Clinical trial results:
Clearance of the probiotic strain Escherichia coli Nissle 1917 in the gastrointestinal tract of healthy volunteers

Summary

EudraCT number	2016-001240-19
Trial protocol	BG
Global end of trial date	19 April 2017

Results information

Result version number	v1 (current)
This version publication date	27 December 2018
First version publication date	27 December 2018
Summary attachment (see zip file)	Synopsis (Study_Synopsis_EcN_V1.0_13-Jul-2017.pdf)

Trial information

Trial identification

Sponsor protocol code	CSL16001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Synlogic Inc
Sponsor organisation address	301 Binney Street, Suite 402, Cambridge, United States, 02142
Public contact	Marja Puurunen, Synlogic Inc, 508 6657667, marja@synlogictx.com
Scientific contact	Marja Puurunen, Synlogic Inc, 508 6657667, marja@synlogictx.com

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 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 April 2017
Global end of trial reached?	Yes
Global end of trial date	19 April 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the clearance of Escherichia coli strain Nissle 1917 in the gastrointestinal tract after administration of an oral test preparation containing 2.5-25 x 10^9 CFU (Test IMP: Mutaflor® capsules) after single or multiple dose administrations of one capsule three times daily for 28 days (48 volunteers) or for 1 day (10 volunteers) taken together with meals.

Protection of trial subjects:

standard ICH-GCP guidelines were followed

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 September 2016
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	Bulgaria: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	58
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The recruitment of subjects was performed by the principal investigator from a pool of healthy subjects generally qualified for participation in clinical studies at the clinical center. After receiving a written volunteer information and informed consent form and after all questions were explained by the informing physician, 83 volunteers were aske

Period 1

Period 1 title	Overall Trial (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	Single Dose Arm

Arm description:

10 subjects received single dose

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

Dosage and administration details:

1 mutalfor capsule 3 times in one day

Arm title	Multiple Dose Arm

Arm description:

multiple administrations of one capsule of mutalfor three times daily for 48 days

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

Dosage and administration details:

1 mutalfor capsule 3 times a day x 28 days

Number of subjects in period 1	Single Dose Arm	Multiple Dose Arm
Started	10	48
Completed	10	48

Baseline characteristics

End points

End points reporting groups	
Reporting group title	Single Dose Arm
Reporting group description: 10 subjects received single dose	
Reporting group title	Multiple Dose Arm
Reporting group description: multiple administrations of one capsule of mutalfor three times daily for 48 days	

Primary: a. Percentage of volunteers with a stool sample positive for EcN, 24 weeks after the start of treatment	
End point title	a. Percentage of volunteers with a stool sample positive for EcN, 24 weeks after the start of treatment
End point description:	
End point type	Primary
End point timeframe: 24 weeks after start of treatment	

End point values	Single Dose Arm	Multiple Dose Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	45		
Units: days	10	45		

Statistical analyses

Statistical analysis title	Clearance
Comparison groups	Single Dose Arm v Multiple Dose Arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	yes or no
Point estimate	1
Confidence interval	
level	Other: 99.5 %
sides	1-sided
lower limit	0

Primary: b. Time to no detection of EcN in the stool (2 consecutively negative fecal

samples by qualitative qPCR)	
End point title	b. Time to no detection of EcN in the stool (2 consecutively negative fecal samples by qualitative qPCR)

End point description:

End point type	Primary

End point timeframe:

2 consecutively negative fecal samples by qPCR within 24 weeks of last dose

End point values	Single Dose Arm	Multiple Dose Arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	45		
Units: negative fecal samples				
number (not applicable)	10	45		

Statistical analyses

Statistical analysis title	qPCR
Comparison groups	Single Dose Arm v Multiple Dose Arm
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	yes or no
Point estimate	1
Confidence interval	
level	Other: 99.5 %
sides	1-sided
lower limit	0

Notes:

[1] - yes or no

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation, the time in which adverse events will be documented, for this study is defined as follows: The time that the informed consent is signed by the subject is designated as start of safety data collection. The data collection period

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Non-Serious Adverse Events

Reporting group description:

Non-Serious Adverse Events

Serious adverse events	Non-Serious Adverse Events		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Non-Serious Adverse Events		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 55 (12.73%)		
General disorders and administration site conditions			
Headache	Additional description: 6 subjects		
subjects affected / exposed	6 / 55 (10.91%)		
occurrences (all)	6		
Hepatobiliary disorders			
Elevated Liver Enzymes	Additional description: 1 subject		
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2016	a. Original protocol stated that "the multi-dose group will be dosed first. The single dose group will be dosed after the multi-dose have completed dosing on day 28." As of 45 healthy volunteer subjects in the multi-dose cohort having received Mutaflor with no adverse events after the first day of taking Mutaflor capsules with each meal and for that matter after several days of dosing with Mutalfor, it was determined there was a low safety risk of subjects taking Mutaflor for one day and therefore no reason to wait until all 45 subjects had completed their day 28 dosing before starting the single dose cohort.

Notes:

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.

qPCR assay variability and possibility that subjects had variable/changes in microorganism content in their intestine over time that cross reacted with the probes used in the qPCR assay.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29194983