Clinical trial results:
Neurokinin 3 Receptor Antagonism as a Novel Treatment for Menopausal Hot Flushes

Summary

EudraCT number	2015-001553-32
Trial protocol	GB
Global end of trial date	30 April 2018

Results information

Result version number	v1 (current)
This version publication date	31 August 2019
First version publication date	31 August 2019
Summary attachment (see zip file)	End of Study Report (End of study report NK3R Antagonist Study.pdf)

Trial information

Trial identification

Sponsor protocol code	MR/M024954/1

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Imperial College London
Sponsor organisation address	JRCO, Charing Cross Hospital, Fulham Palace Road, London, United Kingdom,
Public contact	Research Governance Manager, Imperial College London, 44 2033110205, becky.ward@imperial.ac.uk
Scientific contact	Research Governance Manager, Imperial College London, 44 2033110205, becky.ward@imperial.ac.uk

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 April 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate if AZD4901 is effective in reducing the frequency of menopausal hot flushes by mean Hot Flush (HF) frequency per day (HF/day).

Protection of trial subjects:

Trial subjects undergo regular blood test monitoring and clinical reviews with the investigators to ensure adequate protection of trial subjects. The independent data monitoring committee provides oversight for ensuring any deviation from the protocol is reported and that the protocol is complied with.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2015
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: 37
Worldwide total number of subjects	37
EEA total number of subjects	37

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)	37
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants will be recruited from the UK and will be screened for inclusion commencing in February 2016, until sufficient numbers of participants have been recruited.

Pre-assignment

Screening details:

Study participants will be menopausal women aged 40-62 years with >7HF/day some of which are reported as severe or bothersome who have not been on treatment for menopausal symptoms for the preceding 8 weeks.
Eligibility will be determined after a visit with a doctor who will perform a health check including history, examination and blood tests.

Period 1

Period 1 title	1st Intervention
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

All authors, participants, and trial staff were masked until completion of the study. Unmasking only occurred once all participants had completed the study, and all data had been entered into the electronic case record forms. To ensure safety in the case of a medical emergency, code break packs with individual scratch off panels were held but were never required.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active drug

Arm description:

NK3R antagonist - AZD4901 - 40mg bd - for 4 weeks

Arm type	Experimental
Investigational medicinal product name	AZD4901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg BD

Arm title	Placebo

Arm description:

Placebo - 40mg bd - for 4 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg twice daily.

Number of subjects in period 1	Active drug	Placebo
Started	20	17
Completed	17	15
Not completed	3	2
Physician decision	1	-
Consent withdrawn by subject	1	2
Adverse event, non-fatal	1	-

Period 2

Period 2 title	2nd Intervention
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

All authors, participants, and trial staff were masked until completion of the study. Unmasking only occurred once all participants had completed the study, and all data had been entered into the electronic case record forms. To ensure safety in the case of a medical emergency, code break packs with individual scratch off panels were held but were never required.

Arms

Are arms mutually exclusive?	Yes
Arm title	Active drug

Arm description:

NK3R antagonist - AZD4901 - 40mg bd - for 4 weeks

Arm type	Experimental
Investigational medicinal product name	AZD4901
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg BD

Arm title	Placebo

Arm description:

Placebo - 40mg bd - for 4 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

40mg twice daily.

Number of subjects in period 2	Active drug	Placebo
Started	17	15
Completed	16	12
Not completed	1	3
Physician decision	1	3

Baseline characteristics

Reporting groups	
Reporting group title	Active drug
Reporting group description:	
NK3R antagonist - AZD4901 - 40mg bd - for 4 weeks	
Reporting group title	Placebo
Reporting group description:	
Placebo - 40mg bd - for 4 weeks	

Reporting group values	Active drug	Placebo	Total
Number of subjects	20	17	37
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age 40-62 years	20	17	37
Gender categorical Units: Subjects			
Female	20	17	37
Male	0	0	0

End points

End points reporting groups

Reporting group title	Active drug
Reporting group description: NK3R antagonist - AZD4901 - 40mg bd - for 4 weeks	
Reporting group title	Placebo
Reporting group description: Placebo - 40mg bd - for 4 weeks	
Reporting group title	Active drug
Reporting group description: NK3R antagonist - AZD4901 - 40mg bd - for 4 weeks	
Reporting group title	Placebo
Reporting group description: Placebo - 40mg bd - for 4 weeks	

Primary: Total Number of Hot Flushes During the Final Week of Both Treatment Periods.

