Clinical trial results:
A phase II Clinical Trial on the use of ARA 290 for the treatment of diabetic macular oedema (ARA 290-DMO)

Summary

EudraCT number	2015-001940-12
Trial protocol	GB
Global end of trial date	29 August 2017

Results information

Result version number	v1 (current)
This version publication date	17 August 2019
First version publication date	17 August 2019

Trial information

Trial identification

Sponsor protocol code	14166NL-AS

Additional study identifiers

ISRCTN number	ISRCTN16962255
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Belfast Health & Social Care Trust
Sponsor organisation address	Research & Development, 1st Floor, King Edward Buidling, Royal Hospitals, Grosvenor Road, Belfast, United Kingdom, BT12 6BA
Public contact	NICTU, Northern Ireland Clinical Trials Unit (NICTU), 028 90635794, info@nictu.hscni.net
Scientific contact	NICTU, Northern Ireland Clinical Trials Unit (NICTU), 028 90635794, info@nictu.hscni.net

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	30 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 August 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The aim or primary objective of the study is to determine whether ARA 290 administered at a daily dose of 4mg subcutaneously for 12 weeks to patients with diabetes mellitus (DM) and Diabetic Macular Oedema (DMO) will have a beneficial effect on mean change in best corrected visual acuity (BCVA) from baseline values to week 12.

Protection of trial subjects:

Prior to commencement of recruitment to the study, the following safety measures were introduced:
- On advice from MHRA the protocol was amended to exclude pregnant or breast feeding women. All female potential participants of child bearing age were given a pregnancy test before recruitment to the study. All females of child bearing age, and all male participants who had a female partner of child bearing age, were advised of the need to use effective contraception during and for at least 30 days post administration of the final dose of the study drug. Any participant who could not ensure this was not recruited to the study.
- On advice from the Sponsor, the GP letter was amended to advise the patient GP that ARA 290 may have a possible improvement on the patient's glucose levels which may lead to the necessity to amend the patient's diabetes medicine accordingly.
-Araim (study drug provider) advised that the first DSUR report for the APCP-112 study noted one patient who reported having suicidal thoughts. Although this patient had a history of depression and was receiving a higher dose of ARA 290 (8mg daily), on advice from the FDA it was agreed that all subsequent studies of ARA 290 should include a suicide screening tool. To comply with this, all participants to the ARA 290-DMO study completed the Columbia Suicide Severity Rating Scale (C-SSRS) at each study visit.

The protocol mandated that participants whose sight was determined as deteriorating to the point of a 10 letter drop in sight would have ARA 290 stopped and would be offered the current standard care treatment. Likewise, patients who wished to withdraw from the study, or those who completed the duration of the study and in whom DMO persisted were offered standard care treatment.

Study participants were assessed for adverse events at each study visit and assessed again by telephone 4 weeks after the final dose of study drug was taken.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

Actual start date of recruitment	06 May 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 9

Worldwide total number of subjects	9
EEA total number of subjects	9

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)	6
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The ARA 290-DMO study recruited 9 out of the target of 10 patients before terminating early due to expiry of study drug (see Interruptions Globally section). The first patient was recruited on 06th May 2016. Recruitment was staggered in batches of 2 at the request of the study DMEC. The final patient 9 was recruited on 24th February 2017.

Pre-assignment

Screening details:

Patients attending ophthalmology clinics at Belfast Trust or referred to the CI by other BHSCT ophthalmology consultants.
Patients ≥18 years old with DMO with central subfield thickness of ≥ 400 microns, determined by SD-OCT. Clear media and naïve to previous treatment for DMO. A total of 23 patients were screened.

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Baseline - ARA290

Arm description:

Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks

Arm type	Experimental
Investigational medicinal product name	ARA 290-DMO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

-ARA 290 used for subcutaneous injection is provided as aseptic vials containing 5.6mg ARA 290, which after reconstitution with 0.66ml sterile water for injection contains a solution of 8mg/ml ARA 290 in a 20mM sodium phosphate buffer, pH 6.5, containing 1% sucrose and 4% D-mannitol. A volume of 0.5mL contains 4mg ARA 290.

-Participation in the study involves subcutaneous daily administration of ARA 290 at a dose of 4mg for 12 weeks duration. The first injection is self administered by the patient at the first clinic visit after receiving practical verbal and written instruction. The injection is given in the front or side of the thigh. In the unlikely event that the thigh cannot be used, the injection may be given in the abdomen. Each patient is given an initial pack of 30 vials to provide 28 day treatment and 2 extra to allow for spilling/spoilage. The pack is replaced at week 4, 8 and 12 study visit. Drug accountability of used/unused drug is maintained by BHSCT pharmacy.

Number of subjects in period 1	Baseline - ARA290
Started	9
Completed	9

Period 2

Period 2 title	12 Week
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	12 Week - ARA290

Arm description:

Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks

Arm type	Experimental
Investigational medicinal product name	ARA 290-DMO
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

-ARA 290 used for subcutaneous injection is provided as aseptic vials containing 5.6mg ARA 290, which after reconstitution with 0.66ml sterile water for injection contains a solution of 8mg/ml ARA 290 in a 20mM sodium phosphate buffer, pH 6.5, containing 1% sucrose and 4% D-mannitol. A volume of 0.5mL contains 4mg ARA 290.

-Participation in the study involves subcutaneous daily administration of ARA 290 at a dose of 4mg for 12 weeks duration. The first injection is self administered by the patient at the first clinic visit after receiving practical verbal and written instruction. The injection is given in the front or side of the thigh. In the unlikely event that the thigh cannot be used, the injection may be given in the abdomen. Each patient is given an initial pack of 30 vials to provide 28 day treatment and 2 extra to allow for spilling/spoilage. The pack is replaced at week 4, 8 and 12 study visit. Drug accountability of used/unused drug is maintained by BHSCT pharmacy.

Number of subjects in period 2[1]	12 Week - ARA290
Started	8
Completed	8

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: One patient dropped out post baseline but prior to week 12 due to experiencing a 10 letter loss in vision.
Total number of patients at baseline = 9.
Total number of patients at week 12 = 8.

Baseline characteristics

Reporting groups	
Reporting group title	Baseline Period
Reporting group description:	
Baseline Characteristics are calculated based on 9 patients at baseline. n=17 is presented above as per EudraCT advice on reporting single arm studies.	

Reporting group values	Baseline Period	Total	
Number of subjects	9	9	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	6	6	
From 65-84 years	3	3	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	57.6		
standard deviation	± 13.9	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	5	5	
Weight Units: kg			
arithmetic mean	95.5		
standard deviation	± 20.5	-	
Height Units: metres			
arithmetic mean	1.6		
standard deviation	± 0.12	-	
BMI Units: kg/m2			
arithmetic mean	37.18		
standard deviation	± 12.1	-	
Systolic Blood Pressure Units: mmHg			
arithmetic mean	145.2		
standard deviation	± 17.0	-	
Diastolic Blood Pressure Units: mmHg			
arithmetic mean	74.9		

standard deviation	± 10.1	-	
Heart Rate			
Units: bpm			
arithmetic mean	70.8		
standard deviation	± 14.1	-	
Temperature			
Units: degrees celsius			
arithmetic mean	36.3		
standard deviation	± 0.28	-	
Oxygen Saturation			
Units: Percentage			
arithmetic mean	98.0		
standard deviation	± 1.3	-	
C-peptide			
data available for n=6			
Units: ng/ml			
arithmetic mean	2.5		
standard deviation	± 3.2	-	
Glucose			
data available for n=8			
Units: mmol/L			
arithmetic mean	9.7		
standard deviation	± 3.9	-	
HDL			
Units: mmol/L			
arithmetic mean	1.2		
standard deviation	± 0.26	-	
LDL			
Units: mmol/L			
arithmetic mean	2.1		
standard deviation	± 0.85	-	
Triglycerides			
Units: mmol/L			
arithmetic mean	2.1		
standard deviation	± 1.0	-	
Albumin Creatinine Ratio			
Units: mmoL			
arithmetic mean	32.1		
standard deviation	± 72.2	-	
AST			
data available for n = 8			
Units: mmol/L			
arithmetic mean	25.5		
standard deviation	± 9.5	-	
ALT			
Units: mmol/L			
arithmetic mean	27.8		
standard deviation	± 16.9	-	

End points

End points reporting groups	
Reporting group title	Baseline - ARA290
Reporting group description: Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks	
Reporting group title	12 Week - ARA290
Reporting group description: Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks	

Primary: Primary Outcome; best corrected distance visual acuity (study eye)	
End point title	Primary Outcome; best corrected distance visual acuity (study eye)
End point description: Changes from baseline to week 12 (+/− 7 days) in best corrected distance visual acuity (study eye)	
End point type	Primary
End point timeframe: Change from baseline to week 12 in study eye	

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: logMAR				
arithmetic mean (standard deviation)	68.1 (± 7.9)	66.3 (± 9.5)		

Statistical analyses

Statistical analysis title	Best corrected distance visual activity_Study Eye
Statistical analysis description: 95% Confidence Interval for the primary outcome (study eye)	
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Mean difference (final values)
Point estimate	-2.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.1
upper limit	1.3
Variability estimate	Standard deviation
Dispersion value	5

Notes:

[1] - Mean Difference (95% CI) presented for change from Baseline to Week 12.

Primary: Primary Outcome; best corrected distance visual acuity (non study eye)

End point title	Primary Outcome; best corrected distance visual acuity (non study eye)

End point description:

Changes from baseline to week 12 (+/− 7 days) in best corrected distance visual acuity (non study eye)

End point type	Primary

End point timeframe:

Change from baseline to week 12 in non study eye

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: logMAR				
arithmetic mean (standard deviation)	69.0 (± 14.9)	75.9 (± 9.4)		

Statistical analyses

Statistical analysis title	Primary Outcome (Non study eye)

Statistical analysis description:

95% Confidence Interval

Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Mean difference (final values)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	9.4
Variability estimate	Standard deviation
Dispersion value	6.1

Notes:

[2] - Mean Difference (95% Confidence Interval) presented for change from Baseline to Week 12

Secondary: Central Subfield Thickness (study eye)

End point title	Central Subfield Thickness (study eye)

End point description:

Central subfield retinal thickness (CST), as obtained in the central 1 mm area, will be determined by spectral domain optical coherence tomography (SD-OCT) and used for the analysis. In addition, presence or absence of intraretinal or subretinal fluid will be evaluated and recorded in the appropriate CRF. SD-OCT will be obtained in both eyes by an ophthalmic photographer at baseline and weeks 4, 8

and 12. If at week 12 the retina is dry, a further visit at week 16 will be undertaken and SD-OCT obtained at this visit.

End point type	Secondary

End point timeframe:

Changes from baseline to week 12 (+/− 7 days)

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: microns				
arithmetic mean (standard deviation)	490.3 (± 61.9)	498.5 (± 127.1)		

Statistical analyses

Statistical analysis title	95% Confidence Interval
Comparison groups	12 Week - ARA290 v Baseline - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	10
Confidence interval	
level	95 %
sides	2-sided
lower limit	-69.1
upper limit	89.1
Variability estimate	Standard deviation
Dispersion value	94.6

Secondary: Central subfield thickness (Non study eye)

End point title	Central subfield thickness (Non study eye)

End point description:

Central subfield retinal thickness (CST), as obtained in the central 1 mm area, will be determined by spectral domain optical coherence tomography (SD-OCT) and used for the analysis. In addition, presence or absence of intraretinal or subretinal fluid will be evaluated and recorded in the appropriate CRF. SD-OCT will be obtained in both eyes by an ophthalmic photographer at baseline and weeks 4, 8 and 12. If at week 12 the retina is dry, a further visit at week 16 will be undertaken and SD-OCT obtained at this visit.

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/− 7 days)

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: Microns				
arithmetic mean (standard deviation)	349.7 (± 72.5)	347.9 (± 78.1)		

Statistical analyses

Statistical analysis title	95% Confidence Interval
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.2
upper limit	23.2
Variability estimate	Standard deviation
Dispersion value	20

Secondary: Central Retinal Sensistivity (Study Eye)

End point title	Central Retinal Sensistivity (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: dB				
arithmetic mean (standard deviation)	23.3 (± 2.2)	23.2 (± 2.3)		

Statistical analyses

Statistical analysis title	95% Confidence Interval
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.1
upper limit	1.1
Variability estimate	Standard deviation
Dispersion value	1.9

Secondary: Central Retinal Sensitivity (Non Study Eye)	
End point title	Central Retinal Sensitivity (Non Study Eye)
End point description:	
End point type	Secondary
End point timeframe:	
Change from baseline to week 12 (+/- 7 days)	

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: dB				
arithmetic mean (standard deviation)	23.3 (± 3.4)	24.2 (± 2.4)		

Statistical analyses

Statistical analysis title	95% Confidence Interval
Comparison groups	Baseline - ARA290 v 12 Week - ARA290

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	1.7
Variability estimate	Standard deviation
Dispersion value	2

Secondary: Retinal Perfusion_Macular Ischaemia (Study Eye)

End point title	Retinal Perfusion_Macular Ischaemia (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	5			
N/A	2			
UNOB	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Perfusion_Foveal Ischaemia (Non Study Eye)

End point title	Retinal Perfusion_Foveal Ischaemia (Non Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	1			
N/A	5			
UNOB	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Perfusion_Foveal Ischaemia (Study Eye)

End point title	Retinal Perfusion_Foveal Ischaemia (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	3			
N/A	4			
UNOB	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Perfusion_Macular Ischaemia (Non Study Eye)

End point title	Retinal Perfusion_Macular Ischaemia (Non Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	2			
N/A	4			
UNOB	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Perfusion_Peripheral Ischaemia (Study Eye)

End point title	Retinal Perfusion_Peripheral Ischaemia (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	3			
N/A	4			
UNOB	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Retinal Perfusion_Peripheral Ischaemia (Non Study Eye)

End point title	Retinal Perfusion_Peripheral Ischaemia (Non Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Extension	0			
Reduction	0			
No Change	3			
N/A	3			
UNOB	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Tear Production (Study Eye)

End point title	Tear Production (Study Eye)

End point description:

The Schirmer test will be performed to measure tear production. The test will be undertaken by a Research Nurse at baseline and at week 12. If a further visit at week 16 is undertaken, this test will be also performed at this additional visit. This is a safe test which poses no risk to the patient. A negative test result is normal i.e. more than 10mm of moisture on the filter paper in 5 minutes. As both eyes normally secrete the same amount of tears, this test will be only done in the study eye (see Statistical Considerations section). This test will be done following completion of all functional tests (i.e. BCVA and microperimetry). This test is included as patients with DR often complain of dry eyes, most likely related to reduced corneal nerve fibre density.

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: mm				
arithmetic mean (standard deviation)	13.4 (± 8.8)	13.8 (± 2.4)		

Statistical analyses

Statistical analysis title	95% Confidence Intervals
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.6
upper limit	6.3
Variability estimate	Standard deviation
Dispersion value	7.7

Secondary: Suicide Ideation

End point title	Suicide Ideation

End point description:

Suicidal ideation will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) which will be administered to patients at baseline and weeks 4, 8 and 12. If at 12 weeks the retina is dry a further visit at week 16 will be arranged and questionnaires completed.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: N/A				
Yes	0	0		
No	9	8		

Statistical analyses

No statistical analyses for this end point

Secondary: NEI VFQ-25

End point title	NEI VFQ-25

End point description:

The NEI VFQ-25 is a vision specific patient reported quality of life tool. This validated questionnaire has been used widely to evaluate visual outcomes in patients with eye diseases including DR. In addition to eliciting information about general health and vision it specifically addresses difficulty with near vision, distance vision, driving and the effect of light conditions on vision. This provides a comprehensive evaluation of vision related quality of life.

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: N/A				
arithmetic mean (standard deviation)				
General Health	47.2 (± 29.2)	46.9 (± 20.9)		
General Vision	64.4 (± 21.9)	70.0 (± 10.7)		
Ocular Pain	70.8 (± 22.5)	85.9 (± 10.4)		
Near Activities	69.9 (± 23.2)	80.2 (± 18.9)		
Distance Activities	80.1 (± 22.2)	85.4 (± 16.5)		
Social Functioning	91.7 (± 16.5)	98.4 (± 4.4)		
Mental Health	71.5 (± 27.6)	84.4 (± 12.9)		
Role Difficulties	79.2 (± 23.4)	92.2 (± 13.3)		
Dependency	84.3 (± 24.1)	92.7 (± 15.1)		
Driving	93.1 (± 8.2)	94.4 (± 6.8)		
Colour Vision	94.4 (± 16.7)	96.9 (± 8.8)		
Peripheral Vision	80.6 (± 24.3)	84.4 (± 12.9)		
Composite Score	79.0 (± 20.1)	87.5 (± 6.9)		

Statistical analyses

Statistical analysis title	95% Confidence Interval_General Health
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-6.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.8
upper limit	12.3
Variability estimate	Standard deviation
Dispersion value	22.2

Statistical analysis title	95% Confidence Interval_General Vision
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.9
upper limit	8.9
Variability estimate	Standard deviation
Dispersion value	10.7

Statistical analysis title	95% Confidence Interval_Ocular Pain
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	18.6
Variability estimate	Standard deviation
Dispersion value	11.1

Statistical analysis title	95% Confidence Interval_Near Activities
Comparison groups	Baseline - ARA290 v 12 Week - ARA290

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	6.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.1
upper limit	26.6
Variability estimate	Standard deviation
Dispersion value	24.3

Statistical analysis title	95% Confidence Interval_Distance Activities
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.8
upper limit	11.8
Variability estimate	Standard deviation
Dispersion value	14.1

Statistical analysis title	95% Confidence Interval_Social Functioning
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.1
upper limit	8.3
Variability estimate	Standard deviation
Dispersion value	8

Statistical analysis title	95% Confidence Interval_Mental Health

Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	14.9
Variability estimate	Standard deviation
Dispersion value	11.3

Statistical analysis title	95% Confidence Interval_Role Difficulties
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	9.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4
upper limit	22.8
Variability estimate	Standard deviation
Dispersion value	16

Statistical analysis title	95% Confidence Interval_Dependency
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.4
upper limit	10.5
Variability estimate	Standard deviation
Dispersion value	11.3

Statistical analysis title	95% Confidence Interval_Driving
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.8
upper limit	11.6
Variability estimate	Standard deviation
Dispersion value	9.7

Statistical analysis title	95% Confidence Interval_Colour Vision
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	4.3
Variability estimate	Standard deviation
Dispersion value	8.8

Statistical analysis title	95% Confidence Interval_Peripheral Vision
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	10.3
Variability estimate	Standard deviation
Dispersion value	16

Statistical analysis title	95% Confidence Interval_Composite Score
Comparison groups	Baseline - ARA290 v 12 Week - ARA290
Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	2.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	10
Variability estimate	Standard deviation
Dispersion value	3.1

Secondary: EQ-5D-5L	
End point title	EQ-5D-5L
End point description:	
A generic health status measure EQ-5D-5L will be used to generate utility data. Total scores will be recorded and used for the analysis.	
End point type	Secondary
End point timeframe:	
Change from baseline to week 12 (+/- 7 days)	

End point values	Baseline - ARA290	12 Week - ARA290		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	8		
Units: N/A				
arithmetic mean (standard deviation)	0.7 (± 0.4)	0.8 (± 0.3)		

Statistical analyses

Statistical analysis title	95% Confidence Interval_Index
Comparison groups	Baseline - ARA290 v 12 Week - ARA290

Number of subjects included in analysis	17
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.1
Variability estimate	Standard deviation
Dispersion value	0.2

Secondary: % of participants with >= 10 letter gain (Study Eye)

End point title	% of participants with >= 10 letter gain (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Yes	0			
No	8			

Statistical analyses

No statistical analyses for this end point

Secondary: % of participants with >= 10 letter gain (Non Study Eye)

End point title	% of participants with >= 10 letter gain (Non Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Yes	1			
No	7			

Statistical analyses

No statistical analyses for this end point

Secondary: % of participants with >= 15 letter gain (Study Eye)

End point title	% of participants with >= 15 letter gain (Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Yes	0			
No	8			

Statistical analyses

No statistical analyses for this end point

Secondary: % of participants with >= 15 letter gain (Non Study Eye)

End point title	% of participants with >= 15 letter gain (Non Study Eye)

End point description:

End point type	Secondary

End point timeframe:

Change from baseline to week 12 (+/- 7 days)

End point values	Baseline - ARA290			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: N/A				
Yes	1			
No	7			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting period began upon enrolment into the trial and ended 30 days following the last administration of the study drug.
Each participant was assessed for AEs by telephone 4 weeks after they received the final dose of study drug.

Adverse event reporting additional description:

Participants administered the first dose of ARA 290 at the first study visit. These participants were contacted by phone 2 weeks later to assess them for adverse events (AE). Participants were again assessed in person for AEs at each study visit and again by telephone 4 weeks after the last dose of ARA 290 was taken.

