# 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<br>Units: Subjects | | | |
| <= 18 years | 0 | 0 | 0 |
| Between 18 and 65 years | 23 | 24 | 23 |
| >=65 years | 4 | 3 | 3 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 51.2 | 50 | 49.5 |
| standard deviation | ± 13.8 | ± 12.3 | ± 14.2 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 15 | 10 | 9 |
| Male | 12 | 17 | 17 |
| Region of Enrollment<br>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<br>Units: Subjects | | | |
| <= 18 years | 0 | 0 | |
| Between 18 and 65 years | 21 | 91 | |
| >=65 years | 7 | 17 | |

| | | | |
|---|---|---|---|
| Age continuous<br>Units: years | | | |
| arithmetic mean | 56.6 | | |
| standard deviation | ± 11.6 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 11 | 45 | |
| Male | 17 | 63 | |
| Region of Enrollment<br>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:<br>Time to peak | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>Fasting plasma insulin | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>glycosylated hemoglobin (HbA1c) | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>Adiponectin | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>C-reactive Protein (CRP) | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>glutathione in erythrocytes | |
| End point type | Secondary |
| End point timeframe:<br>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:<br>Hyaluronic acid | |
| End point type | Secondary |
| End point timeframe:<br>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<br>subjects affected / exposed<br>occurrences (all) | 0 / 28 (0.00%)<br>0 | | |
| Gastrointestinal disorders<br>Abdominal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all) | <br><br>2 / 28 (7.14%)<br>2<br><br><br>0 / 28 (0.00%)<br>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.<br>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.<br>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