Clinical trial results:
A Phase III, Multi-National, Multi-Center, Randomized, Masked, Controlled, Safety and Efficacy Study of a Fluocinolone Acetonide Intravitreal (FAI) Insert in Subjects with Chronic Non-Infectious Uveitis Affecting the Posterior Segment of the Eye

Summary

EudraCT number	2013-001810-14
Trial protocol	HU DE GB IT
Global end of trial date	26 March 2018

Results information

Result version number	v1 (current)
This version publication date	31 March 2019
First version publication date	31 March 2019

Trial information

Trial identification

Sponsor protocol code	PSV-FAI-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01694186
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	EyePoint Pharmaceuticals, Inc. (pSivida Corporation)
Sponsor organisation address	480 Pleasant Street, Watertown, MA, United States, 02472
Public contact	Clinical Information, pSivida Corporation, +1 617972-6350, clinical.info@psivida.com
Scientific contact	Clinical Information, pSivida Corporation, +1 617972-6350, clinical.info@psivida.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	21 September 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 March 2018
Global end of trial reached?	Yes
Global end of trial date	26 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of this study are to evaluate the safety and efficacy of a FAI insert in the management of subjects with chronic non-infectious uveitis affecting the posterior segment of the eye.

Protection of trial subjects:

Subjects had the right to withdraw from the study at any time, for any reason, without jeopardizing their medical care. Each subject was followed for safety through the subject’s final visit unless the subject withdrew from the study.

Background therapy:

The protocol allowed investigators to treat subjects prior to entry to meet study inclusion criteria. The objective of prior treatment was to obtain a relatively quiet eye prior to enrollment. If a subject was receiving systemic corticosteroids or immunosuppressants or topical steroids to control uveitis prior to study enrollment, that subject had such treatment ended within 3 months following Day 1, in a manner that followed the standard of care for ending the specific treatment. Systemic medications or topical steroids administered as part of gradual dose reduction were not considered prohibited medications.

Evidence for comparator: -

Actual start date of recruitment	30 June 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	36 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 20
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	United States: 56
Country: Number of subjects enrolled	India: 31
Country: Number of subjects enrolled	Israel: 10
Worldwide total number of subjects	129
EEA total number of subjects	32

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)	111
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male or female subjects at least 18 years old, who had been diagnosed with unilateral or bilateral chronic non-infectious uveitis affecting the posterior segment of the eye for at least 12 months prior to randomization.

Pre-assignment

Screening details:

The Screening period occur within 30 days prior to Day 1. Subjects who failed to meet the inclusion/exclusion criteria during the screening period or on Day 1 could have been rescreened.

Period 1

Period 1 title	Treatment (Day 1)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[1]
Roles blinded	Subject, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The study was designed to mask treatment assignment to study subjects and investigators making study assessments after the administration of the assigned treatment. The study was designed to have both unmasked and masked personnel. Two investigators were used at each study center. One investigator served as the unmasked treating investigator (investigator 1) and the other investigator served as the masked assessing investigator (investigator 2).

Arms

Are arms mutually exclusive?	Yes
Arm title	FAI Insert

Arm description:

One treatment (FAI injection) was administered on Day 1 to each subject. The Fluocinolone Acetonide Intravitreal Insert (FAI insert) is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contained a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm.

Arm type	Experimental
Investigational medicinal product name	FAI insert
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

The dose delivered in the FAI insert was 0.18 mg fluocinolone acetonide delivered into the vitreous humor for 36 months. The FAI insert was administered to the study eye by injection through the pars plana using a preloaded applicator with a 25-gauge needle.

Arm title	Sham injection

Arm description:

During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Arm type	Sham injection
Investigational medicinal product name	Sham Injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implantation matrix
Routes of administration	Intravitreal use

Dosage and administration details:

The sham applicator was an empty 1-mL syringe attached to a blunt 14-gauge needle; it did not contain an FAI insert. During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Notes:

[1] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Two investigators were used at each study center. One investigator served as the unmasked treating investigator (investigator 1) and the other investigator served as the masked assessing investigator (investigator 2).

Number of subjects in period 1	FAI Insert	Sham injection
Started	87	42
Completed	87	42

Period 2

Period 2 title	Follow-up Period (36 months)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

To preserve study masking as much as possible within the imposed ethical constraints, the study personnel who administered the assigned treatment refrained from performing any subject assessments after Day 1. Treatment assignments were masked to the subjects and to those involved in administering routine follow-up care to the subjects. Follow up assessments were performed only by study personnel at the site who were masked to the assigned treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	FAI Insert

Arm description:

One treatment (FAI injection) was administered on Day 1 to each subject. The Fluocinolone Acetonide Intravitreal Insert (FAI insert) is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contained a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm.

