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: A Phase IIa, Multi-Centre, Double-blind, Randomised, Placebo-controlled Study to Assess the Safety, Tolerability and Pharmacokinetics of K(D)PT after Multiple Ascending Doses in Patients with Active Mild to Moderate Ulcerative Colitis		
Identifiers: Sponsor study code: KPT3-07/2010 EudraCT number: 2010-023494-19 NCT number: -		
Study centre(s): The study was conducted at 4 investigational sites in Sweden.		
Publication (reference): -		
Study period: Date of first enrolment: April 12th, 2011 Date of last completed: July 1st, 2011	**Phase of development:** Phase IIa	

Objectives:

Primary Objectives: To assess the safety and tolerability of K(D)PT after administration of multiple ascending doses in patients with active mild to moderate ulcerative colitis

Secondary Objective: To determine the pharmacokinetics (PK) of K(D)PT after administration of multiple ascending doses in patients with active mild to moderate ulcerative colitis

Methodology:

This was a Phase IIa, multi-centre, double-blind, placebo-controlled, randomised investigation of the safety, tolerability, and PK of K(D)PT following administration of multiple ascending doses to patients with active mild to moderate ulcerative colitis in 3 cohorts. If the results from the first 2 cohorts were sufficient to meet the primary and secondary objectives, the study was permitted to be terminated. Within each cohort, patients were randomised 3:1 to active treatment or placebo. K(D)PT or placebo was administered for 6 consecutive days. A follow up visit was conducted 7 to 10 days after the last dose.

Each cohort was separated by a safety period of at least 1 week during which a Safety Review Committee (SRC) and a Data Safety Monitoring Board (DSMB) reviewed available safety, tolerability, and PK data. Proceeding to the next dose level only occurred if no safety or tolerability concerns were identified in the previous cohort(s). Each patient participated in 1 cohort only.

Number of patients (planned and analysed)

Twelve patients were planned to participate in 3 cohorts (4 patients in each cohort). There were 4 patients each in Cohorts 1 and 2 for a total of 8 patients and all 8 patients completed the study. Cohort 3 was not conducted. All 8 subjects were included in the safety analysis and all 6 subjects who received active study drug were included in the pharmacokinetic analysis.

Diagnosis and main criteria for inclusion:

Male or female patients, aged 18 to 70 years (up to 75 years per protocol amendment 1), inclusive, with active mild to moderate ulcerative colitis as defined by a colitis activity index (CAI) between 4 and 9 (between 2 and 9 per protocol amendment 1). Females of childbearing age agreed to use effective methods of contraception or practice true abstinence.

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

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

Dose: 55mg (cohort 1) or 220 mg (cohort 2) K(D)PT (free peptide)

Mode of administration: oral application, once daily

Batch number: 6AH1

Duration of treatment:

Patients received K(D)PT or placebo for 6 consecutive days in each cohort.

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

Matched placebo solution for multiple oral administrations.

Criteria for evaluation:

- Safety evaluation including vital signs, ECG parameters, physical examination, safety laboratory tests and adverse events.
- If data allows, determination of following PK parameters for K(D)PT and its metabolite DKP on Day 1: Cmax, tmax, AUC(0-24), MR
- If data allows, determination of the above PK parameters K(D)PT and its metabolite DKP also on Day 6. In addition, determination of the following PK parameters on Day 6: tlast, AUC(0-t), t½, CL/F, Vz/F, Rac, MRT, Ae, CLR
- Steady-state evaluation by graphical presentation of pre-dose plasma concentrations (Ctrough) Days 2 (i.e. the Day 1 24 hour sample), 6 and 7 (i.e. the Day 6 24 hour sample) versus time (day) plots.
- Determination of additional PK parameters if considered relevant.

Statistical methods:

Pharmacokinetic Parameters:
The PK analysis was performed using standard noncompartmental methods.

Safety Parameters:
Individual and summary blood pressure, heart rate, oral body temperature, ECG, and safety laboratory data were descriptively presented. Adverse events were tabulated and summarised using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). Data

were presented by actual dose, and patients receiving placebo were pooled across cohorts for the purposes of summarising the safety results.

Summary – Conclusions

Pharmacokinetic Results:

The table below summarizes K(D)PT PK parameters by dose group and study day.

