Clinical trial results:
Open-label, Randomized, Parallel-Group, Exploratory Study to Investigate the Effects of Different Doses of S-adenosyl-L-methionine (SAMe) in Subjects with Nonalcoholic Steatohepatitis (NASH) and non-treated matched healthy volunteers as control group

Summary

EudraCT number	2012-000975-18
Trial protocol	DE
Global end of trial date	25 September 2014

Results information

Result version number	v1 (current)
This version publication date	13 July 2016
First version publication date	13 July 2016
Summary attachment (see zip file)	Abbott M-13 397-CSR synopsis (Abbott M-13 397-CSR synopsis.pdf)

Trial information

Trial identification

Sponsor protocol code	M13-397

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01754714
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Abbott Laboratories GmbH
Sponsor organisation address	Freundallee 9a, Hanover, Germany, 30173
Public contact	Suntje Sander-Struckmeier, Abbott, 0049 511 67500, suntje.sander@abbott.com
Scientific contact	Suntje Sander-Struckmeier, Abbott, 0049 511 67500, suntje.sander@abbott.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	26 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 September 2014
Global end of trial reached?	Yes
Global end of trial date	25 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

NASH subjects
The primary objective of this study is to explore the effects of different doses of SAMe on the liver using the methionine tolerance test. The primary efficacy parameter will be the methionine elimination half-life measured in blood.

Healthy volunteers
Primary Objective:
The healthy volunteer group will serve as control group to establish the reference values for the methionine tolerance test.

Protection of trial subjects:

All study investigators expressly agreed not to disclose the identity of the patients treated and to abide by the confidentiality rules as regards data and information to which they had access by participating in the study.
All the data related to the participating patients were recorded and treated according to the regulatory law of data protection.
All information obtained as a result of this study was considered confidential until the sponsor deemed it appropriate. The investigator could only inform on the study conduct and results to the sponsor, EC, and regulatory authorities.

Background therapy:

None

Evidence for comparator: -

Actual start date of recruitment	27 November 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	France: 24
Country: Number of subjects enrolled	Germany: 49
Country: Number of subjects enrolled	Russian Federation: 18
Worldwide total number of subjects	108
EEA total number of subjects	90

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)	90
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited in 25 sites in Germany (10 sites), Poland (5 sites), Russia (5 sites) and France (5 sites) from 27 Dec 2012 to 25 Sep 2014.

Pre-assignment

Screening details:

During the screening period of 4 wks, NASH subjects were evaluated for eligibility: physical examination, pregnancy test, measurement of vital signs incl. body mass index, assessments of routine laboratory, review of their medical history, concomitant medication, AEs, demographics and alcohol consumption questionnaire.

Period 1

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

Blinding implementation details:

Not applicable.

Arms

Are arms mutually exclusive?	Yes
Arm title	1000 mg SAMe (Sadenosyl- L-methionine)

Arm description:

SAMe 1000 mg: 1000 mg dose group: one 500 mg capsule fasting in the morning and one 500 mg capsule before dinner

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

Dosage and administration details:

The NASH subjects took the tablets while fasting, in the morning and before dinner.

Arm title	1500 mg SAMe

Arm description:

SAMe 1500 mg: 1500 mg dose group: two 500 mg capsules fasting in the morning and one 500 mg capsule before dinner

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

Dosage and administration details:

The NASH subjects took the tablets while fasting, in the morning and before dinner.

Arm title	2000 mg SAMe

Arm description:

SAMe 2000 mg: 2000 mg dose group: two 500 mg capsules fasting in the morning and two 500 mg capsules before dinner

Arm type	Experimental

Investigational medicinal product name	Sadenosyl- Lmethionine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

The NASH subjects took the tablets while fasting, in the morning and before dinner.

Arm title	No Treatment

Arm description:

No study drug was administered

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe
Started	27	27	26
Completed	27	26	24
Not completed	0	1	2
Subject did not take investigational study drug	-	-	2
No data for any postbaseline efficacy assessment	-	1	-

Number of subjects in period 1	No Treatment
Started	28
Completed	27
Not completed	1
Subject did not take investigational study drug	-
No data for any postbaseline efficacy assessment	1

Baseline characteristics

Reporting groups	
Reporting group title	1000 mg SAMe (Sadenosyl- L-methionine)
Reporting group description:	
SAMe 1000 mg: 1000 mg dose group: one 500 mg capsule fasting in the morning and one 500 mg capsule before dinner	
Reporting group title	1500 mg SAMe
Reporting group description:	
SAMe 1500 mg: 1500 mg dose group: two 500 mg capsules fasting in the morning and one 500 mg capsule before dinner	
Reporting group title	2000 mg SAMe
Reporting group description:	
SAMe 2000 mg: 2000 mg dose group: two 500 mg capsules fasting in the morning and two 500 mg capsules before dinner	
Reporting group title	No Treatment
Reporting group description:	
No study drug was administered	

Reporting group values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe
Number of subjects	27	27	26
Age categorical Units: Subjects			
<= 18 years	0	0	0
Between 18 and 65 years	23	24	23
>=65 years	4	3	3
Age continuous Units: years			
arithmetic mean	51.2	50	49.5
standard deviation	± 13.8	± 12.3	± 14.2
Gender categorical Units: Subjects			
Female	15	10	9
Male	12	17	17
Region of Enrollment Units: Subjects			
Russian Federation	5	6	5
Poland	3	2	6
France	6	5	4
Germany	13	14	11

Reporting group values	No Treatment	Total	
Number of subjects	28	108	
Age categorical Units: Subjects			
<= 18 years	0	0	
Between 18 and 65 years	21	91	
>=65 years	7	17	

Age continuous Units: years			
arithmetic mean	56.6		
standard deviation	± 11.6	-	
Gender categorical Units: Subjects			
Female	11	45	
Male	17	63	
Region of Enrollment Units: Subjects			
Russian Federation	2	18	
Poland	6	17	
France	9	24	
Germany	11	49	

End points

End points reporting groups

Reporting group title	1000 mg SAMe (Sadenosyl- L-methionine)
Reporting group description:	
SAMe 1000 mg: 1000 mg dose group: one 500 mg capsule fasting in the morning and one 500 mg capsule before dinner	
Reporting group title	1500 mg SAMe
Reporting group description:	
SAMe 1500 mg: 1500 mg dose group: two 500 mg capsules fasting in the morning and one 500 mg capsule before dinner	
Reporting group title	2000 mg SAMe
Reporting group description:	
SAMe 2000 mg: 2000 mg dose group: two 500 mg capsules fasting in the morning and two 500 mg capsules before dinner	
Reporting group title	No Treatment
Reporting group description:	
No study drug was administered	

Primary: 1. Methionine Elimination Half-life Measured in Blood

End point title	1. Methionine Elimination Half-life Measured in Blood
End point description:	
After the methionine load, blood samples will be obtained at 0.5, 1, 1.5, 3, 4.5, 6, 7.5 and 9 hours. Plasma will be analyzed for methionine.	
End point type	Primary
End point timeframe:	
9 hours	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: hour				
arithmetic mean (standard deviation)	4.29 (± 1.86)	4.66 (± 1.57)	4.25 (± 1.64)	4.26 (± 1.44)

Statistical analyses

Statistical analysis title	Analysis of Methionine Half-life Measured in Blood
Statistical analysis description:	
The SAMe 1000 mg group was compared to the no treatment group, on the 95% CI interval for the difference in the least squares mean.	

Comparison groups	1000 mg SAMe (Sadenosyl- L-methionine) v No Treatment

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.944
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.72
upper limit	0.77

Statistical analysis title	Analysis of Methionine Half-life Measured in Blood

Statistical analysis description:

The SAMe 1500 mg group was compared to the no treatment group, on the 95% CI interval for the difference in the least squares mean.

Comparison groups	No Treatment v 1500 mg SAMe
Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.899
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.82
upper limit	0.72

Statistical analysis title	Analysis of Methionine Half-life Measured in Blood

Statistical analysis description:

The SAMe 2000 mg group was compared to the no treatment group, on the 95% CI interval for the difference in the least squares mean.

Comparison groups	No Treatment v 2000 mg SAMe
Number of subjects included in analysis	51
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	0.42

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	1.2

Secondary: 2. Fasting Methionine Concentration and Area Under Curve (AUC) of Average Methionine Concentration Versus Time Curve.

End point title	2. Fasting Methionine Concentration and Area Under Curve (AUC) of Average Methionine Concentration Versus Time Curve.

End point description:

After the methionine load, blood samples will be obtained at 0.5, 1, 1.5, 3, 4.5, 6, 7.5 and 9 hours. Plasma will be analyzed for methionine.

End point type	Secondary

End point timeframe:

9 hours

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: mcg/mL				
arithmetic mean (standard deviation)				
methionine concentration at week 7 (mcg/mL)	4.02 (± 0.92)	3.81 (± 0.67)	5.68 (± 10.13)	5.62 (± 8.53)
methionine AUC at week 7 (mcg*hr/mL)	440.09 (± 149.96)	399.3 (± 148.9)	425.24 (± 231.88)	460.57 (± 135.63)

Statistical analyses

No statistical analyses for this end point

Secondary: 3. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test

End point title	3. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test

End point description:

Parameters cumulative percentage dose of 13 carbon recovered after 30, 60, 90 minutes (cPDR30, cPDR60, cPDR 90) will be evaluated.

End point type	Secondary

End point timeframe:

90 minutes

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: percentage of recovery				
arithmetic mean (standard deviation)				
13C methionine breath test recovery at 30 min (%)	0.93 (± 0.73)	0.77 (± 0.51)	0.88 (± 0.66)	0.69 (± 0.55)
13C methionine breath test recovery at 60 min (%)	3.66 (± 1.99)	3.49 (± 1.74)	3.61 (± 1.78)	2.98 (± 1.72)
13C methionine breath test recovery at 90 min (%)	6.69 (± 2.75)	6.6 (± 2.56)	6.68 (± 2.48)	5.74 (± 2.56)

Statistical analyses

No statistical analyses for this end point

Secondary: 4. Hepatic Panel (Liver Laboratory Parameters)

End point title	4. Hepatic Panel (Liver Laboratory Parameters)

End point description:

Serum Total Bilirubin (STB), Serum Conjugated Bilirubin (SCB), liver-alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma Glutamyl Transpeptidase (GGT), ALT/AST ratio

End point type	Secondary

End point timeframe:

change from baseline at 6 weeks

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: U/L				
arithmetic mean (standard deviation)				
ALP	1.9 (± 7.9)	-0.1 (± 13.7)	3.4 (± 24.1)	-6 (± 16.9)
ALT	-6.2 (± 19.5)	-6.3 (± 23.5)	-4.9 (± 32.2)	-11.9 (± 33.4)
AST	-5.1 (± 15.7)	-3 (± 16.5)	-1.2 (± 10.7)	-11.6 (± 27.7)
GGT	-1.1 (± 33.7)	-10.6 (± 62.7)	-2.7 (± 35.7)	-12.3 (± 48.1)
ALT/AST ratio	-0.02 (± 0.23)	0.01 (± 0.21)	0.03 (± 0.18)	-0.01 (± 0.27)

Statistical analyses

No statistical analyses for this end point

Secondary: 5. Metabolic Panel (Metabolic Laboratory Parameters)

End point title	5. Metabolic Panel (Metabolic Laboratory Parameters)

End point description:

Fasting lipid profile (cholesterol, HDL (High Density Lipoprotein), LDL (Low Density Lipoprotein)), amino acid profile, homeostasis model assessment (HOMA-R) and fasting glucose.

End point type	Secondary

End point timeframe:

change from baseline at 6 weeks

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: mmol/L				
arithmetic mean (standard deviation)				
Cholesterol (mmol/L)	-0.131 (± 0.593)	0.046 (± 0.921)	-0.265 (± 0.601)	-0.134 (± 0.659)
HDL (mmol/L)	-0.094 (± 0.166)	-0.046 (± 0.254)	-0.098 (± 0.169)	-0.065 (± 0.155)
LDL (mmol/L)	0.125 (± 0.452)	0.182 (± 0.762)	-0.202 (± 0.589)	-0.112 (± 0.558)
HOMA-R (mmol/L)	0.837 (± 13.232)	0.127 (± 3.763)	-1.549 (± 13.321)	3.434 (± 10.837)
Glucose (mmol/L)	-0.068 (± 0.968)	0.49 (± 1.486)	-0.163 (± 1.009)	-0.121 (± 1.61)

Statistical analyses

No statistical analyses for this end point

Secondary: 6. The Metabolic Clearance Rate Measured in the Blood.

End point title	6. The Metabolic Clearance Rate Measured in the Blood.

End point description:

After the methionine load, blood samples will be obtained at 0.5, 1, 1.5, 3, 4.5, 6, 7.5 and 9 hours. Plasma will be analyzed for methionine.

End point type	Secondary

End point timeframe:

9 hours

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: L/h				
arithmetic mean (standard deviation)	8.86 (± 2.93)	9.83 (± 3.27)	10.05 (± 4.32)	8.23 (± 2.3)

Statistical analyses

No statistical analyses for this end point

Secondary: 7. Methionine Volume of Distribution at Week 7 (L)

End point title	7. Methionine Volume of Distribution at Week 7 (L)

End point description:

After the methionine load, blood samples will be obtained at 0.5, 1, 1.5, 3, 4, 5, 6, 7.5 and 9 hours. Plasma will be analyzed for methionine.

End point type	Secondary

End point timeframe:

9 hours

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: liter				
arithmetic mean (standard deviation)	54.4 (± 18.43)	62.84 (± 14.04)	64.58 (± 17.77)	53.98 (± 15.21)

Statistical analyses

No statistical analyses for this end point

Secondary: 8. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test

End point title	8. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test

End point description:

Peak

End point type	Secondary

End point timeframe:

90 minutes

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: Atom %C13				
arithmetic mean (standard deviation)	1.0972 (± 0.0062)	1.0964 (± 0.0052)	1.0964 (± 0.0053)	1.0949 (± 0.0045)

Statistical analyses

No statistical analyses for this end point

Secondary: 9. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test

End point title	9. 13 Carbon (Natural, Stable Isotope of Carbon) Methionine Breath Test
End point description: Time to peak	
End point type	Secondary
End point timeframe: 90 minutes	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: minutes				
median (inter-quartile range (Q1-Q3))	70 (50 to 80)	70 (60 to 90)	70 (50 to 80)	70 (60 to 90)

Statistical analyses

No statistical analyses for this end point

Secondary: 10. Metabolic Panel (Metabolic Laboratory Parameters)

End point title	10. Metabolic Panel (Metabolic Laboratory Parameters)
End point description: Fasting plasma insulin	
End point type	Secondary
End point timeframe: Change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: pmol/L				
arithmetic mean (standard deviation)	0.3 (± 191)	-13.6 (± 115.5)	-13.1 (± 248)	69.1 (± 309)

Statistical analyses

No statistical analyses for this end point

Secondary: 11. Metabolic Panel (Metabolic Laboratory Parameters)

End point title	11. Metabolic Panel (Metabolic Laboratory Parameters)
End point description: glycosylated hemoglobin (HbA1c)	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: percentage				
arithmetic mean (standard deviation)	-0.08 (± 0.28)	-0.06 (± 0.36)	-0.05 (± 0.32)	0.02 (± 0.33)

Statistical analyses

No statistical analyses for this end point

Secondary: 12. Metabolic Panel (Metabolic Laboratory Parameters)

End point title	12. Metabolic Panel (Metabolic Laboratory Parameters)
End point description: Adiponectin	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: mcg/mL				
arithmetic mean (standard deviation)	0.754 (± 4.191)	0.425 (± 1.199)	0.219 (± 1.661)	-0.045 (± 1.515)

Statistical analyses

No statistical analyses for this end point

Secondary: 13. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)

End point title	13. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)
End point description: C-reactive Protein (CRP)	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: nmol/L				
arithmetic mean (standard deviation)	-0.79 (± 15.51)	-0.8 (± 14.9)	-8.02 (± 20.4)	-4.8 (± 12.28)

Statistical analyses

No statistical analyses for this end point

Secondary: 14. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)

End point title	14. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)
End point description: glutathione in erythrocytes	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: mcmol/g				
arithmetic mean (standard deviation)	-0.24 (± 2.06)	-0.21 (± 1.01)	0.05 (± 1.41)	-0.3 (± 1.33)

Statistical analyses

No statistical analyses for this end point

Secondary: 15. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)

End point title	15. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)
End point description: oxidative stress marker (isoprostane level)	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: ng/mg Crea				
arithmetic mean (standard deviation)	-0.223 (± 0.801)	0.116 (± 0.699)	0.29 (± 0.691)	-0.223 (± 0.641)

Statistical analyses

No statistical analyses for this end point

Secondary: 16. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)

End point title	16. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)
End point description: Caspase-cleaved cytokeratin (CK 18)	
End point type	Secondary

End point timeframe:
change from baseline at 6 weeks

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: U/L				
arithmetic mean (standard deviation)	-126.8 (± 401.1)	-136.6 (± 257.3)	-47 (± 157.3)	-143.4 (± 532.5)

Statistical analyses

No statistical analyses for this end point

Secondary: 17. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)

End point title	17. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)
End point description: Hyaluronic acid	
End point type	Secondary
End point timeframe: change from baseline at 6 weeks	

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: ng/mL				
arithmetic mean (standard deviation)	4.67 (± 48.52)	2.03 (± 32.26)	9.4 (± 59.63)	3.02 (± 46.56)

Statistical analyses

No statistical analyses for this end point

Secondary: 18. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)

End point title	18. Immunological/Anti-oxidant Panel (Immunological and Anti-oxidant Laboratory Parameters)

End point description:

Cytokine profile (Interleukin-6, IL-8, IL-10 (IL), Tumor Necrosis Factor (TNF -α), monocyte chemoattractant protein (MCP-1), and Granulocyte-colony stimulating factor (G-CSF).

End point type	Secondary

End point timeframe:

change from baseline at 6 weeks

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27[1]	26	24[2]	27[3]
Units: pg/mL				
arithmetic mean (standard deviation)				
IL-6	0.0603 (± 2.0263)	-0.9254 (± 6.4599)	-1.3194 (± 4.5779)	0.1597 (± 1.6243)
IL-8	-14.41 (± 41.07)	0.65 (± 13.37)	-78.73 (± 187.51)	-6.17 (± 16.94)
IL-10	0.27 (± 0)	-0.045 (± 0.106)	-0.3 (± 0)	1.6 (± 1.146)
TNF-alpha	-0.127 (± 0.414)	-1.083 (± 4.782)	-0.601 (± 2.136)	-0.187 (± 1.114)
MCP-1	-29.75 (± 154.75)	-20.6 (± 79.71)	-40.15 (± 96.21)	-44.51 (± 114.85)
G-CSF	-20 (± 52.8)	-0.5 (± 9.7)	20 (± 0)	0 (± 0)

Notes:

[1] - SD IL-10 not calculated as there was data of only 1 patient available.

[2] - SD IL-10 and G-CSF not calculated as there was data of only 1 patient available.

[3] - G-CSF not calculated as there was no data of patients available.

Statistical analyses

No statistical analyses for this end point

Secondary: 19. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)

End point title	19. Fibrosis and Apoptosis Markers (Fibrosis and Apoptosis Laboratory Markers)

End point description:

Non-invasive test for liver disease (ActiTest)/Fibrotest
FibroTest® : diagnoses hepatic fibrosis ActiTest® : assesses viral necro-inflammatory activity Scores between 0 and 1, the higher the score the worse
The FibroTest score is calculated from the results of a six-parameter blood test, combining six serum markers with the age and gender of the patient:Alpha-2-macroglobulin, Haptoglobin, Apolipoprotein A1, Gamma-glutamyl transpeptidase (GGT), Total bilirubin, and Alanine transaminase (ALT). ALT is used in a second assessment called ActiTest that is part of FibroTest.

End point type	Secondary

End point timeframe:

change from baseline at 6 weeks

End point values	1000 mg SAMe (Sadenosyl- L-methionine)	1500 mg SAMe	2000 mg SAMe	No Treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	27	26	24	27
Units: scores on a scale				
arithmetic mean (standard deviation)				
ActiTest Score	-0.017 (± 0.098)	-0.022 (± 0.137)	-0.002 (± 0.168)	-0.042 (± 0.096)
Fibrotest Score	0.036 (± 0.097)	0.028 (± 0.093)	0.05 (± 0.125)	0.02 (± 0.068)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each subject was evaluated from screening through the safety follow-up telephone call and in the event of premature study termination.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	1000 mg SAMe (Sadenosyl- Lmethionine)

Reporting group description:

SAMe 1000 mg: 1000 mg dose group: one 500 mg capsule fasting in the morning and one 500 mg capsule before dinner

Reporting group title	1500 mg SAMe

Reporting group description:

SAMe 1500 mg: 1500 mg dose group: two 500 mg capsules fasting in the morning and one 500 mg capsule before dinner

Reporting group title	2000 mg SAMe

Reporting group description:

SAMe 2000 mg: 2000 mg dose group: two 500 mg capsules fasting in the morning and two 500 mg capsules before dinner

Reporting group title	No Treatment

Reporting group description:

No study drug was administered

Serious adverse events	1000 mg SAMe (Sadenosyl-Lmethionine)	1500 mg SAMe	2000 mg SAMe
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Head injury	Additional description: head injury and neck injury before start of treatment		
subjects affected / exposed	0 / 27 (0.00%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	No Treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 28 (3.57%)		
number of deaths (all causes)	0		

number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Head injury	Additional description: head injury and neck injury before start of treatment		
subjects affected / exposed	1 / 28 (3.57%)		
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	1000 mg SAMe (Sadenosyl-Lmethionine)	1500 mg SAMe	2000 mg SAMe
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 27 (25.93%)	4 / 27 (14.81%)	7 / 24 (29.17%)
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 27 (7.41%)	1 / 27 (3.70%)	1 / 24 (4.17%)
occurrences (all)	2	2	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 27 (7.41%)	0 / 27 (0.00%)	0 / 24 (0.00%)
occurrences (all)	2	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 27 (0.00%)	1 / 27 (3.70%)	3 / 24 (12.50%)
occurrences (all)	0	1	3
Diarrhoea			
subjects affected / exposed	3 / 27 (11.11%)	2 / 27 (7.41%)	4 / 24 (16.67%)
occurrences (all)	3	2	4

Non-serious adverse events	No Treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 28 (7.14%)		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 28 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			

Fatigue subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 2 / 28 (7.14%) 2 0 / 28 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2012	1. The inclusion criteria regarding the diagnosis of NASH were modified without impacting the scientific value of the study and reliability of the indication. The rationale for this change was that the diagnosis of NASH was modified to take local clinical practice into account without impacting the reliability of the diagnosis of fatty liver disease. 2. The change in exclusion criterion was required due to change in the inclusion criterion. The rationale for this change was that the exclusion criterion of BMI> 40 kg/m2 was removed. 3. The current emergency telephone and fax number of the CRO were added. The rationale for this change was that details of CRO were added which were so far documented in a separate instruction to the sites.
13 August 2012	1. The dose of the stable isotope (methyl-13C)-labeled methionine to be administered during the 13C-methionine breath test was changed from "2 mg/kg body weight" to "200 mg." The rationale for this change was that a standardized test kit of 200 mg substrate was recommended by the manufacturer of the 13C-methionine breath test instead of dosing per kg body weight.
21 September 2012	Inclusion and exclusion criteria altered, clarification that the fibrosis/apoptosis marker CK 18 was to be assessed, Pioglitazone treatment prohibited, removal of text on dietary assessments, text on the Methionine Tolerance Test added, the row 'Collect study drug' in the flow chart of study assessments for NASH subjects was changed from Visit 5b to Visit 5a, text added to Section 7.1, text added to Section 8.1, text on recording of the dietary assessment was replaced by text on a protein equilibration diet, 'Dietary assessment/recording' in the flow charts of study assessments was changed to 'Protein equilibration diet/recording', name change of Abbott Products GmbH to Abbott Laboratoires GmbH.
06 May 2013	The study design was changed to an open-label study instead of a double-blind study and the placebo group was replaced by a group of subjects receiving no treatment. Russia was added to the recruiting countries. The 400 mg SAMe capsules were replaced by 500 mg tablets, which affected the dose groups; i.e., 800 mg was changed to 1000 mg, and 1600 mg was to be changed to 1500 mg. Name change of Drug Supply Management. In Sections 7.2 and 7.4 of the protocol, "Drug Supply Management" was changed to "Clinical Supply management." In the Synopsis heading for the 'Name of Sponsor' was changed from "Abbott Laboratoires GmbH" to Abbott Laboratories GmbH." Change in text on statistical analysis on fixed factors in ANCOVA, blinding, and subject samples. Coeliac disease was added as an exclusion criterion. A BMI of 25 kg/m2 was added as an exclusion criterion instead of BMI of 27 kg/m2. Details on the packaging and labeling were no longer to be specified in the Packaging and Labeling Specifications. Capsule formulation was changed to tablet formulation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
14 May 2013	The study design was changed to an open-label study instead of a double-blind study and the placebo group was replaced by a group of subjects receiving no treatment.	30 September 2013

Notes:

Limitations and caveats

None reported