trial protocol	DE
Global end of trial date	15 August 2019

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	ILV-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Johann Wolfgang Goethe University Hospital Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt am Main, Germany, 60590
Public contact	Prof. Dr. Frank Koch, Johann Wolfgang Goethe-University Hospital Frankfurt, Department of Ophthalmology, +49 6963015649, fkoch1@icloud.com
Scientific contact	Prof. Dr. Frank Koch, Johann Wolfgang Goethe University Hospital Frankfurt, Department of Ophthalmology, +49 6963015649, fkoch1@icloud.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	Final
Date of interim/final analysis	04 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 August 2019
Global end of trial reached?	Yes
Global end of trial date	15 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary aim of this pilot study was to show whether intravitreal Iluvien® therapy has an influence on the inflammatory factor IL-6, which, in conjunction with growth factors, is significantly involved in the development of diabetic macular edema. In a possible main study based on this, the presumed influence of the Iluvien® therapy on the inflammatory factor IL-6 is then to be more precisely determined and statistically analyzed with a larger sample over a longer period of time.

Protection of trial subjects:

no specific measures

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 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)	9
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place between September 2018 and February 2019.

Pre-assignment

Screening details:

13 patients were screened for inclusion and deemed eligible to participate. 1 patient chose not to participate and withdrew declaration of consent after completing the screening visit.

Pre-assignment period milestones

Number of subjects started	12
Number of subjects completed	12

Period 1

Period 1 title	T0
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	Overall Trial

Arm description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Arm type	Experimental
Investigational medicinal product name	Iluvien (Fluocinolone acetonide) 190 µg intravitreal implant in applicator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

190 µg, once, intravitreal implant in applicator

Number of subjects in period 1	Overall Trial
Started	12
Completed	12

Period 2

Period 2 title	T2
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

n/a

Arms

Arm title	Overall Trial

Arm description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Arm type	Experimental
Investigational medicinal product name	Iluvien (Fluocinolone acetonide) 190 µg intravitreal implant in applicator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

190 µg, once, intravitreal implant in applicator

Number of subjects in period 2	Overall Trial
Started	12
Completed	12

Period 3

Period 3 title	T4
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Overall Trial

Arm description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Arm type	Experimental
Investigational medicinal product name	Iluvien (Fluocinolone acetonide) 190 µg intravitreal implant in applicator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

190 µg, once, intravitreal implant in applicator

Number of subjects in period 3	Overall Trial
Started	12
Completed	12

Baseline characteristics

Reporting groups	
Reporting group title	T0

Reporting group description: -

Reporting group values	T0	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Adults (18-64 years)	9	9	
From 65-84 years	3	3	
Gender categorical Units: Subjects			
Female	3	3	
Male	9	9	

End points

End points reporting groups

Reporting group title	Overall Trial

Reporting group description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Reporting group title	Overall Trial

Reporting group description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Reporting group title	Overall Trial

Reporting group description:

Single arm study
T0: start of treatment (Iluvien implantation at T0), vitreous probe to measure growth factor concentration
T2: vitreous probe to measure growth factor concentration
T3: vitreous probe to measure growth factor concentration

Primary: IL-6

End point title	IL-6

End point description:

The primary endpoint of the study was the determination of the IL-6 concentration in the posterior compartment of the vitreous.

End point type	Primary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/mL				
arithmetic mean (standard deviation)	84.30 (± 126.81)	49.33 (± 57.08)	46.93 (± 79.63)	

Statistical analyses

Statistical analysis title	Change in IL-6 between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[1] - Single arm study comparing T0(implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: VEGF

End point title	VEGF

End point description:

A secondary endpoint of the study was the determination of the VEGF concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	280.30 (± 351.50)	286.42 (± 337.93)	179.59 (± 163.96)	

Statistical analyses

Statistical analysis title	Change in VEGF between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 0.05 [2]
Method	Friedmann Test

Notes:

[2] - Single arm study comparing T0(implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: IL-1b

End point title	IL-1b

End point description:

A secondary endpoint of the study was the determination of the IL-1b concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	0.00 (± 0.00)	0.00 (± 0.00)	0.00 (± 0.00)	

Statistical analyses

Statistical analysis title	Change in IL-1b between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[3] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: IL-8

End point title	IL-8

End point description:

A secondary endpoint of the study was the determination of the IL-8 concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	39.90 (± 35.33)	37.09 (± 26.74)	33.80 (± 24.97)	

Statistical analyses

Statistical analysis title	Change in IL-8 between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[4] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: IP-10

End point title	IP-10

End point description:

A secondary endpoint of the study was the determination of the IP-10 concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	134.81 (± 241.71)	76.50 (± 125.21)	64.13 (± 88.91)	

Statistical analyses

Statistical analysis title	Change in IP-10 between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial

Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[5] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: ICAM-1

End point title	ICAM-1

End point description:

A secondary endpoint of the study was the determination of the ICAM-1 concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	839.38 (± 793.78)	532.29 (± 354.71)	513.82 (± 343.09)	

Statistical analyses

Statistical analysis title	Change in ICAM-1 between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[6] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: PDGF

End point title	PDGF

End point description:

A secondary endpoint of the study was the determination of the PDGF concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)

T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	31.29 (± 0.00)	31.30 (± 0.00)	31.29 (± 0.00)	

Statistical analyses

Statistical analysis title	Change in PDGF between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[7] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: MCP-1

End point title	MCP-1

End point description:

A secondary endpoint of the study was the determination of the MCP-1 concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	866.46 (± 400.97)	545.63 (± 235.58)	541.85 (± 241.04)	

Statistical analyses

Statistical analysis title	Change in MCP-1 between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[8] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: PGF

End point title	PGF

End point description:

A secondary endpoint of the study was the determination of the PGF concentration in the posterior compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	95.83 (± 108.37)	128.48 (± 157.68)	75.77 (± 63.20)	

Statistical analyses

Statistical analysis title	Change in PGF between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[9] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Secondary: PEDF

End point title	PEDF

End point description:

A secondary endpoint of the study was the determination of the PEDF concentration in the posterior

compartment of the vitreous

End point type	Secondary

End point timeframe:

T0: start of treatment (Iluvien implantation)
T2: 1 month after Iluvien implantation
T4: 6 months after Iluvien implantation

End point values	Overall Trial	Overall Trial	Overall Trial	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	12	12	
Units: pg/ml				
arithmetic mean (standard deviation)	4696.15 (± 315.84)	4742.98 (± 270.44)	4711.48 (± 266.64)	

Statistical analyses

Statistical analysis title	Change in PEDF between T0 and T4
Comparison groups	Overall Trial v Overall Trial v Overall Trial
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	≤ 0.05
Method	Friedmann Test

Notes:

[10] - Single arm study comparing T0 (implantation) to T4 (6 months after implantation). The same 12 subjects were analysed throughout the course of the study.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Recording of new adverse events began at the baseline visit (T0, start of treatment) and ended with the completion of the last examination of the patient (T4). AEs that persisted at the end of the study were followed up for up to 28 days after T4 visit.

Adverse event reporting additional description:

In addition, if available, AEs that occurred before the start of treatment and AEs after the end of study (date of visit T4), were listed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	All study patients

Reporting group description: -

Serious adverse events	All study patients		
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			
Hypertensive emergency			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hypertensive encephalopathy			
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: 0 %

Non-serious adverse events	All study patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 12 (66.67%)		

Vascular disorders unstable blood pressure subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
Cardiac disorders cardiac insufficiency subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) peripheral edema subjects affected / exposed occurrences (all)	 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Eye disorders Blepharitis subjects affected / exposed occurrences (all) Vitreous haemorrhage subjects affected / exposed occurrences (all) Iris adhesions subjects affected / exposed occurrences (all) Intraocular pressure increased subjects affected / exposed occurrences (all) Conjunctival haemorrhage subjects affected / exposed occurrences (all) Eczema eyelids subjects affected / exposed occurrences (all) Vitreous detachment	 1 / 12 (8.33%) 3 3 / 12 (25.00%) 6 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 		

subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Cataract			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Angle closure glaucoma			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Colon polyp			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Product issues			
Implant stuck in top of needle			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
implant extrusion through trocar			
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.

small patient cohort (n=12), monocentric
length of study: effect on cytokine levels was analysed for 6 months

Notes: