



Clinical trial results:

Chemopreventive action of Mesalazine on colorectal cancer: a pilot study for an "in vivo" evaluation of the molecular effects on -catenin signaling pathway

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-001351-40 |
| Trial protocol | IT |
| Global end of trial date | 17 June 2016 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 23 September 2017 |
| First version publication date | 23 September 2017 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | MES-CT01 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02077777 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | SOFAR SPA |
| Sponsor organisation address | via Firenze, 40, Trezzano Rosa, Italy, 20060 |
| Public contact | Dipartimento Medico, SOFAR SPA, +39 02 909362291, laura.patrucco@sofarfarm.it |
| Scientific contact | Dipartimento Medico, SOFAR SPA, +39 02 909362291, laura.patrucco@sofarfarm.it |

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 | 16 June 2017 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|--------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 17 June 2016 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to obtain "in vivo" confirmation that mesalazine induces the gene expression of μ -protocadherin and other genes related to the β -catenin signaling pathway in biopsies of normal colonic mucosa collected at the beginning and at the end of the study through molecular analysis (quantitative RT-PCR). Signal variation from baseline was evaluated analyzing the number of times it varies.

Protection of trial subjects:

The study will be performed in accordance with the Declaration of Helsinki (see Appendix 5) approved by the 18th World Medical Assembly (WMA) General Assembly in Helsinki-Finland, June 1964 and amended by the

29th WMA, Tokyo-Japan, October 1975;

35th WMA in Venice-Italy, October 1983;

41st WMA in Hong Kong, September 1989;

48th WMA, Somerset West, Republic of South Africa, October 1996

52nd WMA, Edinburgh, Scotland, October 2000; and the 59th WMA General Assembly, Seoul, Korea, October 2008.

It is mandatory that all considerations about protection of human subjects are carried out in accordance with the Declaration of Helsinki.

The study descriptions was submitted to the IEC before study start.

All patient received all the information about the study and they gave their written acceptance through informed consent signature.

Sponsor provided a full insurance coverage.

All personal data complied with local law for privacy protection. All data recorded has been coded.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 03 January 2013 |
| 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 | Italy: 21 |
| Worldwide total number of subjects | 21 |
| EEA total number of subjects | 21 |

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) | 6 |
| From 65 to 84 years | 15 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study Period: 1 January 2013 (first enrollment); 11 March 2016 (last completed). 1 investigational centre in Italy.

Pre-assignment

Screening details:

Patients screened n.: 21; Patients screening failure No: 0; Patients Randomized: 21; Safety Population: 21; Per protocol population: 18

Period 1

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

Arms

| | |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 5-ASA Group |

Arm description:

Patients treated with Mesalazine 2,4 g/die for 3 months

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Mesalazine |
| Investigational medicinal product code | |
| Other name | Pentacol 800 |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

1 tablet three times a day

| | |
|------------------|--------------------|
| Arm title | No Treatment Group |
|------------------|--------------------|

Arm description:

Patients not treated

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | 5-ASA Group | No Treatment Group |
|---------------------------------------|-------------|--------------------|
| Started | 11 | 10 |
| Completed | 10 | 10 |
| Not completed | 1 | 0 |
| Consent withdrawn by subject | 1 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | 5-ASA Group |
|-----------------------|-------------|

Reporting group description:

Patients treated with Mesalazine 2,4 g/die for 3 months

| | |
|-----------------------|--------------------|
| Reporting group title | No Treatment Group |
|-----------------------|--------------------|

Reporting group description:

Patients not treated

| Reporting group values | 5-ASA Group | No Treatment Group | Total |
|--|-------------|--------------------|-------|
| Number of subjects | 11 | 10 | 21 |
| Age categorical | | | |
| Adult patients (at least 18 years old) | | | |
| 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) | 4 | 2 | 6 |
| From 65-84 years | 7 | 8 | 15 |
| 85 years and over | 0 | 0 | 0 |
| Gender categorical | | | |
| Patients of either sex | | | |
| Units: Subjects | | | |
| Female | 7 | 3 | 10 |
| Male | 4 | 7 | 11 |

End points

End points reporting groups

| | |
|---|--------------------|
| Reporting group title | 5-ASA Group |
| Reporting group description: | |
| Patients treated with Mesalazine 2,4 g/die for 3 months | |
| Reporting group title | No Treatment Group |
| Reporting group description: | |
| Patients not treated | |

Primary: Gene expression levels of μ -protocadherin and other genes

| | |
|---|--|
| End point title | Gene expression levels of μ -protocadherin and other genes |
| End point description: | |
| Molecular analysis (with quantitative RT-PCR) of gene expression levels of μ -protocadherin and other related proteins: Protocadherin 19, Protocadherin 24, Cadherin E, TCF7L2, c-myc, Cyclin D1, P21waf1, VEGF, CD44, Met, KLF4 e CEBP- α . | |
| End point type | Primary |
| End point timeframe: | |
| 3 months after visit 1 | |

| End point values | 5-ASA Group | No Treatment Group | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: N. of signal variations from baseline | | | | |
| arithmetic mean (standard deviation) | 1.03 (\pm 0.52) | 1.07 (\pm 0.39) | | |

Statistical analyses

| | |
|---|----------------------------------|
| Statistical analysis title | Efficacy Results |
| Statistical analysis description: | |
| This pilot study was not formally powered to assess effect and sample size was related to feasibility. The results obtained thus do not have inferential validity. The focus was on descriptive statistics of gene expression of μ -protocadherin and other genes related to the β -catenin signaling pathway evaluated in terms of the number of signal variations from baseline and was analyzed as mean value between right and left colon as well as separately for right and left colon. | |
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[1] |
| P-value | \leq 0.05 |
| Method | ANOVA |

Notes:

[1] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: DNA Depurination

| | |
|---|------------------|
| End point title | DNA Depurination |
| End point description: | |
| Quantification of number of AP sites per 100,000 DNA bp | |
| End point type | Secondary |
| End point timeframe: | |
| 3 months after Visit 1 | |

| End point values | 5-ASA Group | No Treatment Group | | |
|--|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: number of AP sites per 100,000 DNA bp | | | | |
| arithmetic mean (standard deviation) | 2.91 (\pm 1.25) | 2.64 (\pm 0.8) | | |

Statistical analyses

| | |
|--|----------------------------------|
| Statistical analysis title | Efficacy results |
| Statistical analysis description: | |
| The molecular analysis of the depurination levels of DNA considering mean values did not reveal any differences between treatment groups at Visit 2 for AP (/100,000 bp) | |
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[2] |
| P-value | \leq 0.05 |
| Method | t-test, 2-sided |

Notes:

[2] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: DNA Oxidation

| | |
|---|---------------|
| End point title | DNA Oxidation |
| End point description: | |
| Quantification of nanograms of 8-OhdG (8hydroxyguanine) per micrograms of DNA | |
| End point type | Secondary |
| End point timeframe: | |
| 3 months after Visit 1 | |

| End point values | 5-ASA Group | No Treatment Group | | |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: nanograms | | | | |
| arithmetic mean (standard deviation) | 0.03 (± 0.01) | 0.03 (± 0.01) | | |

Statistical analyses

| Statistical analysis title | Efficacy results |
|----------------------------|------------------|
|----------------------------|------------------|

Statistical analysis description:

The molecular analysis of the oxidation considering mean values between right and left colon, right colon only, and left colon only, did not reveal any differences between treatment groups at Visit 2 for AP (/100,000 bp) and ng 8-OHdG (/µg of DNA).

| | |
|---|----------------------------------|
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[3] |
| P-value | ≤ 0.05 |
| Method | t-test, 2-sided |

Notes:

[3] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: Cells expressing Histone H2Axy

| | |
|-----------------|--------------------------------|
| End point title | Cells expressing Histone H2Axy |
|-----------------|--------------------------------|

End point description:

Percentage of cells expressing Histone H2Axy evaluated by immunohistochemical analysis

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

3 months after visit 1

| End point values | 5-ASA Group | No Treatment Group | | |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | | |

Statistical analyses

| Statistical analysis title | Efficacy results |
|----------------------------|------------------|
|----------------------------|------------------|

Statistical analysis description:

The percentage of cells expressing Histone H2Axy by immunohistochemical analysis did not present any substantial between-group differences, with Histones H2Axy values always equal to 0%.

| | |
|-------------------|----------------------------------|
| Comparison groups | 5-ASA Group v No Treatment Group |
|-------------------|----------------------------------|

| | |
|---|-------------------------|
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[4] |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[4] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: Cells expressing Caspase-3

| | |
|------------------------|--|
| End point title | Cells expressing Caspase-3 |
| End point description: | Percentage of cells expressing Caspase-3 evaluated by immunohistochemical analysis |
| End point type | Secondary |
| End point timeframe: | 3 months after visit 1 |

| End point values | 5-ASA Group | No Treatment Group | | |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Efficacy results |
| Statistical analysis description: | The percentage of cells expressing Caspase-3 by immunohistochemical analysis did not present any substantial between-group differences, with Caspase-3 values always equal to 0%. |
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[5] |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[5] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: Cells expressing Ki-67

| | |
|------------------------|--|
| End point title | Cells expressing Ki-67 |
| End point description: | Percentage of cells expressing Ki-67 evaluated by immunohistochemical analysis |
| End point type | Secondary |
| End point timeframe: | 3 months after visit 1 |

| End point values | 5-ASA Group | No Treatment Group | | |
|--------------------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: percentage | | | | |
| arithmetic mean (standard deviation) | 12.75 (± 3.76) | 16.7 (± 4.1) | | |

Statistical analyses

| Statistical analysis title | Efficacy results |
|---|----------------------------------|
| Statistical analysis description: | |
| The percentage of cells expressing Ki-67 by immunohistochemical analysis did not present any substantial between-group differences. | |
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[6] |
| P-value | ≤ 0.05 |
| Method | t-test, 2-sided |

Notes:

[6] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Secondary: Cells expressing µ-protocadherin

| End point title | Cells expressing µ-protocadherin |
|--|----------------------------------|
| End point description: | |
| Percentage of cells expressing µ-protocadherin evaluated by immunohistochemical analysis | |
| End point type | Secondary |
| End point timeframe: | |
| 3 month after visit 1 | |

| End point values | 5-ASA Group | No Treatment Group | | |
|-----------------------------|-----------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 10 | | |
| Units: score | 100 | 100 | | |

Statistical analyses

| Statistical analysis title | Efficacy results |
|----------------------------|------------------|
|----------------------------|------------------|

Statistical analysis description:

The percentage of cells expressing μ -protocadherin by immunohistochemical analysis did not present any substantial between-group differences, with μ -protocadherin score resulted to be equal to 2+ in both groups of patients at both Visits.

| | |
|---|----------------------------------|
| Comparison groups | 5-ASA Group v No Treatment Group |
| Number of subjects included in analysis | 18 |
| Analysis specification | Pre-specified |
| Analysis type | other ^[7] |
| P-value | ≤ 0.05 |
| Method | Wilcoxon (Mann-Whitney) |

Notes:

[7] - Since this was a pilot study and sample size was related to feasibility, a very small number of patients were enrolled into the study: therefore, all the efficacy results are interpreted only with a descriptive meaning.

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:
within 24 hours for Serious adverse event

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | 5-ASA Group |
|-----------------------|-------------|

Reporting group description:

Patient treated with Mesalazine

| | |
|-----------------------|-------------------|
| Reporting group title | Not Treated Group |
|-----------------------|-------------------|

Reporting group description:

Patients Not treated

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: Only one patient in the treatment Group had an adverse event that was serious. No other adverse events (serious or non-serious) were observed.

| Serious adverse events | 5-ASA Group | Not Treated Group | |
|---|----------------|-------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Gastrointestinal disorders | | | |
| Perforation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 10 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events | 5-ASA Group | Not Treated Group | |
|---|----------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 10 (0.00%) | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 30 October 2014 | The presence "Diverticular disease/diverticular colitis" does not contribute to the definition of the study endpoints while is a critical point in the selection of patients, with impact on the duration of the trial. Study duration was amended to prolong the enrollment phase. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported