Clinical trial results:
pilot study to investigate the effect of e.-coli-nissle as probiotic adjuvant to antidiabetic standard care in patients with diabetic mellitus type 2

Summary

EudraCT number	2014-000936-40
Trial protocol	DE
Global end of trial date	15 December 2015

Results information

Result version number	v1 (current)
This version publication date	27 November 2021
First version publication date	27 November 2021

Trial information

Trial identification

Sponsor protocol code	PUNiDIA-2014

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GWT-TUD GmbH
Sponsor organisation address	Freiberger Str. 33, Dresden, Germany, 01067
Public contact	Medical Consulting, GWT-TUD GmbH, 0049 35125933100, medical.consulting@g-wt.de
Scientific contact	Medical Consulting, GWT-TUD GmbH, +49 35125933100, medical.consulting@g-wt.de

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	28 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2015
Global end of trial reached?	Yes
Global end of trial date	15 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Decrease in HbA1c levels within baseline and end of treatment

Protection of trial subjects:

The conduct of this study was in compliance with the Good Clinical Practice Guidelines and under the guiding principles detailed in the Declaration of Helsinki. The study was also be carried out in keeping with applicable local law(s) and regulation(s).
Mutaflor® contains the bacterium E. coli strain Nissle 1917 (EcN) as active ingredient and is approved under the German Drug Law (AMG). From its use over decades (approx. 90 years) and results of clinical studies, it is known that EcN is very well tolerated in doses of up to 1 x 5 ml/day as a suspension.
Risks associated with additional blood sampling were local hematoma or, very rarely, malpuncture with injury to arteries or nerves. These risks were considered to be low, as the examinations were performed by trained and qualified personnel.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
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	Germany: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	2

From 65 to 84 years	8
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The clinical trial was conducted between September 2014 and December 2015, a total of 18 patients were screened at the Carus General Practitioner's Office at Dresden University Hospital. The study was conducted and completed according to protocol.

Pre-assignment

Screening details:

In total 10 patients were included. The first 5 patients received 1 ml of EcN suspension daily for the entire 24-week treatment period. Based on the first interim results, the dose was increased for the next 5 patients included. They took 5 ml of EcN suspension 5 ml of EcN suspension over the entire treatment period.

Period 1

Period 1 title	Treatment phase (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	1 ml Suspension

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Escherichia coli strain Nissle 1917
Investigational medicinal product code	
Other name	Mutaflor®
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

1 ml of E. coli Nissle 1917 suspension per day over a period of 24 weeks

Arm title	5 ml Suspension

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Escherichia coli strain Nissle 1917
Investigational medicinal product code	
Other name	Mutaflor®
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

5 ml of E. coli Nissle 1917 suspension per day over a period of 24 weeks

Number of subjects in period 1	1 ml Suspension	5 ml Suspension
Started	5	5
Completed	5	5

Baseline characteristics

Reporting groups	
Reporting group title	1 ml Suspension
Reporting group description: -	
Reporting group title	5 ml Suspension
Reporting group description: -	

Reporting group values	1 ml Suspension	5 ml Suspension	Total
Number of subjects	5	5	10
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)	1	1	2
From 65-84 years	4	4	8
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	3	6
Male	2	2	4

End points

End points reporting groups	
Reporting group title	1 ml Suspension
Reporting group description: -	
Reporting group title	5 ml Suspension
Reporting group description: -	

Primary: Decrease of the HbA1c	
End point title	Decrease of the HbA1c
End point description: Change in HbA1c between baseline (visit 2) and EoT (visit 4).	
End point type	Primary
End point timeframe: 24 weeks	

End point values	1 ml Suspension	5 ml Suspension		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	5		
Units: percent				
arithmetic mean (standard deviation)	-0.36 (± 0.54)	-0.14 (± 0.42)		

Statistical analyses

Statistical analysis title	Efficacy analysis
Statistical analysis description: The change in HbA1c between baseline and visit 4 as the primary study endpoint was analyzed using descriptive parameters and progress charts. All descriptive results were made available to the study management for interpretation in order to include group characteristics as well as individual progressions for the evaluation of effectiveness.	
Comparison groups	1 ml Suspension v 5 ml Suspension
Number of subjects included in analysis	10
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Median difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	1-sided
upper limit	0
Variability estimate	Standard deviation

Notes:

[1] - Using these estimators, the study management was able to assess whether adjuvant therapy with E. coli Nissle resulted in an improvement of at least 0.1% or 0.2% in HbA1c at otherwise unchanged standard antidiabetic therapy. The expected decrease in HbA1c of at least 0.1 and 0.2 % was not achieved in both groups of patients.

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from week 0 (visit 1) until week 24 (visit 4)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Overall reported AEs

Reporting group description: -

Serious adverse events	Overall reported AEs		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 10 (10.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Infections and infestations			
Epididymitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall reported AEs		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 10 (60.00%)		
Injury, poisoning and procedural complications			
Ankle distortion			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Reproductive system and breast			

disorders Erectile dysfunction subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Gastrointestinal disorders Reflux esophagitis subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Respiratory, thoracic and mediastinal disorders Coughing subjects affected / exposed occurrences (all)	 2 / 10 (20.00%) 2		
Skin and subcutaneous tissue disorders Exanthema subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1		
Renal and urinary disorders Urinary tract infection subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 3		

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