



## Clinical trial results: The effect of dicloxacillin on oral absorption of drugs

### Summary

EudraCT number	2021-003814-37
Trial protocol	DK
Global end of trial date	21 June 2022

### Results information

Result version number	v1 (current)
This version publication date	08 June 2023
First version publication date	08 June 2023

### Trial information

#### Trial identification

Sponsor protocol code	AKF-400
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05073627
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	University of Southern Denmark
Sponsor organisation address	J.B. Winsløws Vej 19, 2nd floor, Odense, Denmark,
Public contact	Clinical Pharmacology and Pharmacy, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, +45 65502352 , dbiversen@health.sdu.dk
Scientific contact	Clinical Pharmacology and Pharmacy, Clinical Pharmacology, Pharmacy and Environmental Medicine, University of Southern Denmark, +45 65502352 , dbiversen@health.sdu.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	13 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 June 2022
Global end of trial reached?	Yes
Global end of trial date	21 June 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The primary aim of this study is to investigate if treatment with dicloxacillin can lead to drug-drug interactions through induction of the efflux transporter P-glycoprotein (P-gp).

Protection of trial subjects:

Trial subjects were asked about adverse events during the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 November 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	Denmark: 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)	12
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

We recruited healthy men and women from January 2022 until June 2022. All trial subjects consented to participate in the trial. If in- and exclusion criteria were fulfilled trial subjects were randomized to start in period A or period B. Based on In- and exclusion criteria a medical doctor decided if trial subjects could participate in the trial

### Pre-assignment

Screening details:

Trial subjects were screened based on in and exclusion criteria. A medical doctor decided if trial subjects full-filled the criteria and could enter the trial.

### Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Baseline
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Arm description:

We measured the baseline level of P-gp without intake of dicloxacillin.  
All trial subjects worked as their own control. 5 people started in the Baseline period before entering the treatment period, and 5 people started in the treatment period before entering the Baseline period.  
It has been stated later that 12 people completed the trial. This is not correct. 10 people completed the trial and 2 left due to non-fatal adverse events. Due to an error message, it has not been possible to write this correctly in the boxes below.

Arm type	No administration of drugs
Investigational medicinal product name	Dabigatran etexilate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

150 mg of dabigatran etexilate was administered to trial subjects after fasting.

<b>Number of subjects in period 1</b>	Baseline
Started	12
Completed	12

**Period 2**

Period 2 title	Dicloxacillin
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

**Arms**

<b>Arm title</b>	Dicloxacillin
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Arm description:

Trial subjects ingested dicloxacillin for 30 days. We measured induction of P-gp at 10 days and 28 days.

All trial subjects worked as their own control. 5 people started in the Baseline period before entering the treatment period, and 5 people started in the treatment period before entering the Baseline period.

It has been stated later that 12 people completed the trial. This is not correct. 10 people completed the trial and 2 left due to non-fatal adverse events. Due to an error message, it has not been possible to write this correctly in the boxes below.

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

Dosage and administration details:

During the trial, trial subjects ingested 1 gram dicloxacillin 3 times daily.

<b>Number of subjects in period 2</b>	Dicloxacillin
Started	12
Completed	12

## Baseline characteristics

### Reporting groups

Reporting group title	Baseline
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Reporting group description: -

Reporting group values	Baseline	Total	
Number of subjects	12	12	
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)	0	0	
Adults (18-64 years)	12	12	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
median	24		
inter-quartile range (Q1-Q3)	23 to 25	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	7	7	

## End points

### End points reporting groups

Reporting group title	Baseline
Reporting group description: We measured the baseline level of P-gp without intake of dicloxacillin. All trial subjects worked as their own control. 5 people started in the Baseline period before entering the treatment period, and 5 people started in the treatment period before entering the Baseline period. It has been stated later that 12 people completed the trial. This is not correct. 10 people completed the trial and 2 left due to non-fatal adverse events. Due to an error message, it has not been possible to write this correctly in the boxes below.	
Reporting group title	Dicloxacillin
Reporting group description: Trial subjects ingested dicloxacillin for 30 days. We measured induction of P-gp at 10 days and 28 days. All trial subjects worked as their own control. 5 people started in the Baseline period before entering the treatment period, and 5 people started in the treatment period before entering the Baseline period. It has been stated later that 12 people completed the trial. This is not correct. 10 people completed the trial and 2 left due to non-fatal adverse events. Due to an error message, it has not been possible to write this correctly in the boxes below.	

### Primary: Change in AUC of dabigatran after 28 days of treatment

End point title	Change in AUC of dabigatran after 28 days of treatment
End point description: Reporting group 1 is the change in AUC between baseline and 10 days of dicloxacillin Reporting group 2 is the change in AUC between baseline and 28 days of dicloxacillin	
End point type	Primary
End point timeframe: At baseline and 28 days of dicloxacillin treatment	

End point values	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	0.67 (0.42 to 1.1)	0.72 (0.39 to 1.4)		
Dabigatran etexilate	0.32 (0.13 to 0.79)	0.62 (0.17 to 2.3)		

### Statistical analyses

Statistical analysis title	Geometric mean ratio
Statistical analysis description: There were 10 subjects in this analysis as the study was self-controlled	

Comparison groups	Baseline v Dicloxacillin
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
P-value	> 0.05
Method	No p-value

Notes:

[1] - We did not calculate p-values, but instead, the confidence interval 95%. If the geometric mean ratio contained 1, it was not considered statistically significant.

### Secondary: Change in Cmax of the dabigatran and dabigatran etexilate

End point title	Change in Cmax of the dabigatran and dabigatran etexilate
End point description:	
End point type	Secondary
End point timeframe:	
Comparing data from baseline until day 10 and 28 of dicloxacillin treatment	

End point values	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	0.69 (0.40 to 1.2)	0.71 (0.31 to 1.7)		
Dabigatran etexilate	0.43 (0.23 to 0.82)	0.78 (0.35 to 1.8)		

### Statistical analyses

Statistical analysis title	Geometric mean ratio
Statistical analysis description:	
There were 10 subjects in this analysis as the study was self-controlled	
Comparison groups	Baseline v Dicloxacillin
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 <sup>[2]</sup>
Method	No p-value

Notes:

[2] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical significant

### Secondary: Change in T1/2 of the dabigatran and dabigatran etexilate

End point title	Change in T1/2 of the dabigatran and dabigatran etexilate
End point description:	

End point type	Secondary
End point timeframe:	
Measuring baseline and comparing to 10 and 28 days of dicloxacillin treatment	

End point values	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	0.95 (0.80 to 1.1)	0.99 (0.72 to 1.4)		

### Statistical analyses

Statistical analysis title	Geometric mean ratio
Statistical analysis description:	
There were 10 subjects in this analysis as the study was self-controlled	
Comparison groups	Baseline v Dicloxacillin
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 <sup>[3]</sup>
Method	No p-value

Notes:

[3] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical signific

### Secondary: Change in formation clearance of the dabigatran

End point title	Change in formation clearance of the dabigatran
End point description:	
End point type	Secondary
End point timeframe:	
Measuring baseline and comparing to 10 and 28 days of dicloxacillin treatment	

End point values	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	1.5 (0.95 to 2.4)	1.4 (0.74 to 2.6)		



## Statistical analyses

<b>Statistical analysis title</b>	Geometric mean ratio
Statistical analysis description: There were 10 subjects in this analysis as the study was self-controlled	
Comparison groups	Baseline v Dicloxacillin
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 [4]
Method	No p-value

Notes:

[4] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical signific

## Secondary: change in renal clearance of the dabigatran

End point title	change in renal clearance of the dabigatran
End point description:	
End point type	Secondary
End point timeframe:	
Measuring baseline and comparing to 10 and 28 days of flucloxacillin treatment	

<b>End point values</b>	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	1.0 (0.96 to 1.1)	1.0 (0.86 to 1.2)		

## Statistical analyses

<b>Statistical analysis title</b>	Geometric mean ratio
Statistical analysis description: There were 10 subjects in this analysis as the study was self-controlled	
Comparison groups	Baseline v Dicloxacillin

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 <sup>[5]</sup>
Method	No p-value

Notes:

[5] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical significant

### Secondary: Change in Ae (around in urine) of the dabigatran

End point title	Change in Ae (around in urine) of the dabigatran
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End point description:

End point type	Secondary
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End point timeframe:

Measuring baseline and comparing to 10 and 28 days of dicloxacillin treatment

End point values	Baseline	Dicloxacillin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	10		
Units: Geometric mean ratio				
geometric mean (confidence interval 95%)				
Dabigatran	0.68 (0.43 to 1.1)	0.70 (0.34 to 1.4)		

### Statistical analyses

Statistical analysis title	Geometric mean ratio
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Statistical analysis description:

There were 10 subjects in this analysis as the study was self-controlled

Comparison groups	Baseline v Dicloxacillin
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	> 0.05 <sup>[6]</sup>
Method	No p-value

Notes:

[6] - We did not calculate the p-value. instead we calculated the 95% confidence interval. If the geometric mean ratio CI 95% contained 1 it was not considered statistical significant

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from intake of medicine in the trial and 2 weeks after the last dose

Assessment type	Systematic
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### Dictionary used

Dictionary name	None
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Dictionary version	0
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### Reporting groups

Reporting group title	Ingesting Dicloxacillin
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Reporting group description: -

Serious adverse events	Ingesting Dicloxacillin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (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	Ingesting Dicloxacillin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 12 (91.67%)		
General disorders and administration site conditions			
Pain in esophagus			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Heartburn			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	7 / 12 (58.33%)		
occurrences (all)	7		
Discomfort			
subjects affected / exposed	3 / 12 (25.00%)		
occurrences (all)	3		
Stomach pain			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Infections and infestations			
Vaginal yeast infection			
subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

## 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