Clinical trial results:
Phase II-study Anti-inflammatory pulmonal therapy of CF-patients with Amitriptyline and Placebo - a randomised, double-blinded, placebo-controlled, cross over study

Summary

EudraCT number	2006-002259-33
Trial protocol	DE
Global end of trial date	31 July 2007

Results information

Result version number	v1 (current)
This version publication date	29 March 2022
First version publication date	29 March 2022

Trial information

Trial identification

Sponsor protocol code	APA- II

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00515229
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Tübingen
Sponsor organisation address	Geissweg 3 , Tübingen, Germany, 72076
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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	11 May 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2007
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the therapeutic efficacy and safety of Amitriptyline in patients with Cystic Fibrosis (CF)

Protection of trial subjects:

The Helsinki Declaration shall be applied to the clinical trial, as well as Good Clinical Practice (GCP) for conducting clinical trials of medicinal products within the European Community, in its current version. This is a scientific clinical study; the German Medicines Act (AMG) §40 is applicable without restrictions according to section §42. The protocol will be submitted to the Ethics Commission of the Tübingen University Clinical Centre, which is responsible for the principal investigator. In all further proceedings, the investigator at each participating centre will have to submit the protocol to the respective local Ethics Committee. At each individual centre, the study can only begin after the appropriate Ethics Committee has given its approval.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 October 2006
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	Germany: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients will be informed by the investigating physician about side effects and complications of the verum therapy prior to recruitment. All patients were examined after consent has been obtained by the investigating physician to their suitability for this study in terms of the inclusion and exclusion criteria (especially CYP2D6 genotyping).

Pre-assignment

Screening details:

21 cystic fibrosis (CF) patients were screened using the inclusion and exclusion criteria. Nineteen patients were finally enrolled (10 females, 9 males).

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

Blinding implementation details:

The manufacture and distribution of the study medication to the participating pharmacies is handled by the pharmacy facilities of the University of Tuebingen (Fr. Dr. Hartmann). The packaging, blinding, labelling and storage of the medicine at the pharmacy conforms to §10 of the AMG, according to a randomisation list that is only known to the pharmacy. Each individual capsule has a filling volume of 25 mg, 50 mg und 75 mg Amitriptyline and 25 mg placebo.

Arms

Are arms mutually exclusive?	No
Arm title	Amitriptyline arm

Arm description:

The patients were randomly allocated to three treatment groups receiving 2 doses of amitriptyline or placebo once daily for 28 days. Six patients received placebo, 25 mg and 50 mg amitriptyline, six patients received placebo, 25 mg and 75 mg amitriptyline, and another six patients received placebo, 50 mg and 75 mg of amitriptyline.

Arm type	Experimental
Investigational medicinal product name	Amitriptyline
Investigational medicinal product code	549-18-8
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Patients received placebo, 25 mg/d and 50 mg/d amitriptyline, or placebo, 25 mg/d and 75 mg/d amitriptyline, or placebo, 50 mg/d and 75 mg/d amitriptyline.

Arm title	Placebo arm

Arm description:

Patients received either placebo for 28 days and 25 mg of amitriptyline for 28 days and 50 mg for 28 days, or placebo for 28 days and 25 mg of amitriptyline for 28 days and 75 mg for 28 days, or placebo for 28 days and 50 mg of amitriptyline for 28 days and 75 mg for 28 days.

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

Dosage and administration details:

On day 1 of the study, Verum or placebo is administered oral one time daily. For two days at the beginning of each treatment a minimized dosage (25 mg) will be given. The quantity of study medication administered is 25mg, 50 mg or 75 mg of Amitriptyline, 25 mg of Placebo (corn starch). This corresponds to one capsule daily for 28 days.

Number of subjects in period 1	Amitriptyline arm	Placebo arm
Started	19	19
Completed	18	18
Not completed	1	1
Adverse event, non-fatal	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description:

19 adult CF patients were randomly allocated to three treatment groups receiving amitriptyline once daily for 28 days at doses of 25 mg (n=7), 50 mg (n=8), or 75 mg (n=8) or placebo (n=13).

Reporting group values	Overall trial	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Adults (18-64 years)	19	19	
Age continuous Units: years			
arithmetic mean	28.3		
standard deviation	± 10	-	
Gender categorical Units: Subjects			
Female	10	10	
Male	9	9	

End points

End points reporting groups

Reporting group title	Amitriptyline arm

Reporting group description:

The patients were randomly allocated to three treatment groups receiving 2 doses of amitriptyline or placebo once daily for 28 days. Six patients received placebo, 25 mg and 50 mg amitriptyline, six patients received placebo, 25 mg and 75 mg amitriptyline, and another six patients received placebo, 50 mg and 75 mg of amitriptyline.

Reporting group title	Placebo arm

Reporting group description:

Patients received either placebo for 28 days and 25 mg of amitriptyline for 28 days and 50 mg for 28 days, or placebo for 28 days and 25 mg of amitriptyline for 28 days and 75 mg for 28 days, or placebo for 28 days and 50 mg of amitriptyline for 28 days and 75 mg for 28 days.

Subject analysis set title	Amitriptyline 25 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The amitryptiline arm could be divided into 3 subgroups, depending on the dosing levels: 25 mg, 50 mg and 75 mg.

Subject analysis set title	Amitryptiline 50 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The amitryptiline arm could be divided into 3 subgroups, depending on the dosing levels: 25 mg, 50 mg and 75 mg.

Subject analysis set title	Amitryptiline 75 mg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The amitryptiline arm could be divided into 3 subgroups, depending on the dosing levels: 25 mg, 50 mg and 75 mg.

Primary: The primary outcome was the difference of forced expiratory volume in 1 sec (FEV1) at day 14 between amitriptyline and placebo.

End point title	The primary outcome was the difference of forced expiratory volume in 1 sec (FEV1) at day 14 between amitriptyline and placebo.[1]

End point description:

The primary outcome was the difference of FEV1 relative to placebo at day 14 in the per-protocol (PP) group measured by spirometry.

End point type	Primary

End point timeframe:

14 days

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: More information about the statistical analysis can be found in the charts attached

End point values	Placebo arm	Amitriptyline 25 mg	Amitryptiline 50 mg	Amitryptiline 75 mg
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	13	7	8	8
Units: percentage improvement				
arithmetic mean (standard deviation)	-1.2 (± 4)	3 (± 4)	0.7 (± 3)	-0.7 (± 4)

Attachments (see zip file)	Efficacy results and statistical analysis.pdf

Statistical analyses

Statistical analysis title	Statistical analysis amitryptiline 25 mg
Comparison groups	Placebo arm v Amitriptyline 25 mg
Number of subjects included in analysis	20
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.048
Method	t-test, 1-sided

Statistical analysis title	Statistical analysis amitryptiline 50 mg
Comparison groups	Placebo arm v Amitryptiline 50 mg
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.28
Method	t-test, 1-sided

Statistical analysis title	Statistical analysis amitryptiline 75 mg
Comparison groups	Placebo arm v Amitryptiline 75 mg
Number of subjects included in analysis	21
Analysis specification	Post-hoc
Analysis type	non-inferiority
P-value	= 0.79
Method	t-test, 1-sided

Secondary: Ceramide concentrations in respiratory epithelial cells

End point title	Ceramide concentrations in respiratory epithelial cells[2]
End point description:	
Ceramide concentrations in respiratory epithelial cells were measured after 14 days of treatment	
End point type	Secondary
End point timeframe:	
14 days after treatment	

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: More information regarding the statistical analysis can be found in the charts attached

End point values	Amitriptyline arm			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: mg				
arithmetic mean (standard deviation)	2 (± 1.55)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: 28 days	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	1

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

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: Safety results regarding the non-serious adverse events can be found in the attached chart. No serious adverse events were reported in the study.

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/1959019