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Intervention

Reporting group description:

Subcutaneous daily administration of ARA 290 in a dose of 4mg for 12 weeks

Serious adverse events	Intervention		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Intervention		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 9 (100.00%)		
Investigations			
GGT Increased			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Abnormal blood test results			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration site conditions			
Head cold			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	5		
Flu symptoms			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Raised Reticulocytes level			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Eye disorders			
Drop in visual acuity			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Flashing lights			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Pneumonia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Skin and subcutaneous tissue disorders Facial Sunburn subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	1 / 9 (11.11%) 1		
Infections and infestations Infections - other subjects affected / exposed occurrences (all)	2 / 9 (22.22%) 2		
Metabolism and nutrition disorders Hypertriglyceridaemia subjects affected / exposed occurrences (all) Hyperglycaemia subjects affected / exposed occurrences (all) Hypoglycaemia subjects affected / exposed occurrences (all) Metabolism and nutrition disorders - other subjects affected / exposed occurrences (all)	5 / 9 (55.56%) 5 3 / 9 (33.33%) 3 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 November 2015	AMENDMENT 1: Sponsor requested changes: Protocol: -Amended from v1.0 to v2.0 to add advice re the process for recording and reporting of urgent safety measures. Protocol v2.0 to v3.0 to update study schematic to include pregnancy test and to update Recording and Reporting of Urgent Safety Measures to bring the wording in line with Sponsor SOPs. GP Letter: Amended from v1.0 to v2.0 to advise that ARA 290 may have a possible improvement on the patient's glucose levels which may lead to the necessity to amend the patient's diabetes medicine accordingly. Change of CI/PI address updated. Patient Information Sheet: Amended from v1.0 to v2.0 to explain to the participant why they are being asked to complete the C-SSRS questionnaire to ascertain their mental health status. Amended from v2.0 to v3.0 to advise the patient that ARA 290 may have a possible improvement on the patient's glucose levels which may lead to the necessity to amend their diabetes medicine accordingly. ORECNI requested changes: Consent Form: Amended from v1.0 to v2.0 to remove the "witness" signature line. MHRA requested changes: Protocol: Amended from v1.0 to v2.0: •To add the exclusion: "Men who have a female partner and who are unwilling to undertake adequate precautions to prevent pregnancy for the duration of the trial" •A pregnancy test was added for females of child bearing age and advice on contraceptive use and pregnancy reporting added. •The change of address for the CI, Research Nurse and co-investigator was updated. •Advice added that Araim Pharmaceuticals, Inc. may also request consent to collect confidential information about the patient's health and that of the baby in the event of pregnancy. -Study Drug Admin Guidelines: Amended from v1.0 to v2.0 to explain that the study drug should be injected immediately after reconstituting the study drug or discarded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

06 May 2016	As ARA 290 had not been trialled at a dose of 4mg for the study intervention period of 84 days, the study DMEC requested a staggered start to the study to minimise the risk to patient safety. To comply with this the first 2 patients were recruited and recruitment was put on hold until the DMEC had reviewed the data for these patients. Patients 3 and 4 were then recruited and recruitment was put on hold until the data for patients 1 to 4 was reviewed. Patients 5 and 6 were then recruited and recruitment was put on hold until the DMEC had reviewed the data for patients 1 - 6, at this point the DMEC advised that recruitment of patients 7 - 10 could progress. Patients 7 – 9 were recruited, however this delay in recruitment led to the expiry of the study drug. When 9 out of the target of 10 patients had been recruited it became apparent that it would not be possible to recruit patient 10 and have them complete the 84 day treatment period before the expiry of the stock of study drug. The study CI approached Araim Pharmaceuticals (study drug provider) to request an additional 84 day pack of the study drug to allow recruitment of patient 10 to continue. Araim Pharmaceuticals declined to provide this additional study drug, stating that all supplies of ARA 290 were committed to another study. After lengthy discussions between Araim and the study Sponsor it was reluctantly agreed to complete the trial with patient 9 and to report the study as an early termination on the basis that the 10th patient would not be recruited. The date of "end of complete trial" and "date of early termination" reflect the date of database closure as per end of trial definition in the study protocol. A sample size of 10 was considered sufficient to provide an indication of a potential beneficial effect of the drug on the outcomes investigated and further information on safety of ARA 290 in a diabetic population. Nine rather than ten subjects will still be sufficient to meet the objectives.	-

Notes:

Limitations and caveats

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

Early termination of study - 9 out of the intended target of 10 patients recruited. As per protocol the study drug was stopped for patient 3 due to a 10 letter deterioration in sight. Data for this patient is only available up to week 4.

Notes: