# Clinical Study Report Synopsis

Version/Date: Final report v 1.0 / 30 Jul 2015

## Double-blind, randomised, placebo-controlled, multi-centre phase II study to evaluate the efficacy and safety of three different dosages of oral *Trichuris suis* ova (TSO) suspension in active Crohn's disease

| | |
|---|---|
| **Project No.:** | TSU-2/CDA |
| **EudraCT No.:** | 2006-000720-13 |
| **Acronym:** | TRUST-2 |
| **Short title:** | TSO vs. placebo in active Crohn's disease |
| **Investigational drug:** | *Trichuris suis* embryonated, viable eggs (TSO) suspension |
| **Reference drug:** | Placebo solution |
| **Indication:** | Induction of remission in Crohn's disease |
| **Phase of study:** | II (therapeutic exploratory, proof of concept) |
| **First patient enrolled (screened):** | 16 Nov 2010 |
| **Last patient completed (follow-up):** | 18 Feb 2014 |
| **Date of final report:** | 30 Jul 2015 |

**Sponsor:**

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**GCP Statement:** This study was conducted in compliance with Good Clinical Practices (GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

# SYNOPSIS

| *Name of Sponsor/Company*<br><br>**Dr. Falk Pharma GmbH** | *Individual Study Table*<br><br>*Referring to Part of the Dossier* | *(For National Authority Use only)* |
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**Title of Study:**
Double-blind, randomised, placebo-controlled, multi-centre phase II study to evaluate the efficacy and safety of three different dosages of oral *Trichuris suis* ova (TSO) suspension in active Crohn's disease

**Study Centers:**
In total, 53 centers enrolled patients: 1 center in Austria, 5 centers in the Czech Republic, 2 centers in Denmark, 43 centers in Germany, and 2 centers in Switzerland.

| **Study Period:** | **Phase of Development:** |
|---|---|
| First patient enrolled (screened): 16 Nov 2010<br>Last patient completed (followed-up): 18 Feb 2014 | II (therapeutic exploratory, proof of concept) |

**Objectives:**
Primary:
- To evaluate the efficacy of three doses of oral TSO suspension vs. placebo for the induction of remission in Crohn's disease.

Secondary:
- To study safety and tolerability (adverse events (AEs), laboratory parameters) and immunological effects of TSO suspension,
- To evaluate the mucosal healing rate after 12-week treatment with TSO suspension,
- To assess patients' quality of life (QoL).

**Methodology:**
This was a double-blind, randomised, placebo-controlled, multi-centre, 12-week, comparative, therapeutic exploratory, phase II, dose-finding, proof-of-concept trial. The study was conducted with 4 treatment groups in the form of a parallel group comparison and served to compare 3 dose regimens of oral TSO suspension vs. placebo for the induction of remission in Crohn's disease. The 12-week induction of remission phase was followed by a 4-week follow-up period.
The patients were assigned to one of the four following treatment groups at a rate of 1:1:1:1 in conformity with a randomisation list:
Group A: Suspension of 250 embryonated, viable TSO/15 ml/day fortnightly,
Group B: Suspension of 2500 embryonated, viable TSO/15 ml/day fortnightly,
Group C: Suspension of 7500 embryonated, viable TSO/15 ml/day fortnightly,
Group D: Placebo solution (15 ml/day) fortnightly.
Intake of study medication started at V1 (Baseline). The last dose of study medication was scheduled to be taken at V7 (Day 70).
According to the original Clinical Study Protocol (CSP) a fixed sample size design was used. An adaptive 2-stage group sequential design was introduced with Amendment 2. A second interim analysis was introduced with Amendment 5. Sample size adaptation and treatment arm selection were possible at both interim analyses.

**Number of Patients (Total and for Each Treatment):**
Planned/Adapted during Interim Analyses:
According to the original CSP a fixed sample size design was used. It was planned to randomise a total of 212 patients (53 per treatment group) with a 1:1:1:1 allocation ratio.
According to Amendment 2, the design was changed to an adaptive 2-stage group sequential design.

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The interim analysis was planned after observation of 120 patients, and the final analysis was planned after observation of additional 92 patients who were evaluable in the full analysis set (FAS). Thus, the estimated sample size, without sample size adaptation, was 212 evaluable patients.
According to Amendment 5, a second interim analysis was introduced based on the Independent Data Monitoring Committee (IDMC) recommendation after the first interim analysis. The second interim analysis was planned after observation of 240-250 patients, and the final analysis was planned after observation of additional 150-160 patients who were evaluable in the FAS. Thus, the estimated sample size, without sample size adaptation after the second interim analysis, was approximately 400 evaluable patients.
The first interim analysis was performed on 120 patients in the FAS. It showed no effect in the TSO 250 and TSO 2500 groups and a tendency to an effect in the TSO 7500 group. The study was continued, randomisation to the TSO 250 group was stopped, and a second interim analysis was planned after observation of 240 - 250 patients. The study project team as well as the investigators were not informed which dose group was stopped.
The second interim analysis was performed on 239 patients in the FAS. It showed no effect in the TSO 250, TSO 2500, and TSO 7500 groups. Recruitment to the study was stopped. At the time recruitment was stopped, 13 patients were still in the study. The study was carried on in these patients and the final analysis was performed on a total of 252 evaluable patients in the FAS.

Analyzed in the Final Analysis:

| **Number of patients** | **TSO 250** | **TSO 2500** | **TSO 7500** | **Placebo** | **Total** |
|---|---|---|---|---|---|
| Randomised | 39 | 71 | 72 | 70 | 252 |
| Treated | 39 | 71 | 72 | 70 | 252 |
| Safety | 39 | 71 | 72 | 70 | 252 |
| FAS | 39 | 71 | 72 | 70 | 252 |
| PP | 23 | 51 | 47 | 45 | 166 |

In total, 252 patients received study medication and were included in the safety analysis set (SAF). All patients in the SAF received study medication according to the randomisation list and were included in the FAS. In total 86 patients were excluded from the FAS to form the per-protocol (PP) analysis set: 62 patients due to major protocol deviations, 22 patients due to intake of less than 3 doses of study medication), 18 patients due to premature study termination, and 6 patients due to documentation of EOT/Withdrawal Visit more than 21 days after the last study drug administration (multiple response possible).

**Diagnosis and Main Criteria for Inclusion/Exclusion:**
Main Inclusion Criteria:
- Signed informed consent,
- Man or woman between 18 and 75 years of age,
- Established diagnosis of CD confirmed by endoscopic and histological, or endoscopic and radiological criteria, all of which since at least 3 months prior to Screening,
- Localisation of CD either in terminal ileum (L1), in colon (L2) or ileocolitis (L3), all without upper gastrointestinal involvement (- L4) according to the Montreal classification (2005),
- Crohn's disease activity index (CDAI) ≥220 and ≤350 at Baseline,
- Serum C-reactive protein (CRP) level ≥2 x upper limit of normal (ULN) or stool calprotectin >ULN at Screening.

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Main Exclusion Criteria:

- Known Crohn's lesions in the upper gastrointestinal tract (up to and including the jejunum) with present symptoms,
- Evidence of infectious diarrhoea (i.e., pathogenic bacteria or *Clostridium difficile* toxin in stool culture),
- Abscess, perforation, active fistulas, or active perianal lesions,
- Clinical signs of stricturing disease,
- Treatment with immunosuppressants or anti-cancer drugs, e.g., anti-TNF-α agents, anti-integrin agents, azathioprine or 6-mercaptopurine (6-MP), 6-thioguanine (6-TG), methotrexate, tacrolimus, cyclophosphamide, or cyclosporine within the last 3 months prior to Baseline,
- Treatment with antibiotics (e.g., metronidazole or ciprofloxacin), antiparasitic medications within the last 2 weeks prior to Baseline,
- Treatment with topical or systemic glucocorticosteroid within the last 4 weeks prior to Baseline, or within the last 8 weeks, if patients had been treated for longer than 3 months,
- Patients known to be steroid-dependent or refractory, as defined in ECCO consensus guideline 2010,
- Patients that had been unresponsive to both treatment with a biologic (e.g., anti-TNF-α agents or anti-integrin agents) AND treatment with a thiopurine (i.e., azathioprine, 6-MP, or 6-TG),
- Application of non-steroidal anti-inflammatory drugs (NSAIDs) within 2 weeks before the Baseline Visit for more than 3 consecutive days, except acetylsalicylic acid ≥350 mg/day which was allowed,
- Immunisation with live vaccines within 12 weeks prior to Baseline or during the study.

**Duration of Treatment:**

12 weeks

**Test Drug, Dose and Mode of Administration, Batch Number:**

A) 15 ml suspension of 250 embryonated, viable TSO for oral fortnightly administration

Batch numbers:

| | | |
|---|---|---|
| 910092401 | Manufacturing date: 09/2010 | Expiry date: 10/2011 |
| 911090101 | Manufacturing date: 09/2011 | Expiry date: 01/2012 |
| 911101101 | Manufacturing date: 10/2011 | Expiry date: 12/2012 |

B) 15 ml suspension of 2500 embryonated, viable TSO for oral fortnightly administration

Batch numbers:

| | | |
|---|---|---|
| 910092402 | Manufacturing date: 09/2010 | Expiry date: 10/2011 |
| 911081201 | Manufacturing date: 08/2011 | Expiry date: 01/2012 |
| 911092801 | Manufacturing date: 09/2011 | Expiry date: 12/2012 |
| 912102401 | Manufacturing date: 10/2012 | Expiry date: 01/2014 |

C) 15 ml suspension of 7500 embryonated, viable TSO for oral fortnightly administration

Batch numbers:

| | | |
|---|---|---|
| 910092403 | Manufacturing date: 09/2010 | Expiry date: 10/2011 |
| 911081101 | Manufacturing date: 08/2011 | Expiry date: 01/2012 |
| 911093001 | Manufacturing date: 09/2011 | Expiry date: 12/2012 |
| 912101001 | Manufacturing date: 10/2012 | Expiry date: 01/2014 |

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|---|---|---|
| 912101101 | Manufacturing date: 10/2012 | Expiry date: 01/2014 |

**Reference Drug, Dose and Mode of Administration, Batch Number:**
15 ml placebo solution for oral fortnightly administration
Batch numbers (fictitious batch number: TSU-0509):

| | | |
|---|---|---|
| 910080401 | Manufacturing date: 08/2010 | Expiry date: 10/2011 |
| 910121501 | Manufacturing date: 12/2010 | Expiry date: 01/2012 |
| 911102401 | Manufacturing date: 10/2011 | Expiry date: 12/2012 |
| 912091901 | Manufacturing date: 09/2012 | Expiry date: 03/2014 |

**Criteria for Evaluation:**
Primary Efficacy Variable:
The primary efficacy variable in this clinical trial was the rate of patients with clinical remission at week 12 (last observation carried forward [LOCF]) defined as a CDAI <150.

Major Secondary Efficacy Variables:
- Rate of patients with clinical remission at weeks 2, 4, 6, 8, 10, and 12 (LOCF)
- Rate of patients with a reduction of ≥70 points compared to Baseline in CDAI at week 12 (LOCF),
- Rate of patients with a reduction of ≥100 points compared to Baseline in CDAI at week 12 (LOCF),
- Change of CDAI from Baseline to week 12 (LOCF),
- Change of CRP from Baseline to week 12 (LOCF),
- Change of calprotectin from Baseline to week 12 (LOCF),
- Physician's global assessment (PGA) at week 12 (LOCF),
- Immunological effects,
- Change from Baseline to week 12 (LOCF) in Quality of Life measured by Short Health Scale (SHS) and Gastrointestinal Quality of Life Index (GIQLI).

Safety Variables:
- Adverse events (AEs),
- Vital signs (blood pressure, heart rate) and body weight,
- Haematology, blood chemistry, urinalysis,
- Assessment of tolerability by investigator and patient.

**Statistical Methods:**
For statistical analysis 3 data sets were defined:
- SAF - The safety data set: All randomised patients (as treated) who received at least one dose of study medication and had at least one follow-up value for the safety variables to be analysed,
- FAS – The full analysis data set(all randomised patients (as randomised) who received at least one dose of study medication,
- PP data set – The per-protocol data set: All patients of the FAS who fulfilled all of the major inclusion criteria and none of the major exclusion criteria, who had no major protocol deviation, who were correctly allocated to treatment groups, who had efficacy data after Baseline under study medication (at least one post-baseline CDAI), who administered at least 3 doses of study medication, who were sufficiently compliant concerning administration of study medication, who had the EOT/Withdrawal Visit documented not more than 21 days after last administration of study drug. Premature discontinuations were included only if the reason for discontinuation was lack of

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efficacy, or an AE with certain or probable/likely or possible causal relationship with the study medication, or an intolerable AE which was a deterioration of study disease.

This was an exploratory Phase II study. The aim was to demonstrate superiority of TSO 250, TSO 2500, and TSO 7500 compared to placebo in terms of rate of patients with clinical remission, defined as CDAI <150, at week 12 (LOCF) (primary efficacy variable). The primary efficacy variable was to be analysed for the FAS and for the PP data set. The primary analysis for confirmatory testing was to be based on the FAS.

The analysis consisted of two separate steps. The one-sided significance level for each step was set at 2.5%. Hypothesis testing of the 2nd step was performed only if all hypotheses of the 1st step were rejected. Because of this and the fact that the order of the steps was defined a priori the one-sided probability for a type I error was kept at 2.5%. At the 1st step, each of the active treatment groups were compared to the placebo group, the 2nd step was used for pairwise comparisons among the three active treatment groups. Normal approximation tests for rates were used to test the three null hypotheses on each step against their alternative hypotheses. In order to adjust for multiplicity, a closed testing procedure with the Simes intersection test was employed for hypothesis testing on each step.

The study was conducted using an adaptive 2-stage group sequential design. The interim analysis was planned after observation of 120 patients who were evaluable in the FAS (approximately 30 patients per treatment group). The global null hypothesis was tested and the study could be stopped at the interim analysis if the global test statistic resulting from the inverse normal method exceeded the critical value 2.63246. In this case, it was determined which of the elementary hypothesis could be rejected by the closed testing procedure. If the null hypothesis could not be rejected, the study could be continued with the pre-specified stage 2 sample size of 23 further patients per treatment group, or with a recalculated sample size based on the effect size estimation of the interim analysis. Additionally, an additional interim analysis could be introduced based on IDMC recommendation allowing the same adaptations. The critical value at the final analysis was 1.98747 if no additional interim analysis was introduced. This procedure preserved the overall (experiment-wise) one-sided type I error rate of $\alpha = 0.025$ in a strong sense.

For confirmatory hypothesis testing at the interim analysis as well as at the final analysis, the inverse normal method of combining the p-values of the normal approximation tests for the comparison of rates was used. All p-values resulting from further statistical tests were interpreted in the exploratory sense.

According to the IDMC recommendation, the study was continued, randomisation to the TSO 250 group was stopped, and a second interim analysis was planned after observation of 240-250 patients. The sponsor followed the IDMC recommendation of the second interim analysis and recruitment to the study was stopped for futility. Patients already recruited could continue in the study.

The result of the second interim analysis represented the confirmatory result of the study.

**Summary:**

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Patient Disposition:

A total of 254 patients were enrolled in this study. Thereof 252 patients were randomised and received at least one dose of study medication. Two patients withdrew consent prior to randomisation. A total of 184/252 patients (73.0%) completed the study. The study was prematurely terminated by 68/252 patients (27.0%). Primary reasons for premature termination were lack of efficacy (17.9%, 22.5%, 13.9%, and 22.9%) and lack of patient's cooperation (5.1%, 4.2%, 8.3%, and 1.4%) in the TSO 250, TSO 2500, TSO 7500, and placebo groups, respectively.

| **Demographic and baseline characteristics (FAS)** | | **TSO 250 (n = 39)** | **TSO 2500 (n = 71)** | **TSO 7500 (n = 72)** | **Placebo (n = 70)** | **Total (n = 252)** |
|---|---|---|---|---|---|---|
| **Sex** | | | | | | |
| Male | n (%) | 19 (48.7%) | 29 (40.8%) | 24 (33.3%) | 26 (37.1%) | 98 (38.9%) |
| Female | n (%) | 20 (51.3%) | 42 (59.2%) | 48 (66.7%) | 44 (62.9%) | 154 (61.1%) |
| **Race** | | | | | | |
| White | n (%) | 39 (100.0%) | 70 (98.6%) | 70 (97.2%) | 70 (100.0%) | 249 (98.8%) |
| Hispanic | n (%) | --- | --- | 1 (1.4%) | --- | 1 (0.4%) |
| Arabic | n (%) | --- | 1 (1.4%) | --- | --- | 1 (0.4%) |
| Inuit- | n (%) | --- | --- | 1 (1.4%) | --- | 1 (0.4%) |
| **Age [years]** | Mean (SD) | 37.8 (9.5) | 37.8 (11.0) | 34.8 (11.0) | 37.7 (12.8) | 36.9 (11.3) |
| **Weight [kg]** | Mean (SD) | 70.4 (14.9) | 72.2 (14.6) | 73.9 (18.8) | 71.2 (13.5) | 72.1 (15.7) |
| **BMI [kg/m$^2$]** | Mean (SD) | 23.1 (4.2) | 24.5 (4.6) | 24.9 (5.9) | 24.2 (4.4) | 24.3 (4.9) |
| **Smoking habits** | | | | | | |
| Current | n (%) | 14 (35.9%) | 20 (28.2%) | 21 (29.2%) | 18 (25.7%) | 73 (29.0%) |
| Former | n (%) | 10 (25.6%) | 23 (32.4%) | 18 (25.0%) | 22 (31.4%) | 73 (29.0%) |
| Never | n (%) | 15 (38.5%) | 28 (39.4%) | 33 (45.8%) | 30 (42.9%) | 106 (42.1%) |
| **CDAI at Baseline** | Mean (SD) | 267.3 (40.0) | 265.9 (38.8) | 270.7 (46.8) | 270.6 (46.5) | 268.8 (43.3) |
| | Median | 257.0 | 259.0 | 262.0 | 271.0 | 260.5 |
| | (Range) | (219–394) | (187–360) | (177–368) | (176–406) | (176–406) |
| **Calprotectin at Baseline [µg/g]** | Mean (SD) | 1073 (1473) n=38 | 1614 (2115) n=71 | 1452 (2226) n=71 | 1146 (1846) n=70 | 1355 (1991) n=250 |
| | Median | 551 | 892 | 557 | 503 | 592 |
| | (Range) | (77–6322) | (33–12000) | (56–12000) | (48–12000) | (33–12000) |
| >ULN | n (%) | 38 (97.4%) | 70 (98.6%) | 71 (98.6%) | 69 (98.6%) | 248 (98.4%) |
| >5 x ULN | n (%) | 29 (74.4%) | 58 (81.7%) | 50 (69.4%) | 49 (70.0%) | 186 (73.8%) |
| **CRP at Baseline [mg/l]** | Mean (SD) | 15.3 (22.4) | 18.0 (25.7) | 20.4 (26.1) | 18.9 (24.2) | 18.5 (24.8) |
| | Median | 6.9 | 8.8 | 12.8 | 10.8 | 10.6 |
| | (Range) | (0.1–99.9) | (0.1–135.5) | (0.1–121.2) | (0.1–150.8) | (0.1–150.8) |
| >ULN | n (%) | 22 (56.4%) | 43 (60.6%) | 48 (66.7%) | 47 (67.1%) | 160 (63.5%) |
| >2 x ULN | n (%) | 17 (43.6%) | 32 (45.1%) | 41 (56.9%) | 38 (54.3%) | 128 (50.8%) |
| **CRP >ULN or Calprotectin >5x ULN at Baseline** | n (%) | 31 (79.5%) | 61 (85.9%) | 59 (81.9%) | 54 (77.1%) | 205 (81.3%) |
| **Duration of disease since first symptoms of CD [years]** | Mean (SD) | 11.4 (8.7) n=39 | 9.3 (7.6) n=71 | 8.2 (7.8) n=71 | 11.5 (7.5) n=70 | 9.9 (7.9) n=251 |
| | Median | 9.4 | 8.3 | 6.2 | 10.1 | 8.1 |
| | (Range) | (0.6–32.7) | (0.3–35.3) | (0.3–38.8) | (1.2–31.8) | (0.3–38.8) |
| <5 years | n (%) | 8 (20.5%) | 27 (38.0%) | 30 (41.7%) | 15 (21.4%) | 80 (31.7%) |
| ≥5 years | n (%) | 31 (79.5%) | 44 (62.0%) | 41 (56.9%) | 55 (78.6%) | 171 (67.9%) |
| **Duration of disease since first diagnosis of CD [years]** | Mean (SD) | 8.0 (6.8) | 7.9 (7.8) | 6.4 (6.4) | 9.5 (7.4) | 7.9 (7.2) |
| | Median | 5.9 | 5.6 | 4.1 | 7.2 | 5.9 |
| | (Range) | (0.3–29.1) | (0.0–34.3) | (0.1–30.2) | (0.5–30.7) | (0.0–34.3) |
| <5 years | n (%) | 16 (41.0%) | 33 (46.5%) | 39 (54.2%) | 24 (34.3%) | 112 (44.4%) |

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| ≥5 years | n (%) | 23 (59.0%) | 38 (53.5%) | 33 (45.8%) | 46 (65.7%) | 140 (55.6%) |
| **Case history** | | | | | | |
| Established disease | n (%) | 29 (74.4%) | 41 (57.7%) | 51 (70.8%) | 46 (65.7%) | 167 (66.3%) |
| Chronic course | n (%) | 8 (20.5%) | 19 (26.8%) | 18 (25.0%) | 23 (32.9%) | 68 (27.0%) |
| New diagnosis | n (%) | 2 (5.1%) | 11 (15.5%) | 3 (4.2%) | 1 (1.4%) | 17 (6.7%) |
| **Localisation** | | | | | | |
| Ileocoecal * | n (%) | 18 (46.2%) | 34 (47.9%) | 38 (52.8%) | 37 (52.9%) | 127 (50.4%) |
| Ileocolonic ** | n (%) | 12 (30.8%) | 16 (22.5%) | 16 (22.2%) | 14 (20.0%) | 58 (23.0%) |
| Colonic *** | n (%) | 9 (23.1%) | 13 (18.3%) | 12 (16.7%9 | 12 (17.1%) | 46 (18.3%) |
| **Number of relapses** | | | | | | |
| In the last year before Baseline | Mean (SD) | 0.7 (1.0) n=29 | 0.6 (1.1) n=42 | 0.5 (0.7) n=51 | 0.6 (1.0) n=46 | 0.6 (1.0) n=168 |
| In the second year before Baseline | Mean (SD) | 0.9 (1.0) n=28 | 1.1 (1.3) n=42 | 0.9 (1.2) n=50 | 0.8 (1.0) n=46 | 0.9 (1.2) n=166 |
| In the third year before Baseline | Mean (SD) | 0.5 (0.9) n=28 | 1.0 (1.4) n=42 | 0.7 (1.1) n=50 | 1.1 (1.4) n=46 | 0.8 (1.3) n=166 |
| **Duration of previous acute episode [years]** | Mean (SD) | 0.3 (0.8) n=26 | 1.0 (3.0) n=39 | 0.6 (2.2) n=49 | 0.7 (1.7) n=44 | 0.7 (2.1) n=158 |
| **Duration of previous remission phase [years]** | Mean (SD) | 1.3 (1.5) n=28 | 1.2 (1.2) n=41 | 1.4 (1.7) n=50 | 1.4 (1.3) n=45 | 1.3 (1.5) n=164 |
| **Concomitant treatment** | | | | | | |
| Mesalazine | n (%) | 9 (23.1%) | 16 (22.5%) | 17 (23.6%) | 12 (17.1%) | 63 (23.8%) |

* Inflammation in terminal ileum, neoterminal ileum, and/or coecum only

** Inflammation in terminal ileum, neoterminal ileum, and/or coecum AND in at least one of the following segments: ascending colon, transverse colon, descending colon, sigmoid and/or rectum

*** Inflammation only in at least on eof the following segments: ascending colon, transverse colon, descending colon, sigmoid and/or rectum

Overall, no obvious clinical relevant differences in baseline anamnestic characteristics between treatment groups could be detected.

**Efficacy Results:**

Primary Efficacy Evaluation:

Primary efficacy variable - clinical remission at week 12 (LOCF)

Results of the first and second interim analysis (FAS):

| | **Numbers (%) of patients with clinical remission at week 12 (LOCF)** | | **Difference in proportions compared to placebo** | | **Testing of $H_0$*** | |
|---|---|---|---|---|---|---|
| | **n/N (%)** | **95% CI limits** | **%** | **95% CI limits** | **Critical value to reject $H_0$** | **Overall test statistics** |
| **1st interim analysis** | | | | | | |
| **TSO 250** | 12/30 (40.0%) | [22.5, 57.5] | 6.7 | [-17.7, 31.0] | 2.632 | 0.536 |
| **TSO 2500** | 6/30 (20.0%) | [5.7, 34.3] | -13.3 | [-35.5, 8.8] | 2.632 | -1.168 |
| **TSO 7500** | 16/30 (53.3%) | [35.5, 71.2] | 20.0 | [-4.6, 44.6] | 2.632 | 1.563 |
| **Placebo** | 10/30 (33.3%) | [16.5, 50.2] | | | | |
| **2nd interim analysis** | | | | | | |
| **TSO 250** | 15/39 (38.5%) | [23.2, 53.7] | -5.5 | [-24.9, 13.9] | 1.960 | -0.550 |
| **TSO 2500** | 24/67 (35.8%) | [24.3, 47.3] | -8.1 | [-24.7, 8.5] | 1.960 | -0.956 |
| **TSO 7500** | 31/67 (46.3%) | [34.3, 58.2] | 2.3 | [-14.6, 19.2] | 1.960 | 0.270 |

| *Name of Sponsor/Company* | *Individual Study Table* | *(For National Authority Use only)* |
|---|---|---|
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| ***Trichuris suis* embryonated, viable eggs** | | |

| | | | |
|---|---|---|---|
| **Placebo** | 29/66 (43.9%) | [32.0, 55.9] | |

* Testing of $H_0$ ($\pi_{Pla} > \pi_{Low}$ , $\pi_{Pla} > \pi_{Mid}$ , $\pi_{Pla} > \pi_{High}$) by means of the normal approximation test for rates ($\alpha = 0.025$ one-sided). In order to adjust for multiplicity, a closed testing procedure with the Simes intersection test was used.

At the first interim analysis, none of the overall test statistics exceeded the critical value to reject $H_0$, however, a tendency to an effect of TSO was seen in the TSO 7500 group. Therefore, the IDMC recommended to continue the study, to drop one dose group, and to adapt the sample size of additional 3 x 96 patients in the second sequence, or to plan an additional interim analysis after about further 120 patients.

The IDMC recommendations were implemented in such a way that the study was continued, randomisation to the TSO 250 group was stopped, the study team and investigators were kept blinded of the dose group closed, and a second interim analysis was planned after 240-250 patients were evaluable.

At the second interim analysis, none of the overall test statistics exceeded the critical value to reject $H_0$. As the remission rates of the 4 treatment groups were very similar, the IDMC recommended to stop recruitment to the study for futility reasons. Patients already recruited could continue in the study as no safety concern was seen and in order to generate further valid data.

The IDMC recommendations were implemented in such a way that recruitment to the study was stopped and patients already recruited could continue in the study.

The result of the second interim analysis represented the confirmatory result of the study.

**Results of the final analysis (FAS, PP):**

| | | Numbers (%) of patients with clinical remission at week 12 (LOCF) | | Difference in proportions of patients compared to placebo | | Testing of $H_0$* | |
|---|---|---|---|---|---|---|---|
| | | n/N (%) | 95% CI limits | % | 95% CI limits | Critical value to reject $H_0$ | Overall test statistics |
| **Overall analysis** | | | | | | | |
| **FAS** | **TSO 250** | 15/39 (38.5%) | [23.2, 53.7] | -4.4 | [-23.6, 14.8] | 1.960 | -0.447 |
| | **TSO 2500** | 25/71 (35.2%) | [24.1, 46.3] | -7.6 | [-23.7, 8.4] | 1.960 | -0.931 |
| | **TSO 7500** | 34/72 (47.2%) | [35.7, 58.8] | 4.4 | [-12.0, 20.7] | 1.960 | 0.523 |
| | **Placebo** | 30/70 (42.9%) | [31.3, 54.5] | | | | |
| **PP** | **TSO 250** | 7/23 (30.4%) | [11.6, 49.2] | -20.7 | [-44.5, 3.1] | 1.960 | -1.625 |
| | **TSO 2500** | 19/51 (37.3%) | [24.0, 50.5] | -13.9 | [-33.6, 5.9] | 1.960 | -1.366 |
| | **TSO 7500** | 29/47 (61.7%) | [47.8, 75.6] | 10.6 | [-9.6, 30.8] | 1.960 | 1.024 |
| | **Placebo** | 23/45 (51.1%) | [36.5, 65.7] | | | | |

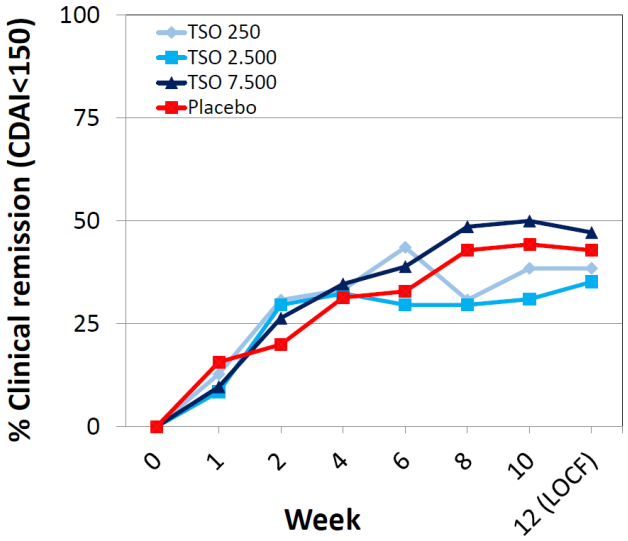
* Testing of $H_0$ ($\pi_{Pla} > \pi_{Low}$ , $\pi_{Pla} > \pi_{Mid}$ , $\pi_{Pla} > \pi_{High}$) by means of the normal approximation test for rates ($\alpha = 0.025$ one-sided). In order to adjust for multiplicity, a closed testing procedure with the Simes intersection test was used.

The final analysis included an overrun of 13 patients.

In the overall analysis, none of the overall test statistics exceeded the critical value to reject $H_0$. Thus, the final analysis confirmed the result of the second interim analysis.

**Secondary Efficacy Evaluation (FAS):**

**Rate of patients with clinical remission at weeks 2, 4, 6, 8, 10, and 12 (LOCF)**




**CDAI reduction ≥70 or ≥100 points at week 12 (LOCF)**

| | Numbers (%) of patients with | | | |
|---|---|---|---|---|
| | **TSO 250 (n = 39)** | **TSO 2500 (n = 71)** | **TSO 7500 (n = 72)** | **Placebo (n = 70)** |
| **CDAI reduction** | | | | |
| ≥70 points | 22/39 (56.4%) | 39/71 (54.9%) | 44/72 (61.1%) | 41/70 (58.6%) |
| ≥100 points | 16/39 (41.0%) | 31/71 (43.7%) | 36/72 (50.0%) | 32/70 (45.7%) |

Proportions of patients with a CDAI reduction ≥70 points or ≥100 points did not show meaningful differences between treatment groups.

**Change in total CDAI from baseline to week 12 (LOCF)**

| | Change from Baseline to week 12 (LOCF) | | Difference in change compared to placebo | | t-test* | |
|---|---|---|---|---|---|---|
| | **Mean (SD)** | **95% CI limits** | **Mean (SD)** | **95% CI limits** | **\| t \|** | **p-value** |
| **Total CDAI** | | | | | | |
| **TSO 250 (n=39)** | -67.3 (100.6) | [-99.9, -34.6] | 15.3 (118.3) | [-31.6, 62.1] | 0.65 | 0.5197 |
| **TSO 2500 (n=71)** | -83.2 (111.6) | [-109.7, -56.8] | -0.7 (119.5) | [-40.5, 39.1] | 0.04 | 0.9719 |
| **TSO 7500 (n=72)** | -101.5 (111.4) | [-127.7, -75.4] | -19.0 (119.3) | [-58.6, 20.6] | 0.95 | 0.3441 |
| **Placebo (n=70)** | -82.5 (127.0) | [-112.8, -52.2] | | | | |

*Comparison of difference in change of total CDAI and individual items of CDAI from Baseline to week 12 (LOCF) between active treatment groups and placebo.

Total CDAI did not show any meaningful differences in changes from Baseline to week 12 (LOCF) between active treatment groups and placebo (p>0.05).

**Calprotectin and C-reactive protein**

| | Mean (SD) change from Screening/Baseline to week 12 (LOCF) | | | |
|---|---|---|---|---|
| | **TSO 250 (n = 39)** | **TSO 2500 (n = 71)** | **TSO 7500 (n = 72)** | **Placebo (n = 70)** |
| **Calprotectin** | 325.1 (1907.8) n=38 | -465.3 (2401.0) n=68 | 182.8 (2394.2) n=68 | 25.8 (1352.6) n=62 |
| **C-reactive protein** | 3.9 (26.4) n=39 | -1.2 (15.7) n=71 | 2.6 (23.8) n=71 | 0.8 (18.8) n=70 |

Calprotectin and C-reactive protein did not show any meaningful differences in changes from Screening/Baseline to week 12 (LOCF) between active treatment groups and placebo.

Physician's Global Assessment (PGA) of efficacy did not show meaningful differences between treatment groups.

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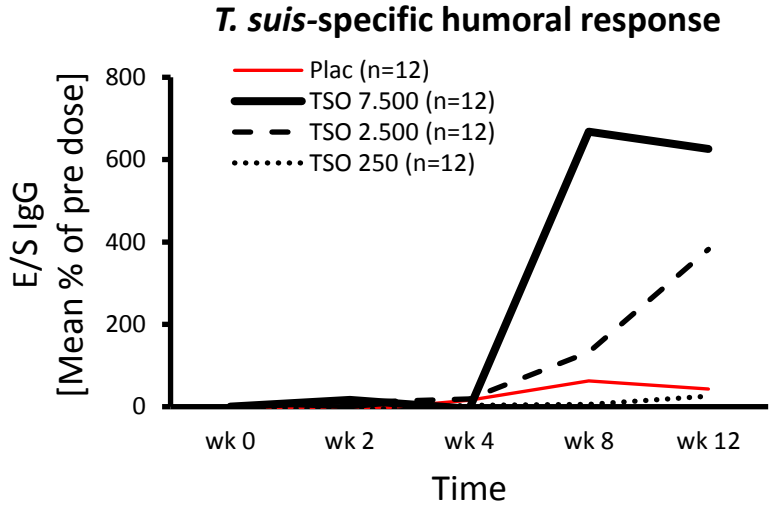
**Immunological Response**

| | Mean (SD) relative change from Baseline | | | |
|---|---|---|---|---|
| | **TSO 250 (n = 39)** | **TSO 2500 (n = 71)** | **TSO 7500 (n = 72)** | **Placebo (n = 70)** |
| **Blood eosinophils count (at week 8)** | 148% (191%) | 167% (373%) | 241% (363%) | 25% (111%) |

Administration of TSO induced a dose-dependent pharmacodynamic response. Beside an unspecific immunological response (increase in blood eosinophils; see table above), also a specific, dose-dependent humoral response (*T. suis*-specific E/S Ag [IgG]) was induced (see figure on next page), indicating a proof of hatching and thereby confirm the viability of the used embryonated *T suis* eggs.




**Quality of Life**

The patients' quality of life, as measured by the 4 scores of the SHS questionnaire (symptom burden, social function, disease-related worry, and general well-being) as well as the global GIQLI score, improved from Baseline to week 12 (LOCF) in all treatment groups. No meaningful differences in changes from Baseline to week 12 (LOCF) between active treatment groups and placebo were observed.

**Safety Results:**

In total, 205/252 patients experienced at least one AE within the scope of this study. Proportions of patients with at least one AE did not show meaningful differences between treatment groups. Based on SOCs, most patients experienced gastrointestinal disorders, followed by infections and infestations, and nervous system disorders in descending order. In total, 26/252 patients experienced at least one SAE within the scope of this study. The proportion of patients with at least one SAE was largest in the placebo group followed by TSO 7500, TSO 2500, and TSO 250 in descending order. Except for hypersensitivity observed in a patient of the placebo group no other SAE was assessed as at least possibly related to the study medication. The hypersensitivity reaction following administration of the placebo solution was the only SUSAR report in this trial.

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Treatment emergent AEs, SAEs, ADRs - numbers of events and numbers (%) of patients with events

| | **TSO 250 (n=39)** | | **TSO 2500 (n=71)** | | **TSO 7500 (n=72)** | | **Placebo (n=70)** | |
|---|---|---|---|---|---|---|---|---|
| | Events | Patients | Events | Patients | Events | Patients | Events | Patients |
| TEAEs | 83 | 28 (71.8%) | 172 | 56 (78.9%) | 154 | 54 (75.0%) | 138 | 53 (75.7%) |
| Serious TEAEs | 2 | 2 (5.1%) | 3 | 3 (4.2%) | 7 | 7 (9.7%) | 11 | 11 (15.7%) |
| ADRs[1] | 8 | 5 (12.8%) | 30 | 16 (22.5%) | 10 | 6 ( 8.3%) | 26 | 13 (18.6%) |
| TEAEs leading to[2] | 9 | 9 (23.1%) | 16 | 15 (21.1%) | 13 | 13 (18.1%) | 17 | 17 (24.3%) |
| TEAEs leading to[3] | 2 | 2 (5.1%) | 1 | 1 (1.4%) | 1 | 1 (1.4%) | 1 | 1 (1.4%) |

[1] All ADRs were treatment emergent AEs assessed at least possibly related to the study medication.
[2] discontinuation of study medication; [3] premature study termination

In spite of documentation of an effective method of birth control (i.e., failure rate less than 1% per year) two patients on TSO 7500 became pregnant during the course of the study resulting in birth of a healthy baby in one case but spontaneous abortion in the other case. Neither pregnancies nor abortion were classified as ADRs by the responsible investigators. A comparison of ADRs following administration of TSO in this clinical with those given in previous clinical trials does not raise a safety concern. The list of new ADRs mainly comprises non-serious gastrointestinal disorders. As expected, TSO treatment resulted in a marked increase in eosinophils in blood.

In two patients on TSO 7500, eggs of *T. suis* were detected microscopically in faeces at week 12.

Tolerability of TSO was assessed as very good or good in the vast majority of patients by both the investigators and patients. In one patient each in the TSO 250 and TSO 2500 groups the investigator rated tolerability as poor. Two patients each in the TSO 250 and TSO 7500 groups and one patient in the TSO 2500 group rated tolerability of TSO as poor.

**Conclusions:**

- TSO treatment led to a dose-dependent increase in the percentage of blood eosinophils and stool eosinophil-derived neurotoxin levels as can be expected in patients affected with *T. suis*. Together with the dose-dependent specific humoral immunological response to E/S antigen of *T. suis*, which was analysed in a subgroup of patients in each treatment group, these data provided indirect evidence of hatching of the larvae and that indeed embryonated, viable eggs of *T. suis* were administered in this study,
- However, the study failed to prove superiority of TSO treatment vs. placebo for the induction of clinical remission at week 12 (LOCF) in patients with active CD,
- Also the secondary efficacy variables did not show any advantage of TSO over placebo for the treatment of active CD,
- Despite a wide range of performed post-hoc analyses, no obvious reason could be found which might explain the extreme high placebo response observed in this study,
- A comparison of ADRs following intake of TSO reported in this clinical with those given in previous clinical trials does not raise a safety concern. The list of new ADRs mainly comprises non-serious gastrointestinal disorders. As expected, TSO treatment resulted in a marked increase in eosinophils in blood,
- Tolerability of TSO was assessed as very good or good in the vast majority of patients by both the investigators and patients.

| **Date of the Report:** | 30 Jul 2015 |
|---|---|

[3]