End point title	Total Number of Hot Flushes During the Final Week of Both Treatment Periods.
End point description: To ensure accurate records, participants recorded their flushes in real time using either a tally chart on a piece of paper (n=34) or an application on their smartphone such as Tally Counter (Pixel Research Labs, Minneapolis-Saint Paul, MN, USA; n=3), and then collated their total number of flushes twice daily on waking to record previous overnight symptoms and before bed to record daytime symptoms.	
End point type	Primary
End point timeframe: 4 weeks	

End point values	Active drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Number				
arithmetic mean (confidence interval 95%)	19.35 (15.99 to 23.42)	49.01 (40.81 to 58.56)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - Active drug vs Placebo
Statistical analysis description: Whole group ITT analysis irrespective of treatment assignment order using adjusted means from crossover analysis with 95% CIs: percentage change in total no. hot flush frequency during final week of 4 week treatment period with MLE4901 and placebo compared with total no. hot flush frequency during the final week of the 2 week baseline period.	
Comparison groups	Active drug v Placebo

Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	generalised linear mixed model with a Po

Secondary: Hot Flush Severity

End point title	Hot Flush Severity

End point description:

HF severity (rated as 1-nil, 2-mild, 3-moderate, 4-severe, as per Joffe 2014) will be recorded twice daily (day/night as described above for HF frequency). The data will be analysed as detailed above for the HF frequency

End point type	Secondary

End point timeframe:

14 weeks.

End point values	Active drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: numerical rating of severity by particip				
arithmetic mean (confidence interval 95%)	3.27 (2.92 to 3.66)	5.70 (5.09 to 6.38)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - Active drug vs Placebo
Comparison groups	Active drug v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Hot Flush Bother

End point title	Hot Flush Bother

End point description:

HF bother (rated as 1-none, 2-a little, 3-moderate, 4-a lot, as per Joffe 2014) will be recorded twice daily (day/night as described above for HF frequency). The data will be analysed as detailed above for the HF frequency.

End point type	Secondary

End point timeframe:

14 weeks

End point values	Active drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Bother score on a scale recorded by part				
arithmetic mean (confidence interval 95%)	2.92 (2.61 to 3.27)	5.56 (4.96 to 6.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - Active Drug vs Placebo
Comparison groups	Placebo v Active drug
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Hot Flush Interference

End point title	Hot Flush Interference

End point description:

HF interference (Hot Flash Related Daily Interference Scale, as per Carpenter 2001) will be recorded daily at bedtime. The data will be analysed as detailed above for the HF frequency.

End point type	Secondary

End point timeframe:

14 weeks

End point values	Active drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Score by participant on 'interference sc				
arithmetic mean (confidence interval 95%)	7.94 (5.76 to 10.95)	26.48 (20.02 to 35.03)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - Active Drug vs Placebo
Comparison groups	Active drug v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Secondary: Skin Conductance Monitor Data.	
End point title	Skin Conductance Monitor Data.
End point description:	
End point type	Secondary
End point timeframe:	
14 weeks	

End point values	Active drug	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	17		
Units: Number hot flushes detected by monitor				
arithmetic mean (confidence interval 95%)	16.22 (13.99 to 18.8)	26.91 (23.16 to 31.27)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 - Active Drug vs Placebo
Comparison groups	Active drug v Placebo
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 10 weeks	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	10.0
Reporting groups	
Reporting group title	Subjects affected vs at risk

Reporting group description: -

Serious adverse events	Subjects affected vs at risk		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 37 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Subjects affected vs at risk		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 37 (8.11%)		
Hepatobiliary disorders			
transaminase elevations by treatment and CTCAE grade	Additional description: Transient transaminase rise (alanine aminotransferase [ALT] greater than aspartate aminotransferase [AST]) with a normal bilirubin following treatment with AZD4901		
subjects affected / exposed	3 / 37 (8.11%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The number of participants was small, short treatment duration, and higher than anticipated dropout rate. A larger and longer trial is needed to establish whether the treatment effect is long lasting in a greater number of individual

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29533369

http://www.ncbi.nlm.nih.gov/pubmed/28385352