Summary of K(D)PT PK parameters following 55 and 220 mg oral single and multiple dose administration (Day 1 and Day 6) – PK analysis set

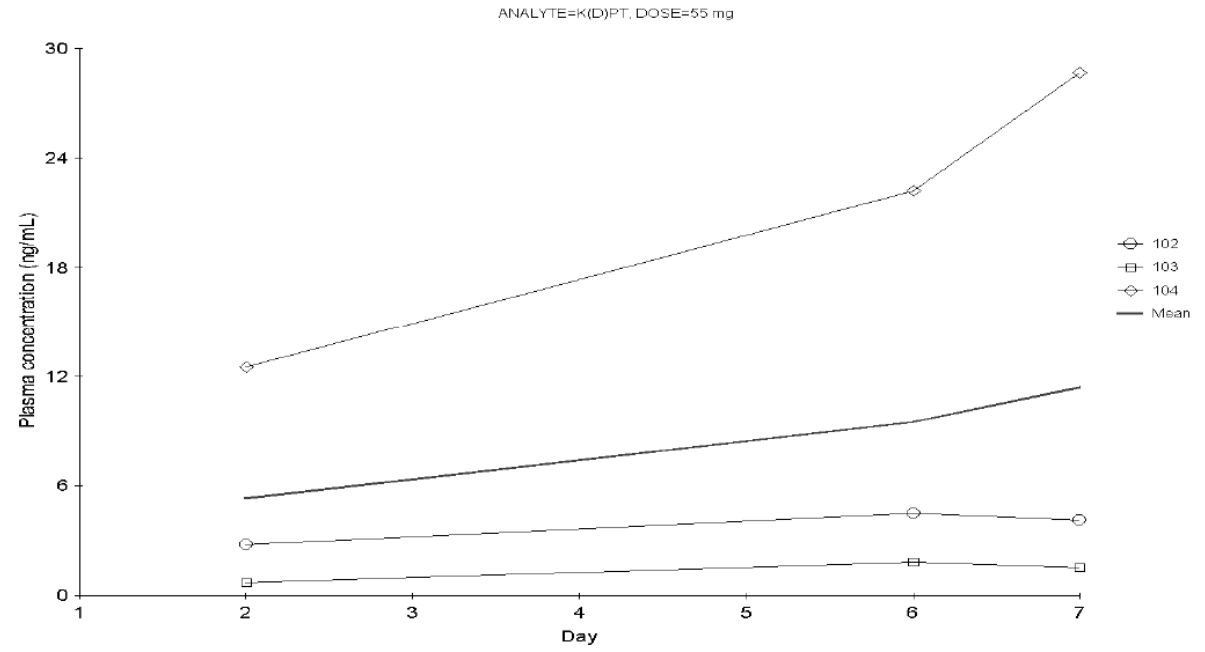
Parameter[a]	55 mg (N=3)	220 mg (N=3)
DAY 1		
Cmax (ng/mL)	25.6 (20.8)	75.0 (44.2)
tmax (h)	1.50 (1.03-1.50)	1.50 (1.50-8.00)
AUC(0-24) (h*ng/mL)	199 (62.0)	699 (73.9)
DAY 6		
Cmax (ng/mL)	30.6 (45.8)	102 (1.1)
tmax (h)	1.00 (1.00-1.52)	3.00 (1.50-3.00)
AUC(0-24) (h*ng/mL)	391 (94.0)	758 (12.6)
t1/2 (h)	24.3 (20.9)	22.5 (71.5)
CL/F (L/h)	242 (72.7)	293 (12.0)
CLR (L/h)	6.71 (15.5)	5.53 (24.5)
Vz/F (L)	9240 (89.5)	10100 (77.7)
MRT (h)	26.3 (38.3)	22.2 (38.8)
Rac	1.73 (34.6)	1.52 (63.5)

