Clinical trial results:
Pharmacokinetic study with a loading dose of clofazimine in adult patients with nontuberculous mycobacterial disease

Summary

EudraCT number	2021-002062-40
Trial protocol	NL
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	14 September 2024
First version publication date	14 September 2024

Trial information

Trial identification

Sponsor protocol code	UMCN-AKF-21.04

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05294146
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Radboud university medical center
Sponsor organisation address	Geert grooteplein Zuid 10, Nijmegen, Netherlands, 6525GA
Public contact	Rob Aarnouste, Radboud university medical center, +31 243617744, rob.aarnoutse@radboudumc.nl
Scientific contact	Rob Aarnouste, Radboud university medical center, +31 243617744, rob.aarnoutse@radboudumc.nl

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	08 August 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2023
Global end of trial reached?	Yes
Global end of trial date	31 August 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The overarching aim of this study is to contribute to dose optimization of CFZ in the treatment of NTM diseases.

The primary objective of this study is to describe the PK of CFZ, after 4 weeks of treatment with a loading dose regimen of 300 mg once daily, in adult patients with NTM disease.

Protection of trial subjects:

Written informed consent is to be obtained from all subjects prior to any trial procedures being performed. Investigators may discuss the availability of the trial and the opportunity for entry with a potential patient without first obtaining consent. The patients are informed about the study by a letter (PIF) before their first appointment and will be seen by a physician. The investigators have both ethical and legal responsibility to ensure that each patient being considered for inclusion in this trial is given a full explanation of the protocol. This shall be documented on a written Informed Consent Form that shall be approved by the same METC responsible for approval of this protocol. The principal investigator or other study doctor asks for participation. Informed consent is given at least 24 hours later.
In case the medical doctor of the participant is also the investigator, it will be emphasized to the participant that participation in this study is strictly voluntary and that the decision on whether or not to participate will by no means influence the clinical care they will receive. Also, as described in the PIF, participants have the possibility to ask questions to an independent expert.
The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. Only an identification code (i.e., not names) should be recorded on any form submitted to the IEC. The investigator must keep a screening log showing codes, for all patients screened and for all patients enrolled in the study.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	05 April 2021
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	Netherlands: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients will be included at the Radboudumc center of expertise for mycobacterial diseases. Patients from all over the country are referred to the Radboudumc. Informed consent will be obtained at the Radboudumc. We will include all adult patients with NTM disease who are eligible for treatment with CFZ.

Pre-assignment

Screening details:

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- The participant is diagnosed with pulmonary or extrapulmonary NTM disease and is eligible for treatment with CFZ
- The participant is at least 18 years of age

Period 1

Period 1 title	CFZ dosing (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

not applicable

Arms

Are arms mutually exclusive?	No
Arm title	CFZ loading dose

Arm description:

300mg CFZ daily for 28 days

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

Dosage and administration details:

daily use of 3 tablets of 100mg for 28 days, followed by the 100mg daily dose for 14 weeks

Arm title	CFZ standard dose

Arm description:

100mg CFZ daily for 14 weeks

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

Dosage and administration details:

daily use of 3 tablets of 100mg for 28 days, followed by the 100mg daily dose for 14 weeks

Number of subjects in period 1	CFZ loading dose	CFZ standard dose
Started	12	12
Completed	12	8
Not completed	0	4
Adverse event, serious fatal	-	2
Consent withdrawn by subject	-	1
clinical deterioration	-	1

Baseline characteristics

Reporting groups	
Reporting group title	CFZ dosing

Reporting group description: -

Reporting group values	CFZ dosing	Total	
Number of subjects	12	12	
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			
median	69		
full range (min-max)	39 to 82	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	6	6	

End points

End points reporting groups	
Reporting group title	CFZ loading dose
Reporting group description: 300mg CFZ daily for 28 days	
Reporting group title	CFZ standard dose
Reporting group description: 100mg CFZ daily for 14 weeks	

Primary: Cmax	
End point title	Cmax
End point description:	
End point type	Primary
End point timeframe: Day 28 and 4 months	

End point values	CFZ loading dose	CFZ standard dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mg/L				
geometric mean (confidence interval 95%)	0.87 (0.69 to 1.11)	0.96 (0.71 to 1.2)		

Statistical analyses

Statistical analysis title	descriptive
Comparison groups	CFZ loading dose v CFZ standard dose
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	confidence interval
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.11

Adverse events

Adverse events information

Timeframe for reporting adverse events:

entire trial

Assessment type	Non-systematic

Dictionary used

Dictionary name	none
Dictionary version	1

Reporting groups

Reporting group title	all subjects

Reporting group description: -

Serious adverse events	all subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 12 (50.00%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	0		
Gastrointestinal disorders			
nausea and vomiting			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
pulmonary hemorrhage			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
COPD			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Renal and urinary disorders			
tubulo-interstitial nephritis			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Influenza A			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
weight loss, dyspnea			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		

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

Non-serious adverse events	all subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)		
Investigations			
Elektrolyte imbalance			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	10		
Hypoalbuminaemia			
subjects affected / exposed	6 / 12 (50.00%)		
occurrences (all)	8		
Cardiac disorders			
QTc prolongation			
subjects affected / exposed	9 / 12 (75.00%)		
occurrences (all)	9		
Ear and labyrinth disorders			
Ototoxicity			
subjects affected / exposed	12 / 12 (100.00%)		
occurrences (all)	12		
Gastrointestinal disorders			
GI complaints			
subjects affected / exposed	11 / 12 (91.67%)		
occurrences (all)	28		
Skin and subcutaneous tissue disorders			

skin-related subjects affected / exposed occurrences (all)	10 / 12 (83.33%) 20		

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.

no formal statistical test was done, in the statistical analysis section we reported the GM of Cmax and 95%CI of Cmax after the load dose.

Notes: