



## Clinical trial results:

### Thiamin against robust IBD fatigue

- The effect of oral thiamin supplement in 4 weeks to patients with inflammatory bowel disease (IBD) in remission and chronic fatigue.

### A randomised placebo controlled crossover study

#### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2018-002324-17  |
| Trial protocol           | DK              |
| Global end of trial date | 27 October 2020 |

#### Results information

|                                |                   |
|--------------------------------|-------------------|
| Result version number          | v1 (current)      |
| This version publication date  | 25 September 2021 |
| First version publication date | 25 September 2021 |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | TARIF |
|-----------------------|-------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT03634735 |
| WHO universal trial number (UTN)   | -           |

Notes:

##### Sponsors

|                              |                                                                                           |
|------------------------------|-------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Aarhus University Hospital                                                                |
| Sponsor organisation address | Palle Juul-Jensens Boulevard 99, Aarhus N, Denmark, 8230                                  |
| Public contact               | Palle Bager, Aarhus University Hospital, 45 51500697, pallbage@rm.dk                      |
| Scientific contact           | Christian Lodberg Hvas, Aarhus University Hospital, 45 28351839, christian.hvas@auh.rm.dk |

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                       | 01 September 2021 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 27 October 2020   |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 27 October 2020   |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To investigate if the levels of fatigue can be reduced after 4 weeks treatment with Thiamin, among patients with inflammatory bowel disease in remission and chronic fatigue

Protection of trial subjects:

Safety were continuous monitored for all subjects

Background therapy: -

Evidence for comparator: -

|                                                           |                                       |
|-----------------------------------------------------------|---------------------------------------|
| Actual start date of recruitment                          | 27 November 2018                      |
| Long term follow-up planned                               | Yes                                   |
| Long term follow-up rationale                             | Safety, Efficacy, Scientific research |
| Long term follow-up duration                              | 6 Months                              |
| Independent data monitoring committee (IDMC) involvement? | Yes                                   |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Denmark: 40 |
| Worldwide total number of subjects   | 40          |
| EEA total number of subjects         | 40          |

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)                      | 39 |
| From 65 to 84 years                       | 1  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details:

All subjects were included from the outpatient clinic at Aarhus University Hospital, Denmark.

### Pre-assignment

Screening details:

A total of 84 patients were screened. 44 were not included, primary due to: low level of fatigue, fatigue duration or disease activity.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Blinded period                 |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Double blind                   |
| Roles blinded                | Subject, Investigator, Monitor |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | No           |
| <b>Arm title</b>             | Intervention |

Arm description:

Thiamine tablets for 4 weeks.

Daily dose 600 -1800 mg, depending of body weight and gender.

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

Dosage and administration details:

600 - 1800 mg daily

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Placebo tablets for 4 weeks.

The number of tablet taken was depending of body weight and gender and was equal to the number of tablets taken in the intervention arm.

|                                        |          |
|----------------------------------------|----------|
| Arm type                               | Placebo  |
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |          |
| Other name                             |          |
| Pharmaceutical forms                   | Tablet   |
| Routes of administration               | Oral use |

Dosage and administration details:

2 - 6 tablets daily for 4 weeks

| Number of subjects in period 1 | Intervention | Placebo |
|--------------------------------|--------------|---------|
| Started                        | 40           | 40      |
| Completion of the blinded part | 40           | 40      |
| Completed                      | 40           | 40      |

## Period 2

|                              |                         |
|------------------------------|-------------------------|
| Period 2 title               | Unblinded period        |
| Is this the baseline period? | No                      |
| Allocation method            | Randomised - controlled |
| Blinding used                | Not blinded             |

## Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | Intervention |

Arm description:

300 mg thiamine tablets daily for 12 weeks

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

Dosage and administration details:

300 mg daily for 12 weeks

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | No thiamine |
|------------------|-------------|

Arm description:

No thiamine supplementation for 12 weeks

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

| Number of subjects in period 2 | Intervention | No thiamine |
|--------------------------------|--------------|-------------|
| Started                        | 20           | 20          |
| End of open label              | 20           | 20          |
| Completed                      | 20           | 20          |

|                                                                             |                             |
|-----------------------------------------------------------------------------|-----------------------------|
| <b>Period 3</b>                                                             |                             |
| Period 3 title                                                              | Follow up period            |
| Is this the baseline period?                                                | No                          |
| Allocation method                                                           | Non-randomised - controlled |
| Blinding used                                                               | Not blinded                 |
| <b>Arms</b>                                                                 |                             |
| <b>Arm title</b>                                                            | Observation                 |
| Arm description:                                                            |                             |
| All subjects were followed for 6 months after the two interventions studies |                             |
| Arm type                                                                    | No intervention             |
| No investigational medicinal product assigned in this arm                   |                             |

| <b>Number of subjects in period 3</b> | Observation |
|---------------------------------------|-------------|
| Started                               | 40          |
| End of follow up                      | 38          |
| Completed                             | 38          |
| Not completed                         | 2           |
| Lost to follow-up                     | 2           |

## Baseline characteristics

### Reporting groups

|                       |                |
|-----------------------|----------------|
| Reporting group title | Blinded period |
|-----------------------|----------------|

Reporting group description:

40 subjects were enrolled in the intervention trial.

20 subjects were enrolled for one visit only and acted as a control group for the group of 40 subjects

| Reporting group values                                | Blinded period | Total |  |
|-------------------------------------------------------|----------------|-------|--|
| Number of subjects                                    | 40             | 40    |  |
| Age categorical                                       |                |       |  |
| Units: Subjects                                       |                |       |  |
| In utero                                              | 0              | 0     |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0              | 0     |  |
| Newborns (0-27 days)                                  | 0              | 0     |  |
| Infants and toddlers (28 days-23<br>months)           | 0              | 0     |  |
| Children (2-11 years)                                 | 0              | 0     |  |
| Adolescents (12-17 years)                             | 0              | 0     |  |
| Adults (18-64 years)                                  | 39             | 39    |  |
| From 65-84 years                                      | 1              | 1     |  |
| 85 years and over                                     | 0              | 0     |  |
| Gender categorical                                    |                |       |  |
| Units: Subjects                                       |                |       |  |
| Female                                                | 35             | 35    |  |
| Male                                                  | 5              | 5     |  |

## End points

### End points reporting groups

|                                                                                                                                                                                                          |              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| Reporting group title                                                                                                                                                                                    | Intervention |
| Reporting group description:<br>Thiamine tablets for 4 weeks.<br>Daily dose 600 -1800 mg, depending of body weight and gender.                                                                           |              |
| Reporting group title                                                                                                                                                                                    | Placebo      |
| Reporting group description:<br>Placebo tablets for 4 weeks.<br>The number of tablet taken was depending of body weight and gender and was equal to the number of tablets taken in the intervention arm. |              |
| Reporting group title                                                                                                                                                                                    | Intervention |
| Reporting group description:<br>300 mg thiamine tablets daily for 12 weeks                                                                                                                               |              |
| Reporting group title                                                                                                                                                                                    | No thiamine  |
| Reporting group description:<br>No thiamine supplementation for 12 weeks                                                                                                                                 |              |
| Reporting group title                                                                                                                                                                                    | Observation  |
| Reporting group description:<br>All subjects were followed for 6 months after the two interventions studies                                                                                              |              |

### Primary: Fatigue improvement

|                                                                                                                                         |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                                                         | Fatigue improvement |
| End point description:<br>An improvement $\geq 3$ points on the IBD-F, Section I scale was defined as a clinically relevant improvement |                     |
| End point type                                                                                                                          | Primary             |
| End point timeframe:<br>After 4 weeks of treatment compared to placebo                                                                  |                     |

| End point values                   | Intervention    | Placebo         |  |  |
|------------------------------------|-----------------|-----------------|--|--|
| Subject group type                 | Reporting group | Reporting group |  |  |
| Number of subjects analysed        | 40              | 40              |  |  |
| Units: Fatigue severity on a scale |                 |                 |  |  |
| IBD-F, Section I                   | 40              | 40              |  |  |

### Statistical analyses

|                                                                                                                 |                           |
|-----------------------------------------------------------------------------------------------------------------|---------------------------|
| Statistical analysis title                                                                                      | Comparison between groups |
| Statistical analysis description:<br>Change in fatigue severity: intervention period compared to placebo period |                           |
| Comparison groups                                                                                               | Placebo v Intervention    |

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Number of subjects included in analysis | 80                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority                |
| P-value                                 | < 0.001 <sup>[1]</sup>         |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 4.5                            |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | 2.6                            |
| upper limit                             | 6.2                            |

Notes:

[1] - A reduction of fatigue in the intervention period of 4.5 points compared to an increase in fatigue of 0.75 points in the placebo period.

### Primary: Fatigue maintenance

|                                                                                                                            |                     |
|----------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                                            | Fatigue maintenance |
| End point description:                                                                                                     |                     |
| The 20 subjects who were randomised to thiamine 300 mg daily were compared to the 20 subjects who did not receive thiamine |                     |
| End point type                                                                                                             | Primary             |
| End point timeframe:                                                                                                       |                     |
| After 12 weeks of thiamine treatment vs. no thiamine                                                                       |                     |

| End point values            | Intervention    | No thiamine     |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 20              | 20              |  |  |
| Units: Fatigue severity     |                 |                 |  |  |
| IBD.F, Section I            | 20              | 20              |  |  |

### Statistical analyses

|                                         |                                |
|-----------------------------------------|--------------------------------|
| Statistical analysis title              | Comparison between groups      |
| Comparison groups                       | Intervention v No thiamine     |
| Number of subjects included in analysis | 40                             |
| Analysis specification                  | Pre-specified                  |
| Analysis type                           | non-inferiority <sup>[2]</sup> |
| P-value                                 | = 0.75 <sup>[3]</sup>          |
| Method                                  | t-test, 2-sided                |
| Parameter estimate                      | Mean difference (final values) |
| Point estimate                          | 1.4                            |
| Confidence interval                     |                                |
| level                                   | 95 %                           |
| sides                                   | 2-sided                        |
| lower limit                             | -0.6                           |
| upper limit                             | 3.5                            |



|                      |                    |
|----------------------|--------------------|
| Variability estimate | Standard deviation |
| Dispersion value     | 3.5                |

Notes:

[2] - Comparison of the fatigue severity between groups after 12 weeks

[3] - The thiamine group had a mean increase of fatigue of 1.4 points vs. the no thiamine group who had an increase of 1.9. point.

## Adverse events

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### Adverse events information<sup>[1]</sup>

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Timeframe for reporting adverse events:

From study start to end of trial

Adverse event reporting additional description:

Data on adverse events were collected at every visit. Furthermore, the subjects were able to report adverse events at any time during the study period

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

### Dictionary used

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

|                    |     |
|--------------------|-----|
| Dictionary version | 2.1 |
|--------------------|-----|

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

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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: We found no serious adverse events. The number of adverse events were < 5 %

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33210299>