Clinical trial results:
Effects of anti-TSLP on airway hyperresponsiveness and mast cell phenotype in asthma
- A randomized double-blind, placebo-controlled trial of MEDI9929

The UPSTREAM study

Summary

EudraCT number	2015-005542-56
Trial protocol	DK
Global end of trial date	14 November 2019
Results information	
Result version number	v1 (current)
This version publication date	06 August 2021
First version publication date	06 August 2021
Summary attachment (see zip file)	UPSTREAM trial ERJ 2021 (Sverrild et al. UPSTREAM. Eur Respir J 2021.pdf)

Trial information

Trial identification	
Sponsor protocol code	ESR-15-10870
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02698501
WHO universal trial number (UTN)	-

Notes:

Sponsors	
Sponsor organisation name	Bispebjerg Hospital, lungemedicinsk afdeling
Sponsor organisation address	Ebba Lunds vej 48, København NV, Denmark, 2400
Public contact	Asger Sverrild, Copenhagen University Hospital Bispebjerg, 45 35313569, asger.sverrild@regionh.dk
Scientific contact	Asger Sverrild, Copenhagen University Hospital Bispebjerg, 45 35313569, asger.sverrild@regionh.dk

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	01 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2019
Global end of trial reached?	Yes
Global end of trial date	14 November 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether airway hyperresponsiveness to mannitol decreases in response to treatment with MEDI9929 in patients with asthma

Protection of trial subjects:

Serial ECGs, physical examinations, blood samples, vital parameters and systematic collection of information on any adverse event

Background therapy:

Inhaled corticosteroids +/- long-acting beta2-agonists +/- leucotriene receptor modifiers +/- long-acting muscarinic antagonists

Evidence for comparator:

According to Global Initiative for Asthma (GINA), the selected group of patients on GINA-step 2-to-4 would otherwise have to be treated with the above mentioned background therapy

Actual start date of recruitment	01 April 2016
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	Denmark: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	35
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited through advertisement in newspapers and online as well as through advertising in the outpatient clinic.

Pre-assignment

Screening details:

84 were assessed for eligibility

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Independent pharmacists at The Hospital Pharmacy at the Capital Region of Denmark dispensed either placebo or tezepelumab according to a computer-generated randomisation list (www.randomization.com). The allocation sequence was blinded from all staff at the study site and was kept in envelopes with aluminium foil inside to render the envelope impermeable to intense light. Patients, investigators, and study site staff, laboratory technicians responsible for processing samples

Arms

Are arms mutually exclusive?	Yes
Arm title	Active - tezepelumab

Arm description:

intravenous tezepelumab 700 mg in 100ml 5% dextrose

Arm type	Experimental
Investigational medicinal product name	tezepelumab
Investigational medicinal product code	MEDI9929 anti-TSLP mAb (AMG157)
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

700mg administered over 60 minutes

Arm title	Placebo

Arm description:

intravenous placebo in 100ml 5% dextrose

Arm type	Placebo
Investigational medicinal product name	5% dextrose
Investigational medicinal product code	5% dextrose
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

100ml administered over 60 minutes

Number of subjects in period 1	Active - tezepelumab	Placebo
Started	20	20
Completed	20	19
Not completed	0	1
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Active - tezepelumab
Reporting group description: intravenous tezepelumab 700 mg in 100ml 5% dextrose	
Reporting group title	Placebo
Reporting group description: intravenous placebo in 100ml 5% dextrose	

Reporting group values	Active - tezepelumab	Placebo	Total
Number of subjects	20	20	40
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	42	40	
standard deviation	± 20	± 15	-
Gender categorical Units: Subjects			
Female	11	12	23
Male	9	8	17

End points

End points reporting groups

Reporting group title	Active - tezepelumab
Reporting group description: intravenous tezepelumab 700 mg in 100ml 5% dextrose	
Reporting group title	Placebo
Reporting group description: intravenous placebo in 100ml 5% dextrose	

Primary: Change in PD15 to inhaled mannitol from baseline to week-12

End point title	Change in PD15 to inhaled mannitol from baseline to week-12
End point description: change in PD15 (expressed as doubling doses) to inhaled mannitol from baseline to week-12	
End point type	Primary
End point timeframe: 12 weeks	

End point values	Active - tezepelumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: doubling dose				
log mean (confidence interval 95%)	1.9 (1.2 to 2.5)	1.0 (0.3 to 1.6)		

Statistical analyses

Statistical analysis title	change in PD15 from baseline to week-12
Statistical analysis description: mean change in log2 PD15 from baseline to week-12 adjusting for baseline log2PD15 and ICS (high/low)	
Comparison groups	Active - tezepelumab v Placebo
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.06
Method	Mixed models analysis

Primary: Number of mannitol test negative at week-12

End point title	Number of mannitol test negative at week-12

End point description:

End point type	Primary

End point timeframe:
12 weeks

End point values	Active - tezepelumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: number of negative tests	9	3		

Statistical analyses

Statistical analysis title	Number of negative tests at week-12

Statistical analysis description:
the number of subjects who achieved a negative mannitol test (PD15 >635mg) at week-12

Comparison groups	Active - tezepelumab v Placebo
Number of subjects included in analysis	39
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Chi-squared

Secondary: Ratio between geometric means - eosinophils

End point title	Ratio between geometric means - eosinophils

End point description:
change in airway tissue eosinophils from baseline to week-12

End point type	Secondary

End point timeframe:
12 weeks

End point values	Active - tezepelumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: ratio between geometric means				
number (confidence interval 95%)	0.26 (0.13 to 0.54)	1.28 (0.61 to 2.70)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ratio between geometric means - mast cells

End point title	Ratio between geometric means - mast cells

End point description:

Change in airway tissue mast cells from baseline to week-12

End point type	Secondary

End point timeframe:

12 weeks

End point values	Active - tezepelumab	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: ratio between geometric means				
number (confidence interval 95%)	0.75 (0.53 to 1.06)	1.18 (0.82 to 1.69)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from signing informed consent to last visit	
Assessment type	Systematic
Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	2020
Reporting groups	
Reporting group title	placebo
Reporting group description: -	
Reporting group title	tezepelumab
Reporting group description: -	

Serious adverse events	placebo	tezepelumab	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	1 / 20 (5.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Respiratory, thoracic and mediastinal disorders			
Asthma	Additional description: hospitalised due to asthma exacerbation		
subjects affected / exposed	0 / 20 (0.00%)	1 / 20 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
influenza	Additional description: admitted to hospital due to influenza A and respiratory worsening		
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: admitted due to pneumonia		
subjects affected / exposed	1 / 20 (5.00%)	0 / 20 (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	placebo	tezepelumab	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 20 (65.00%)	12 / 20 (60.00%)	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 20 (20.00%)	3 / 20 (15.00%)	
occurrences (all)	4	3	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	3 / 20 (15.00%)	5 / 20 (25.00%)	
occurrences (all)	3	5	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	7 / 20 (35.00%)	9 / 20 (45.00%)	
occurrences (all)	7	9	

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

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34049943