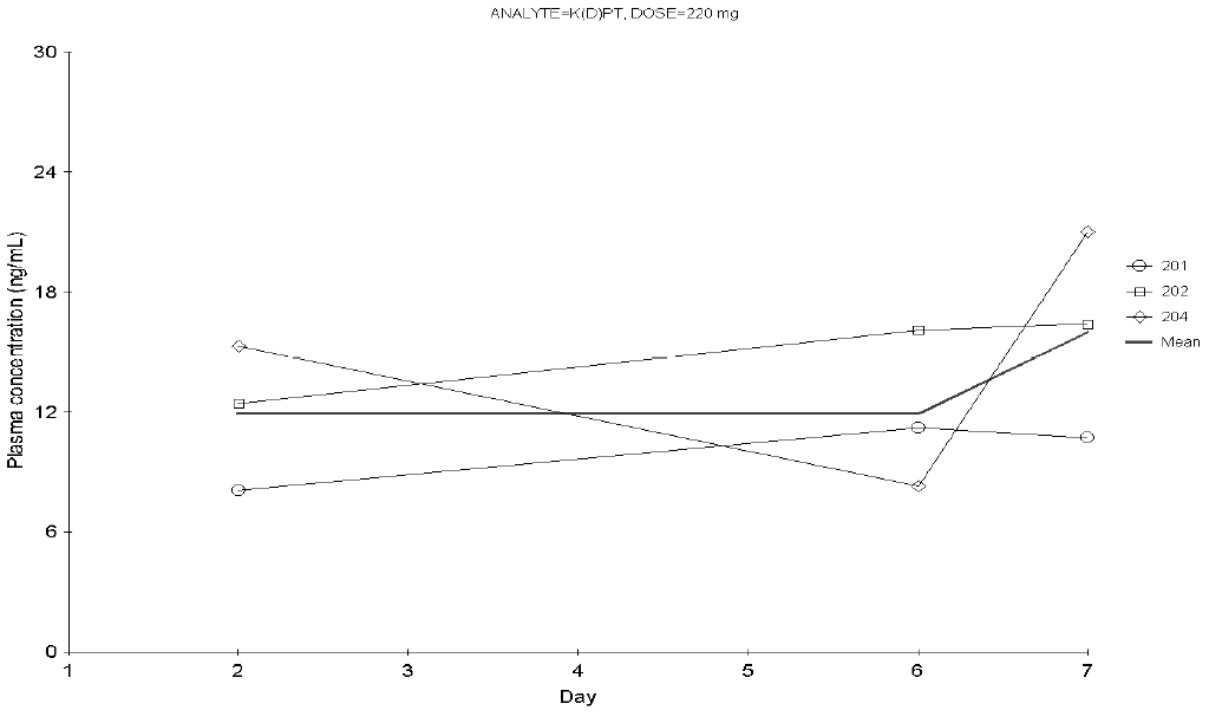
[a] Mean and (CV%) except for tmax where median (range) is presented

The PK of K(D)PT in plasma following once-daily multiple oral dose administration of 55 mg and 220 mg doses in patients with active mild to moderate ulcerative colitis was characterised by a moderate absorption rate, multiple or broad peaks followed by multiphasic decline, a high oral clearance at steady state, moderate to long terminal half-life, low accumulation, and a low degree of urine excretion.

DKP plasma concentrations were below the lower limit of quantification at most time points, or were very low. DKP AUC(0-24) was approximately 3% of K(D)PT AUC(0-24) on Day 6. The amount of DKP excreted in urine was a minor fraction of the K(D)PT dose.

The figures below show individual and mean plasma concentrations of K(D)PT on linear scale versus day (PK analysis set). K(D)PT concentrations measured on Days 2, 6, and 7 suggested that approximate steady-state conditions had been achieved in 4 of the 6 subjects by Day 6.





Safety Results:

No safety concerns were identified in the study following administration of 55 and 220 mg K(D)PT once daily for 6 days. There were no SAEs, discontinuations from the study due to AEs, or other significant AEs reported. All AEs were of mild or moderate intensity. The incidence of AEs overall was slightly higher in the K(D)PT-treated groups (5,83%) compared to placebo (1,50%).

Nasopharyngitis was reported in 3 patients (1 patient in each of the K(D)PT groups and the placebo group); otherwise, reported AEs occurred in 1 patient each. There were 4 AEs in 2 patients judged by the investigator to be possibly related to IMP, including mild dizziness and moderate diarrhea in one patient (55 mg) and mild heartburn and moderate vomiting in one patient (220 mg).

There were no clinically relevant abnormalities in laboratory, vital sign, ECG values throughout the study. Marked decreases from Day 1 to Day 6 in mean fecal calprotectin were noted in the placebo (approximately 70%) and 55 mg (approximately 90%) groups; however, the mean calprotectin for the 220 mg group increased (approximately 200%).

Conclusions:

- K(D)PT was well tolerated by patients in the study and no safety concerns were identified as assessed by evaluation of clinical laboratory parameters, ECGs, vital signs and AEs.
- The PK of K(D)PT in plasma following once-daily multiple oral dose administration of 55 mg and 220 mg doses in patients with active mild to moderate ulcerative colitis was characterised by a moderate absorption rate, multiple or broad peaks followed by multi-phasic decline, a high oral clearance at steady state, moderate to long terminal half-life, low accumulation, and a low degree of urine excretion.
- DKP plasma concentrations were below the lower limit of quantification at most time points, or were very low. DKP AUC(0-24) was approximately 3% of K(D)PT AUC(0-24) on Day 6. The amount of DKP excreted in urine was a minor fraction of the K(D)PT dose.

Date of report: 6th of February 2012