Clinical trial results:
Lung Clearance Index as an OUTcome parameter to detect the efficacy f Aztreonam Lysine Inhalation in cystic fibrosis patients with near normal spirometry - an observational proof-of concept study

Summary

EudraCT number	2013-004295-35
Trial protocol	AT
Global end of trial date	11 July 2017

Results information

Result version number	v1 (current)
This version publication date	27 January 2023
First version publication date	27 January 2023

Trial information

Trial identification

Sponsor protocol code	LCI-OUT

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Medical University Innsbruck
Sponsor organisation address	Christoph-Probst-Platz 1, Innrain 52, Innsbruck, Austria, 6020
Public contact	Clinical Trial Center, Medical University Innsbruck, Department of Child and Adolescent Health, Paediatrics III, +43 (0)512 9003 70086, KKS-Innsbruck@i-med.ac.at
Scientific contact	Clinical Trial Center, Medical University Innsbruck, Department of Child and Adolescent Health, Paediatrics III, +43 (0)512 9003 70086, KKS-Innsbruck@i-med.ac.at

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	31 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 May 2016
Global end of trial reached?	Yes
Global end of trial date	11 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the changes in lung clearance index before and after each 4-week-on/4-week-off cycle of different inhaled antibiotics

Protection of trial subjects:

The standard inhaled antibiotic was tobramycin in all subjects, with n = 5 subjects using TOBI Podhaler® 112 mg BID and n = 3 inhaling TOBI® 300 mg/5 ml nebuliser solution BID. Since previous authors had reported comparable safety and efficacy profiles of the two tobramycin treatments, we analysed the combined results from both treatments.

Background therapy:

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Evidence for comparator:

This single-centre, observational, open-label, feasibility study compared two treatment phases, each consisting of 4-week on/off-cycles with inhaled antibiotics: Phase 1, weeks 0 to 8: standard inhaled antibiotic (tobramycin/TOBI® 300mg/5ml BID or TOBI Podhaler® 112mg BID), and Phase 2, weeks 8 to 16: AZLI 75 mg TID. ALZI was provided by Gilead Sciences, the manufacturer of AZLI.

Actual start date of recruitment	15 November 2013
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	Austria: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	1

Adults (18-64 years)	7
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The patient recruitment period was from June 2014 to January 2016.

Pre-assignment

Screening details:

The main inclusion criteria were: clinically stable patients aged ≥ 12 years with CF, FEV1 ≥ 75% of the predicted normal value, chronic P. aeruginosa lung infection, and at least two previous on/off cycles or > 8 weeks of continuous inhaled antibiotic treatment with tobramycin.

Period 1

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

Arms

Arm title	TOBI

Arm description:

Phase 1, weeks 0 to 8: standard inhaled antibiotic (tobramycin/TOBI1 300mg/5ml BID or TOBI Podhaler1 112mg. For each patient, the study started at the end of a 4-week off-period without standard inhaled antibiotic (“washout”).

Arm type	Active comparator
Investigational medicinal product name	Tobramycin Sulfate
Investigational medicinal product code	
Other name	Tobi
Pharmaceutical forms	Nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

300 mg/5 ml BID

Investigational medicinal product name	Tobramycin
Investigational medicinal product code	
Other name	TOBI Podhaler®
Pharmaceutical forms	Powder for nebuliser solution
Routes of administration	Inhalation use

Dosage and administration details:

112mg/BID

Number of subjects in period 1	TOBI
Started	8
Completed	8

Period 2

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

Arms

Arm title	AZLI

Arm description:

Phase 2, weeks 8 to 16: AZLI 75 mg TID. ALZI was provided by Gilead Sciences, the manufacturer of AZLI. For each patient, the study started at the end of a 4-week off-period without standard inhaled antibiotic (“washout”).

Arm type	Experimental
Investigational medicinal product name	Aztreonam
Investigational medicinal product code	
Other name	Cayston 75 mg
Pharmaceutical forms	Powder for nebuliser suspension
Routes of administration	Inhalation use

Dosage and administration details:

75 mg TID

Number of subjects in period 2	AZLI
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1

Reporting group description: -

Reporting group values	Phase 1	Total	
Number of subjects	8	8	
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)	1	1	
Adults (18-64 years)	7	7	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	28		
full range (min-max)	15 to 49	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	4	4	

End points

End points reporting groups

Reporting group title	TOBI
Reporting group description:	
Phase 1, weeks 0 to 8: standard inhaled antibiotic (tobramycin/TOBI1 300mg/5ml BID or TOBI Podhaler1 112mg. For each patient, the study started at the end of a 4-week off-period without standard inhaled antibiotic ("washout").	
Reporting group title	AZLI
Reporting group description:	
Phase 2, weeks 8 to 16: AZLI 75 mg TID. ALZI was provided by Gilead Sciences, the manufacturer of AZLI. For each patient, the study started at the end of a 4-week off-period without standard inhaled antibiotic ("washout").	

Primary: Lung clearance index (LCI)

End point title	Lung clearance index (LCI)
End point description:	
The primary endpoint was lung clearance index (LCI) measured by nitrogen multiple breath washout using 100% oxygen (EasyOne Pro® LAB MBW Module, ndd Medical Technologies, Zürich, Switzerland), with an upper limit of normal of 7.0	
End point type	Primary
End point timeframe:	
After 4 weeks of AZLI treatment, the primary endpoint LCI improved (i.e. declined) in 7 of 8 patients.	

End point values	TOBI	AZLI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	8		
Units: LCI				
number (not applicable)	1	7		

Statistical analyses

Statistical analysis title	LCI
Statistical analysis description:	
The treatment responses determined with LCI were more favourable after AZLI than after tobramycin (-0.365 vs. +0.120, p = 0.039).	
Comparison groups	TOBI v AZLI
Number of subjects included in analysis	16
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

15.11.2013-31.05.2016

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	5.0

Reporting groups

Reporting group title	Phase 1

Reporting group description:

For each patient, the study started at the end of a 4-week off-period without standard inhaled antibiotic ("washout").

Serious adverse events	Phase 1		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (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	Phase 1		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No AEs or SAEs were observed during this tral.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2016	Extension of study duration

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.

The patients cohort of this single-centre study was small compared to the international, multi-centre pivotal studies. We were unable to recruit the desired number of 10 patients within a reasonable time. This limits the power of the study.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31498805