



## Clinical trial results:

### Intravenous induction therapy followed by oral therapy against exclusive oral therapy: randomized trial for the treatment of Whipple's disease

#### Summary

EudraCT number	2008-003951-54
Trial protocol	DE
Global end of trial date	05 November 2020

#### Results information

Result version number	v1 (current)
This version publication date	04 August 2024
First version publication date	04 August 2024
Summary attachment (see zip file)	Synopsis (Synopsis EudraCT.docx)

#### Trial information

##### Trial identification

Sponsor protocol code	MWD08
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##### Additional study identifiers

ISRCTN number	ISRCTN45658456
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Charité - University medicine Berlin
Sponsor organisation address	Charitéplatz 1, Berlin, Germany, 10117
Public contact	Prof. Dr. Dr. Thomas Schneider, Charité - University medicine Berlin CBF, Medical clinic I, infectious diseases, 0049 84452286, thomas.schneider@charite.de
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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	27 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 November 2020
Global end of trial reached?	Yes
Global end of trial date	05 November 2020
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

Whipple's disease is a fatal infection with *Tropheryma (T.) whipplei* if left untreated. The efficacy of antibiotics in the treatment of Whipple's disease has only been demonstrated in case series and in a study that has only been published as an abstract.

The current treatment of Whipple's disease is therefore empirical, without an evidence-based foundation such as randomised controlled trials. The latter is a systematic problem due to the rarity of the disease. The rarity of the disease is also the reason why the drugs ceftriaxone, hydroxychloroquine, trimethoprim and sulfamethoxazole have not yet been approved.

Here, we wanted to test the non-inferiority of oral antibiotic therapy alone for Whipple's disease compared to a combined therapy of intravenous induction therapy followed by oral maintenance therapy.

Primary endpoint was clinical remission without relapse after 24 months (12 months of treatment and 12 months of follow-up).

Protection of trial subjects:

Regular follow up visits and the possibility for physicians and patients to contact the principle investigator at any time guaranteed safety of the subjects

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 May 2010
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Scientific research
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	43
From 65 to 84 years	17
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The first patient was included on 26.05.2010, the last on 31.08.2018, the last examination as part of the follow-up was on 05.11.2020.

### Pre-assignment

Screening details:

310 patients were screened of whom 64 were assigned to the study. In 4 of the 64 patients, diagnosis could not be confirmed, so that 60 patients with initial diagnosis of WD started the study medication.

### Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

due to the different applications (iv and oral) blinding would have been a challenge.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	arm B

Arm description:

sole oral therapy with doxycycline and hydroxychloroquine

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

Dosage and administration details:

2x 100mg Doxycycline per day

Investigational medicinal product name	Hydroxychloroquine
Investigational medicinal product code	
Other name	Quensyl
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2x 200mg oral per day

Investigational medicinal product name	Trimethoprim Sulfamethoxazol
Investigational medicinal product code	
Other name	Cotrim, Bactrim
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

In case of positive PCR from cerebrospinal fluid 5x oral Trimethoprim Sulfamethoxazol forte (800mg/160mg) per day till PCR-negativity

<b>Arm title</b>	arm A
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Arm description:

Arm A intravenous treatment

Arm type	Control standard treatment
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Investigational medicinal product name	Ceftriaxone
Investigational medicinal product code	
Other name	Rocephine, Cefotrix
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

2g intravenously once a day for 14 days

Investigational medicinal product name	Trimethoprim Sulfamethoxazol
Investigational medicinal product code	
Other name	Cotrim, Bactrim
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2x oral Trimethoprim Sulfamethoxazol forte (800mg/160mg) per day for 12 months

<b>Number of subjects in period 1</b>	arm B	arm A
Started	29	31
Completed	28	24
Not completed	1	7
Adverse event, serious fatal	-	2
Physician decision	1	1
Consent withdrawn by subject	-	1
Pregnancy	-	1
Lost to follow-up	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	arm B
Reporting group description: sole oral therapy with doxycycline and hydroxychloroquine	
Reporting group title	arm A
Reporting group description: Arm A intravenous treatment	

Reporting group values	arm B	arm A	Total
Number of subjects	29	31	60
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)	19	24	43
From 65-84 years	10	7	17
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62	55	
inter-quartile range (Q1-Q3)	56 to 68	49 to 64	-
Gender categorical Units: Subjects			
Female	11	13	24
Male	18	18	36
Height Units: cm			
arithmetic mean	171	169	
inter-quartile range (Q1-Q3)	164 to 173	165 to 178	-
Weight Units: kg			
arithmetic mean	65	62	
inter-quartile range (Q1-Q3)	58 to 78	51 to 68	-
Erythrocyte sedimentation rate Units: mm/h			
arithmetic mean	34.5	62.5	
inter-quartile range (Q1-Q3)	22 to 52	23 to 79	-
C-reactive protein level Units: mg/L			
arithmetic mean	72	76	
inter-quartile range (Q1-Q3)	33 to 98	39 to 118	-

Hemoglobin level			
Units: g/dL			
arithmetic mean	10.8	11.7	
inter-quartile range (Q1-Q3)	9.8 to 12.4	11 to 12.9	-

## End points

### End points reporting groups

Reporting group title	arm B
Reporting group description: sole oral therapy with doxycycline and hydroxychloroquine	
Reporting group title	arm A
Reporting group description: Arm A intravenous treatment	

### Primary: Clinical Remission

End point title	Clinical Remission
End point description: The primary endpoint was clinical complete remission without recurrence during the observation period of 24 months, which required a value of $\leq 2$ of a composite clinical score including WD-specific symptoms, C-reactive protein (CRP), and hemoglobin (Hb). Persistent WD-associated diseases, not indicative for a persistent infection (i.e. osteoarthritis) and irreversible neuronal damage acquired before diagnosis were not considered as treatment failure. Clinical remission was assumed at a score of 0-2, scores $> 2$ indicated failure of clinical remission.	
End point type	Primary
End point timeframe: 24months	

End point values	arm B	arm A		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28	24		
Units: score				
score 0-2	27	20		
score $> 2$	1	4		

### Statistical analyses

Statistical analysis title	non-inferiority testing
Statistical analysis description: Composite outcome of complete clinical remission at 24 months. Point estimates and two-sided 95% confidence intervals are shown for the treatment effect, defined as the risk difference for complete remission between groups in the intention-to-treat (ITT) and per protocol (PP) analysis. The non-inferiority margin for doxycycline and hydroxychloroquine as compared with the combination of ceftriaxone and TMP-SMX was $-18$ percentage points. For ITT and PP analysis, the lower end of the two-sided 95%	
Comparison groups	arm B v arm A



Number of subjects included in analysis	52
Analysis specification	Post-hoc
Analysis type	non-inferiority
Parameter estimate	Risk difference (RD)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.2
upper limit	33.1

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

24 months

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	9.1
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### Reporting groups

Reporting group title	Arm A intravenous
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Reporting group description: -

Reporting group title	arm B oral-only
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Reporting group description: -

Serious adverse events	Arm A intravenous	arm B oral-only	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 31 (41.94%)	8 / 29 (27.59%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
arteria radialis stenosis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
fever			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
excicosis			

subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Cytokine release syndrome			
alternative dictionary used: MedDRA 9.1			
subjects affected / exposed	7 / 31 (22.58%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 11	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Allergic reaction			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast cancer recurrent			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accident at work			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident at home			
subjects affected / exposed	1 / 31 (3.23%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Shock			

subjects affected / exposed	3 / 31 (9.68%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AV block			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
artery temporalis inferior stenosis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Perforation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal transplant			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Hip TEP			
subjects affected / exposed	0 / 31 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia bacterial			
subjects affected / exposed	3 / 31 (9.68%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 29 (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: 1 %

Non-serious adverse events	Arm A intravenous	arm B oral-only	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)	14 / 29 (48.28%)	
Investigations			

Creatine increased subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 29 (3.45%) 1	
Vital capacity abnormal subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 29 (0.00%) 0	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	0 / 29 (0.00%) 0	
Gastrointestinal disorders Vomiting subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	6 / 29 (20.69%) 6	
Tooth discolouration subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	1 / 29 (3.45%) 1	
Skin and subcutaneous tissue disorders Dermatitis allergic subjects affected / exposed occurrences (all)	5 / 31 (16.13%) 5	4 / 29 (13.79%) 4	
Photodermatosis subjects affected / exposed occurrences (all)	1 / 31 (3.23%) 1	9 / 29 (31.03%) 9	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported