Clinical Trial Synopsis

The content and information given in this clinical trial synopsis does not replace medical advice provided by a patient's physician or other qualified healthcare providers. Patients should always consult their physician before making conclusions regarding their treatment. Healthcare professionals are advised to refer to the approved labelling and prescribing information. Results from a single study may not reflect the overall results of a drug and need to be interpreted in the context of all relevant scientific data.

Name of Sponsor/ Company: Dr. August Wolff GmbH & Co. KG Arzneimittel	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Name of Finished Product: K(D)PT		
Name of Active Ingredient: Lysine-D-Proline-Threonine		
Title of study: Randomised, double-blind, placebo-controlled prospective clinical trial to evaluate the efficacy and safety of K(D)PT in patients with mild to moderate ulcerative colitis		
Identifiers: Sponsor study code: KPT4-01/2011 EudraCT number: 2011-002462-20 NCT number: -		
Study centre(s): 33 recruiting sites: Czech Republic (7), Poland (6), Slovakia (3), Hungary (8), Italy (3) and Germany (6); 9 sites were closed before recruiting patients		
Publication (reference): Kucharzik T; Lemmnitz G, Abels C, Maaser C. Tripeptide KDPT Accelerates Disease Remission in Patients With Mild to Moderate Active Ulcerative Colitis. Gastroenterology; 146/ 5 Suppl 1, S-588, Mo1216 (2014) Kucharzik T; Lemmnitz G; Abels C; Maaser C. Tripeptide K(D)PT Is Well Tolerated in Mild-to-moderate Ulcerative Colitis: Results from a Randomized Multicenter Study. Inflammatory Bowel Diseases; 23/2, 261–271 (2017)		

Study period:	**Phase of development:**
Date of first enrolment: January 31st, 2012 Date of last completed: April 3rd, 2013	Phase IIa

Objectives:

This is a proof of concept placebo-controlled study to determine the efficacy and safety of 3 dose groups of K(D)PT in patients with acute mild to moderate ulcerative colitis (UC).

The primary objective is to determine the time to response to K(D)PT, defined as the time from Day 0 to the earliest treatment visit at which a sustained improvement in CAI (Colitis Activity Index) of ≥50% is determined (CAI scored according to Rachmilewitz, 1989). The improvement in CAI must be ≥ 50 % at week 8 (Visit 7), irrespective of any interim decline, for the improvement to be classified as sustained.

Methodology:

The study was conducted as a multi-centre, randomised, double-blind, placebo-controlled, parallel-group, prospective study with 3 dose groups of K(D)PT: K(D)PT 2 x 20 mg (free peptide), K(D)PT 2 x 50 mg (free peptide), and K(D)PT 2 x 100 mg (free peptide). Study products were given as add-on treatment additionally to baseline medication (aminosalicylates and/or corticosteroids and/or azathioprine).

Number of patients (planned and analysed)

Planned: 160

Included: 168

Drop-outs: 35

Analysed: 162 (Safety, Full analysis set); 116 (per protocol)

Diagnosis and main criteria for inclusion:

Male and female patients with mild to moderately active UC proven by endoscopy and criteria according to European Crohn's and Colitis Organisation (ECCO) guidelines and defined as a CAI of 6 to 12, aged from 18 to 70 years and body mass index ≥19 and ≤30 kg/m^2

Test product, dose and mode of administration, batch number:

Product: K(D)PT containing solution for oral administration

Dose: 20 mg, 50 mg, or 100 mg K(D)PT (free peptide)

Mode of administration: oral application, twice daily

Batch number: 654XX110052 (bulk 20 mg: 1003732, 50 mg: 1003734, 100 mg: 1003370)

Duration of treatment:

8 weeks

Reference therapy, dose and mode of administration, batch number:

Matched placebo solution for multiple oral administrations.

Batch number: 1003736

Criteria for evaluation:

Primary objective:

- Time to response to K(D)PT, defined as the time from Day 0 to the earliest treatment visit at which a sustained improvement in CAI of ≥50% is determined (CAI scored according to Rachmilewitz, 1989). The improvement in CAI must be ≥ 50 % at week 8 (Visit 7), irrespective of any interim decline, for the improvement to be classified as sustained.

Secondary objectives:

- Remission at Weeks 4, 8 and 12, defined as CAI ≤3
- Response at Weeks 4, 8 and 12, defined as an improvement in CAI of ≥50% from Day 0
- Improvement in CAI during the (total) treatment period defined as the area under the curve of CAI values from Day 1 until Week 8
- Response at Week 8, defined as a decrease from baseline in Disease Activity Index (DAI) of 30% or more
- Response at Week 8, defined as a change from baseline in endoscopy index (EI) of >1.5
- Endoscopic remission, defined as flexible proctosigmoidoscopy score of 0 to 1 at Week 8
- The improvement in faecal calprotectin concentration from baseline to Weeks 4, 8, and 12
- The improvement in C-reactive protein (CRP) from baseline to Weeks 4, 8, and 12
- The improvement in the score for Inflammatory Bowel Disease Questionnaire (IBDQ) from baseline to Weeks 8 and 12
- The incidence of adverse events (AEs) throughout the study

Statistical methods:

Efficacy:
Data were summarised with descriptive statistics. In the primary analysis, the time to response in the placebo group was compared to the pooled K(D)PT groups using one-sided log rank test.

Safety:
Safety data were summarised with descriptive statistics. The frequency of AEs in the pooled K(D)PT arm was compared to the placebo arm using Fisher's exact test.

Summary – Conclusions

Efficacy results:
The results show that cumulative sustained response rates by time point were increasing in all treatment groups. There was an earlier response in the pooled K(D)PT treated group as compared to placebo (shown as decrease of probability of non-response; see figure 1). However, there was a dramatic increase in the placebo response rate after Week 4 resulting in an unusually high response rate in the placebo group. This non-proportional progress indicates that assumptions for the statistical evaluation of the primary endpoint (classical Log-rank test as per statistical analysis plan) were violated, especially the assumption of the proportional hazards. Assuming non-proportional hazards, according to the literature appropriate statistical tests like Renyi type Log-rank test or Wilcoxon test were performed to compare treatment groups with regard to time to sustained response (Klein and Moeschberger 2003, Davis and Xie 2011). Comparing the K(D)PT (pooled) and the placebo group with regard to the time to sustained response the Renyi type Log rank test approached statistical significance (PP: p = 0.0525, one-sided).

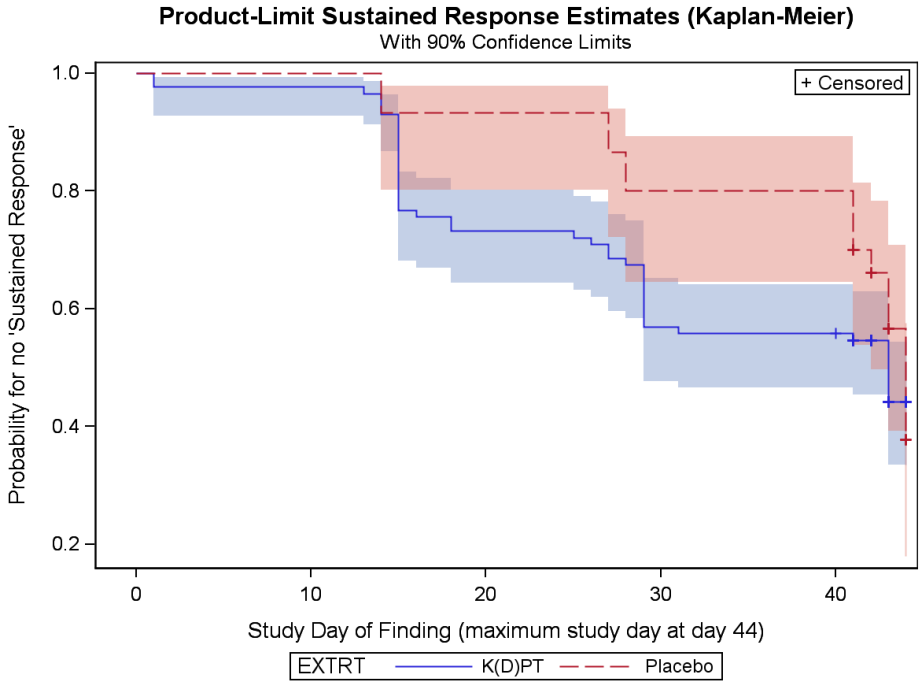

Figure 1: CAI – Time to sustained response curve (Probability for no "Sustained Response") – pooled K(D)PT and placebo with 90% Confidence Limits (PP)

Additional statistical analyses showed that the hazard ratios for all treatment comparisons are >1 (pooled K(D)PT vs. Placebo, see figure 2), favouring K(D)PT treatment (CAI Response und Remission) even in a significant way. The summary of treatment differences for CAI-AUC(0-56d) for pooled K(D)PT data shows that point estimates are >0, favouring K(D)PT treatment significantly. Only for DAI and IBDQ point the estimate is <0. For CRP and faecal calprotectin, the point estimate favours K(D)PT treatment as well, however, not statistically significant ("statistically significant" means here and below an only "exploratory significance" with p-values ≤0.05 [without adjustment of alpha error]) due to the fact, that only a small part of patients had evaluable data. Most importantly, subgroups where identified which reflect patients with active and more severe disease (CAI ≥9, aminosalicylates + corticosteroids and/or azathioprine). In these subgroups marked or statistically significant differences between pooled K(D)PT and placebo are observed, all favouring the K(D)PT treated group, even if not statistically significant. CAI response rates at earlier time points (up to 4 weeks of treatment) were significantly higher in the K(D)PT-treated groups as compared to placebo (Fisher's exact test, 2-sided, Week 2: p = 0.0466, Week 4: p = 0.0501). Moreover, regarding the primary endpoint there is a statistically significant difference in patients taking K(D)PT in addition to their baseline therapy of aminosalicylates + corticosteroids and/or azathioprine (e.g. Renyi type Log-rank test: p = 0.0333, one-sided).

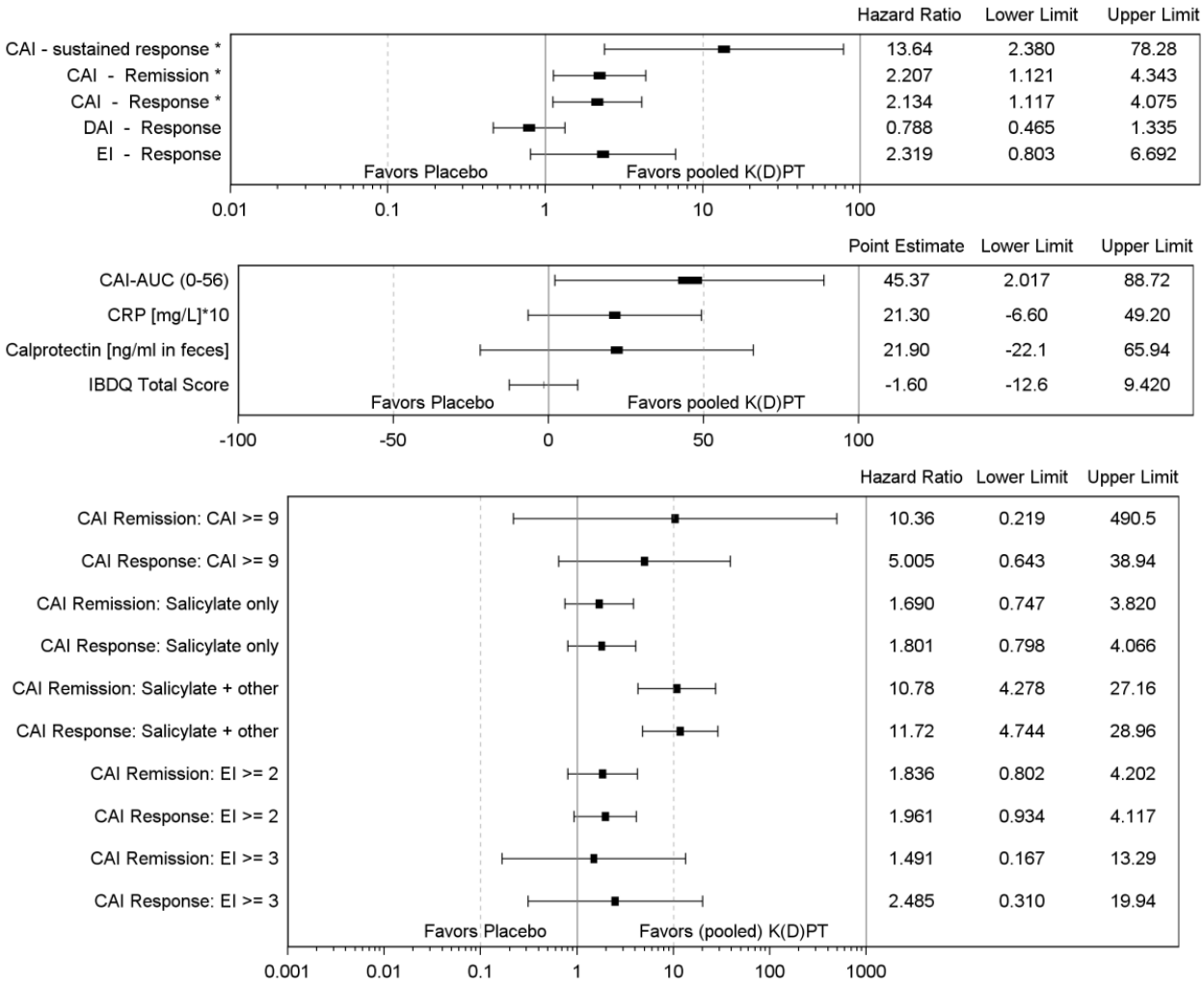

Figure 2: Hazard ratios for treatment comparisons

Safety results:

In the placebo treatment arm, 21 patients (50%) experienced at least 1 AE. The proportion of patients with at least 1 AE was 13 (31.7%), 16 (38.1%), and 16 (43.2%) in the 20, 50, and 100 mg twice daily (bid) K(D)PT treatment arms, respectively. The intensity of the events was mainly mild or moderate, only 4 events were severe.

Descriptive statistics of the AEs do not show marked differences between the four treatment arms in the number of patients with AEs or the number of AEs or specific patterns showing a relationship of AE frequency, severity, or kind of AEs to the treatment arm, as most events occurred only once or twice in a treatment arm.

Statistical comparison of the pooled K(D)PT data vs. placebo data show no significant difference between placebo and K(D)PT in the occurrence of gastrointestinal disorders, infections and infestations, investigations, or musculoskeletal and connective tissue disorders ($p>0.05$ for all comparisons).

Conclusions:

This Proof of Concept (PoC) Phase II study was conducted according to the guideline for treatment of ulcerative colitis (CHMP/EWP/18463/2006) in patients with mild to moderate UC for the induction of remission as add-on treatment to baseline medication. K(D)PT was safe and tolerated well at the investigated doses. Overall, the safety data observed in this trial are consistent with the indication studied.

In summary, the results of this study show an early statistically significant pharmacological effect of K(D)PT while being safe and well tolerated (see below). Moreover, given as an add-on to baseline therapy, K(D)PT accelerates disease remission and leads to an earlier response in patients treated for ulcerative colitis.

Based on the data of this PoC trial as highest dose 50 mg twice daily is recommended, moreover, it seems to be worthwhile to include as lowest dose 20 mg once daily. The next study (Phase IIb) will confirm the results including patients with mild to moderate UC (Modified Mayo Score at entry >4 with endoscopy subscore >2 and rectal bleeding score >1) verified by central reading to reduce the placebo response.

Date of report: 12th of December 2013