Arm type	Experimental
Investigational medicinal product name	FAI insert
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Intravitreal implant in applicator
Routes of administration	Intravitreal use

Dosage and administration details:

The dose delivered in the FAI insert was 0.18 mg fluocinolone acetonide delivered into the vitreous humor for 36 months. The FAI insert was administered to the study eye by injection through the pars plana using a preloaded applicator with a 25-gauge needle.

Arm title	Sham Injection

Arm description:

During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Arm type	Sham Injection
Investigational medicinal product name	Sham Injector
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implantation matrix
Routes of administration	Intravitreal use

Dosage and administration details:

The sham applicator was an empty 1-mL syringe attached to a blunt 14-gauge needle; it did not contain an FAI insert. During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Number of subjects in period 2	FAI Insert	Sham Injection
Started	87	42
Completed	80	36
Not completed	7	6
Consent withdrawn by subject	1	-
Physician decision	2	-
Death	1	-
Lost to follow-up	3	4
Lack of efficacy	-	2

Baseline characteristics

Reporting groups

Reporting group title	FAI Insert

Reporting group description:

One treatment (FAI injection) was administered on Day 1 to each subject. The Fluocinolone Acetonide Intravitreal Insert (FAI insert) is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contained a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm.

Reporting group title	Sham injection

Reporting group description:

During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Reporting group values	FAI Insert	Sham injection	Total
Number of subjects	87	42	129
Age categorical Units: Subjects			
Adults (18-64 years)	75	36	111
From 65-84 years	12	6	18
Age continuous Units: years			
median	48	48	
full range (min-max)	20 to 77	18 to 73	-
Gender categorical Units: Subjects			
Female	50	29	79
Male	37	13	50

Subject analysis sets

Subject analysis set title	Intent-to-treat (ITT) Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A total of 129 subjects were enrolled in the study (all-randomized population). Of these, all 129 subjects were included in the intent-to-treat (ITT) population (87 subjects and 42 subjects in the FAI insert and sham injection treatment groups, respectively).

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 129 subjects were enrolled in the study (all-randomized population). Of these, all 129 subjects were included in the Safety population (87 subjects and 42 subjects in the FAI insert and sham injection treatment groups, respectively).

Reporting group values	Intent-to-treat (ITT) Set	Safety Set	
Number of subjects	129	129	
Age categorical Units: Subjects			
Adults (18-64 years)	111	111	
From 65-84 years	18	18	

Age continuous Units: years			
median	48	48	
full range (min-max)	18 to 77	18 to 77	
Gender categorical Units: Subjects			
Female	79	79	
Male	50	50	

End points

End points reporting groups

Reporting group title	FAI Insert

Reporting group description:

One treatment (FAI injection) was administered on Day 1 to each subject. The Fluocinolone Acetonide Intravitreal Insert (FAI insert) is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contained a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm.

Reporting group title	Sham injection

Reporting group description:

During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Reporting group title	FAI Insert

Reporting group description:

One treatment (FAI injection) was administered on Day 1 to each subject. The Fluocinolone Acetonide Intravitreal Insert (FAI insert) is an injectable intravitreal sustained-release FA delivery system preloaded into an injection device. Each insert contained a drug core of FA as the active ingredient within a cylindrical polyimide polymer tube 3.5-mm long with an external diameter of 0.37 mm.

Reporting group title	Sham Injection

Reporting group description:

During study Day 1, the sham applicator was gently pressed against the study eye to provide the subject with the perception that an intravitreal injection was being performed. This procedure was performed to mask study subjects to their assigned treatment.

Subject analysis set title	Intent-to-treat (ITT) Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

A total of 129 subjects were enrolled in the study (all-randomized population). Of these, all 129 subjects were included in the intent-to-treat (ITT) population (87 subjects and 42 subjects in the FAI insert and sham injection treatment groups, respectively).

Subject analysis set title	Safety Set
Subject analysis set type	Safety analysis

Subject analysis set description:

A total of 129 subjects were enrolled in the study (all-randomized population). Of these, all 129 subjects were included in the Safety population (87 subjects and 42 subjects in the FAI insert and sham injection treatment groups, respectively).

Primary: Recurrence of Uveitis in the Study Eye at 6 Months

End point title	Recurrence of Uveitis in the Study Eye at 6 Months

End point description:

The primary efficacy analysis was performed on the ITT population at 6 months and was the difference between study groups in the proportion of subjects who had a recurrence of uveitis.

End point type	Primary

End point timeframe:

The primary efficacy analysis was conducted after all subjects in the study completed 6 months of treatment or discontinued from the study.

End point values	FAI Insert	Sham Injection		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	87	42		
Units: Patients				
RECURRENCE WITHIN 6 MONTHS	25	38		
Row-defined recurrence	1	12		
Imputed recurrence	24	26		
NO RECURRENCE WITHIN 6 MONTHS	62	4		

Statistical analyses

Statistical analysis title	Statistical Analysis Plan (SAP)
Comparison groups	FAI Insert v Sham Injection
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Chi-squared corrected
Parameter estimate	Odds ratio (OR)
Point estimate	23.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	7.61
upper limit	72.94

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety analyses were performed on the safety population at Month 6, Month 12, and Month 36.

Adverse event reporting additional description:

Descriptive statistics were provided for all treatment-emergent AEs (TEAEs). Frequency counts and percentage of subjects within each treatment group were provided by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT) by treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	FAI Insert

Reporting group description: -

Reporting group title	Sham Injection

Reporting group description: -

Serious adverse events	FAI Insert	Sham Injection	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 87 (40.23%)	15 / 42 (35.71%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Uterine cancer			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Premature baby			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Post-traumatic stress disorder			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Product issues			
Device dislocation			
subjects affected / exposed	2 / 87 (2.30%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Intraocular pressure fluctuation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraocular pressure increased			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural inflammation			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	2 / 87 (2.30%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			

subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Central nervous system lesion			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual field defect			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Lymphadenopathy			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	8 / 87 (9.20%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	4 / 87 (4.60%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotony of eye			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	1 / 87 (1.15%)	3 / 42 (7.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-infectious endophthalmitis			
subjects affected / exposed	0 / 87 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ocular hypertension			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			

subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	7 / 87 (8.05%)	5 / 42 (11.90%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitritis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subcapsular			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choroidal detachment			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal epithelium defect			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystoid macular oedema			
subjects affected / exposed	2 / 87 (2.30%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			

subjects affected / exposed	3 / 87 (3.45%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			
subjects affected / exposed	2 / 87 (2.30%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 87 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Foot deformity			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 87 (2.30%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations			
Septic shock			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Corneal infection			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 87 (1.15%)	0 / 42 (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: 5 %

Non-serious adverse events	FAI Insert	Sham Injection	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 87 (96.55%)	40 / 42 (95.24%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	49 / 87 (56.32%)	17 / 42 (40.48%)	
occurrences (all)	49	17	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 87 (6.90%)	4 / 42 (9.52%)	
occurrences (all)	6	4	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 87 (6.90%)	3 / 42 (7.14%)	
occurrences (all)	6	3	
Visual field defect			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	0 / 87 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	2 / 87 (2.30%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Eye disorders			
Anterior chamber flare			
subjects affected / exposed	0 / 87 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Cataract			
subjects affected / exposed	45 / 87 (51.72%)	13 / 42 (30.95%)	
occurrences (all)	45	13	
Cataract subcapsular			
subjects affected / exposed	6 / 87 (6.90%)	4 / 42 (9.52%)	
occurrences (all)	6	4	
Conjunctival haemorrhage			
subjects affected / exposed	21 / 87 (24.14%)	5 / 42 (11.90%)	
occurrences (all)	21	5	
Cystoid macular oedema			
subjects affected / exposed	31 / 87 (35.63%)	21 / 42 (50.00%)	
occurrences (all)	31	21	
Dry eye			
subjects affected / exposed	25 / 87 (28.74%)	9 / 42 (21.43%)	
occurrences (all)	25	9	
Eye pain			
subjects affected / exposed	19 / 87 (21.84%)	12 / 42 (28.57%)	
occurrences (all)	19	12	
Eye pruritus			
subjects affected / exposed	1 / 87 (1.15%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Eyelid ptosis			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Foreign body sensation in eyes			

subjects affected / exposed	8 / 87 (9.20%)	2 / 42 (4.76%)	
occurrences (all)	8	2	
Iridocyclitis			
subjects affected / exposed	8 / 87 (9.20%)	7 / 42 (16.67%)	
occurrences (all)	8	7	
Macular fibrosis			
subjects affected / exposed	10 / 87 (11.49%)	6 / 42 (14.29%)	
occurrences (all)	10	6	
Macular oedema			
subjects affected / exposed	15 / 87 (17.24%)	22 / 42 (52.38%)	
occurrences (all)	15	22	
Ocular discomfort			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Ocular hyperaemia			
subjects affected / exposed	7 / 87 (8.05%)	5 / 42 (11.90%)	
occurrences (all)	7	5	
Photopsia			
subjects affected / exposed	5 / 87 (5.75%)	3 / 42 (7.14%)	
occurrences (all)	5	3	
Posterior capsule opacification			
subjects affected / exposed	12 / 87 (13.79%)	3 / 42 (7.14%)	
occurrences (all)	12	3	
Uveitis			
subjects affected / exposed	49 / 87 (56.32%)	40 / 42 (95.24%)	
occurrences (all)	49	40	
Vision blurred			
subjects affected / exposed	2 / 87 (2.30%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Visual acuity reduced			
subjects affected / exposed	35 / 87 (40.23%)	9 / 42 (21.43%)	
occurrences (all)	35	9	
Visual impairment			
subjects affected / exposed	23 / 87 (26.44%)	5 / 42 (11.90%)	
occurrences (all)	23	5	
Vitreous floaters			

subjects affected / exposed	16 / 87 (18.39%)	8 / 42 (19.05%)	
occurrences (all)	16	8	
Vitreous opacities			
subjects affected / exposed	12 / 87 (13.79%)	6 / 42 (14.29%)	
occurrences (all)	12	6	
Anterior chamber cell			
subjects affected / exposed	8 / 87 (9.20%)	1 / 42 (2.38%)	
occurrences (all)	8	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 87 (3.45%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 87 (1.15%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Psychiatric disorders			
Depression			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	5 / 87 (5.75%)	1 / 42 (2.38%)	
occurrences (all)	5	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 87 (13.79%)	5 / 42 (11.90%)	
occurrences (all)	12	5	
Viral upper respiratory tract infection			
subjects affected / exposed	2 / 87 (2.30%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Conjunctivitis			
subjects affected / exposed	2 / 87 (2.30%)	3 / 42 (7.14%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 October 2013	An exclusion criterion was added to harmonize the protocol with existing recommendation in the IB (pSivida 2017). An exclusion criterion was clarified to harmonize the protocol with existing tests conducted during eligibility screening. The original text for FAI insert delivery was updated. The PK data for FA release from Iluvien in human subjects were updated based on the publicly available 36-month data reported in Campochiaro et al 2013. The screening section was revised to clarify that the physical examination conducted by the investigative site should be consistent with the physical examination typically administered by the investigator in the investigator's ophthalmology practice. Laboratory testing of electrolytes was revised to allow investigators to use local standard test for bicarbonate. Text was updated throughout to state that investigative sites were allowed to use local standard TB testing and not necessarily require all sites to use a serology TB testing. The text was updated throughout to clarify that the protocol required dilated indirect ophthalmoscopy only, as some investigators had interpreted the protocol to suggest that direct ophthalmoscopy was also required. The ICF sections were revised to accommodate different national requirements regarding the number of signed original ICF forms. The unmasking section was revised to clarify the authority of the investigator and to avoid any suggestion that the investigator must contact PPD/ EyePoint before breaking the mask for a subject. The OCT section was edited to indicate that sites with alternative OCT instruments were allowed to participate in the study. Anterior chamber cell scoring convention and vitreous haze scoring convention figures were added to clarify the scoring convention that was used in the study for the recurrence of uveitis.
12 December 2013	The exclusion criteria were updated to: - Clarify that the exclusion criteria pertain to the study eye. - Clarify that concurrent therapy of the study eye with any IOP-lowering medication is an exclusion criterion. Permit the enrollment of subjects with previous, successful incisional surgery to control IOP (e.g., filtration surgery, shunt, or tube placement) and the following: - Stable IOP in the normal range (10-21 mmHg) - No concurrent therapy with IOP-lowering medication The IOP section was updated to clarify that applanation tonometers with different brand names were acceptable to use in the study.
10 September 2014	The concomitant medications/procedures section was revised to clarify the conditions under which topical steroid use was permitted at time of study entry and at time following an ocular surgical procedure. Revision clarified conditions under which topical steroid use should be used to treat recurrences of uveitis. The data imputation section was updated for the conditions under which recurrence of uveitis would be imputed in the efficacy analysis. The measurement of BCVA by EDTRS was updated to clarify that the Tumbling E-ETDRS chart would be used for subjects who were illiterate or not familiar with the standard English alphabet.

22 December 2014	Revisions made as part of Amendment 4 for the US and EMEA countries were applied in Amendment 7 for India. Exclusion criterion regarding positive test for HIV, TB, or syphilis was clarified; positive HIV or syphilis test at screening would result in exclusion. An exclusion criterion was added to exclude subjects with infectious mycobacterial uveitis. The FAI insert injection procedure was revised to clarify that administration of a second FAI insert within the study eye was not permitted.
02 July 2015	The primary efficacy endpoint analysis was revised from Month 12 to Month 6. Text was revised throughout the protocol for consistency with revised timing of the primary efficacy endpoint analysis. Exploratory analyses text was revised throughout the protocol to be consistent with the revised timing of the primary efficacy endpoint analysis (Month 6). Efficacy and safety data analyses were revised for consistency with revised timing of primary efficacy endpoint analysis (Month 6). Sample size was adjusted for consistency with revised timing of primary efficacy endpoint analysis (Month 6), assuming that 80% of events observed within 12 months were observed within 6 months.
20 October 2015	The visit window for the Month 6 and Month 9 study visits was revised to ±28 days.

Notes:

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.

Not reported.

Notes: