Abbreviated Report

Title:	A randomised, double-blind, placebo-controlled parallel group study to assess the safety and efficacy of a new oral formulation of 2-propyl pentanoic acid (2-PPA, PEAC® minitablets) for the treatment of colorectal polyps in patients with familial adenomatous polyposis (FAP).
Test drug:	2-propyl pentanoic acid (2-PPA)
Indication:	Familial Adenomatous Polyposis (FAP)
Sponsor's name and address:	Topotarget Germany AG (former G2M Cancer Drugs AG), Paul-Ehrlich Str. 42-44 D-60596 Frankfurt am Main Germany
Study number(s):	G2M-777 SYS01/2004
Development phase:	II
Co-ordinating Investigator	Dr. med. Reiner Caspari Universitätsklinikum Bonn, Medizinische Klinik und Poliklinik I Sigmund-Freud-Str. 25, 53105 Bonn, Germany (current address: Paracelsus-Klinik Am See, Dehneweg 6, 37581 Bad Gandersheim, Germany)
Study dates:	First informed consent signed:09 December 2005 First screening: 12 January 2006 Study stopped: 19. December 2008 Last subject out: 07 March 2009
Date of Report:	Version: final, Date: 28 October 2011

This study was set up to be performed in compliance with Good Clinical Practices, (GCP), including the archiving of essential documents.

2 STUDY SYNOPSIS

Name of Sponsor: Topotarget Germany AG	Individual Study Table Referring to Dossier Part	(For National Authority Use Only)
Name of Finished Product: PEAC® Minitablets	Volume:	
Name of Active Ingredient: 2-propyl pentanoic acid (2-PPA)	Report:	

Title of the study:	A randomised, double-blind, placebo-controlled parallel group study to assess the safety and efficacy of a new oral formulation of 2-propyl pentanoic acid (2-PPA, PEAC® minitablets) for the treatment of colorectal polyps in patients with familial adenomatous polyposis (FAP).
Co-ordinating Investigator:	Dr. med. Reiner Caspari, Universitätsklinikum Bonn, Medizinische Klinik und Poliklinik I, Sigmund-Freud-Str. 25, 53105 Bonn, Germany (current address: Paracelsus-Klinik Am See, Dehneweg 6, 37581 Bad Gandersheim, Germany)
Study centre(s):	Six international centres (three centres in Germany, two centres in Russia and one centre in Denmark). • Medizinische Klinik und Poliklinik I Bonn, Allgemeine Innere Medizin, Sigmund-Freud-Str. 25, 53105 Bonn, Germany • Klinikum Herford/Chirurgie, Schwarzernmoorstr. 70, 32049 Herford, Germany • St. Josef-Hospital, Bochum-Linden Axstrasse 35, 44879 Bochum, Germany • State Scientific Center of Colon proctology of Ministry of Health of Russian Federation, Department of General Colon Proctology, 2 Salama Adila street, 123154 Moscow, Russia • Samara State Medical University, Department of Hospital Surgery, 165b Karla Marxa street, 443021 Samara city, Russia • Hvidovre University Hospital, Department of Surgical Gastroenterology, Kettegard Alle 30, 2650 Hvidovre, Denmark
Delegation of tasks:	The study conduct was outsourced to FOCUS Clinical Drug Development GmbH (FOCUS), who co-ordinated, managed and monitored the trial on behalf of the sponsor Topotarget Germany AG. FOCUS was also assigned to do data management, statistical work and study report writing
Publications (references):	None to date
Period of study:	First informed consent signed:09 December 2005 First screening: 12 January 2006 Study stopped: 19. December 2008 Last subject out: 07 March 2009
Clinical phase:	II
Objectives:	To assess the efficacy and safety of a new oral formulation of 2-propyl pentanoic acid (2-PPA, PEAC® minitablets), given as a 6-months treatment of colorectal polyps in patients with familial adenomatous polyposis (FAP) in comparison to a placebo treatment.

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Methodology (design of study):	A phase II, randomised, double-blind, placebo-controlled, parallel group study. Subjects with a confirmed diagnosis of familial adenomatous polyposis (FAP) entered the study for a 6-months treatment of their colorectal polyps. Prior to start of the treatment subjects underwent a colonoscopy for quantitative assessment of number and size of colorectal polyps. The procedure was videotaped for a subsequent quantitative and qualitative assessment by three independent physicians qualified in the area of colonoscopy. Furthermore, one polyp was excised from an area with dense polyposis and biopsies were taken from an area with normal mucosa, which were sent to a central pathologist for histo-pathological examination and for immuno-histochemical examination of HDAC-2 expression. Subjects aged above 30 years additionally had to pass a videotaped gastroduodenoscopy, which served for assessment of the duodenal polyp burden. In case of any present duodenal polyps, one polyp was to be excised for histo-pathological and immuno-histochemical examination. The total daily dose for each individual subject was defined by means of a dosing scheme, which provided weight ranges for 24 possible total daily doses, ensuring that the individual dose was as close as possible to the ideal daily dose of 45 mg/kg. Subjects started treatment according to the dosing scheme with approx. 25% of the final dose. Dose escalation up to the final dose was achieved in 3 steps each time adding approximately another 25% of the final dose, thus reaching the final target level after 10 days. During the treatment period subjects visited the study site at the end of weeks 2, 4, 8, 12 and 24 for blood sampling and report of any possible adverse events (AEs). The blood samples served for examination of safety parameters and for the subsequent analysis of 2-PPA serum concentrations. During the visit at the end of week 24 a second colonoscopy and – dependent on the subject's age – a second gastroduodenoscopy were performed and used for the same quantitative and qualitative macroscopic assessments of the colon and duodenum as described above and for taking polyps and biopsies as for the baseline examination. In Denmark, subjects were requested to come to the study site for two further safety assessments at the end of weeks 16 and 20.
Number of subjects:	66 subjects were to be enrolled in order to complete the study with 60 subjects (40 subjects in the active treatment group and 20 subjects in the placebo group). The study was prematurely stopped due to slow accrual, lack of complete investigation program for many subjects, and because of disqualification of a large pool of subjects at the second Russian centre (centre R02), after inclusion of 49 subjects (13 subjects in centre R02 and 36 subjects in all other centres). From the 36 subjects in the other centres 24 were in the 2-PPA group and 12 subjects in the placebo group (8 and 5, respectively, in centre R02); 19 subjects (52.8%, 11 subjects [45.8%] in the PPA and 8

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	subjects [66.7%] in the placebo group) completed the dosing period of 24 weeks; 12 subjects entered the extension period, 8 subjects (66.6%) completed the extension phase.

Main part of the study (excluding subjects from centre R02)	**2-PPA**	**Placebo**	**Overall**
Number of subjects treated	24 (100%)	12 (100%)	36 (100%)
Number of subjects completing the study	11 (45.8%)	8 (66.7%)	19 (52.8%)
Number of subjects withdrawn from the study	13 (54.2%)	4 (33.3%)	17 (47.2%)

	Contributing reasons for premature withdrawal were AEs/SAEs (9 subjects in the PPA group in the main part of the study and 4 subjects in the extension phase). In centre R02 all 13 excluded subjects of the main part except for 1 subject in the placebo group, were stated as having completed the 24-week treatment phase; 7 subjects were stated as having entered the extension phase and all completed this phase.
Diagnosis and main criteria for inclusion:	Male and female subjects aged above 16 years with FAP, confirmed either by molecular analysis or by a characteristic family history or by the presence of more than 100 colorectal adenomas.
Test product, dose and mode of administration, batch number:	2-propyl pentanoic acid (2-PPA) as an oral minitablet formulation (PEAC®). The test drug was provided in sachets at strength of 450 mg and 750 mg (batch numbers: 450 mg – 2839, 051001 and 070802; 750 mg – 2840, 051002 and 070803). The daily target dose for chronic treatment had to correspond to approximately 45 mg/kg/day. Treatment was started with approximately 25% of this target dose and was escalated in 3 steps within the first 10 days of treatment up to the final dose level. The total daily dose was divided in a morning and an evening dose. The contents of the appropriate number of sachets had to be swallowed with sufficient fluid without chewing the minitablets or could be dispersed in sufficient fluid prior to intake.
Duration of treatment:	24 weeks After termination of the blinded treatment all subjects were offered a 6-months treatment extension with an unblinded treatment with PEAC® minitablets containing 2-PPA.
Reference therapy, dose and mode of administration, batch number:	Placebo was provided in optically identical sachets for a twice daily oral dosing (batch numbers: matching to 450 mg – 2839 and 051001; matching to 750 mg 2840 and 051002).
Criteria of	Efficacy: • Total number of colorectal polyps as assessed during the

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evaluation:	colonoscopy at screening and at the end of the treatment period (week 24). • Change score in endoscopic appearance in colon and duodenum. • Score-change for HDAC-2 expression. • Change of pathological status of polyp. • Absolute change in the total number of duodenal polyps. Following the decision to prematurely terminate the study the evaluation of the efficacy objectives was not performed. Evaluable videotapes of endoscopic investigations at both time points, screening and week 24, were available for less than 20 subjects, all other subjects could therefore not be categorised as completed subjects. This was considered insufficient to achieve the efficacy objectives. The remaining subjects not only contributed much less data than expected for meaningful efficacy conclusions; due to the high proportion of drop-outs or non-evaluable subjects it remained unclear whether these remaining subjects could represent the true treatment effects for the population of enrolled subjects. It has, therefore, been decided to waive the evaluation of efficacy endpoints. After unblinding of data it was discovered that subjects from centre R02 had very low concentrations of 2 PPA; no post-dose concentrations above the detection limit were observed in several subjects, indicating that these subjects either had received no active drug or that samples were from other subjects. Based on this, data from the 13 subjects in site R02 has been excluded from the combined safety analysis and are reported separately. Safety: Adverse events, clinical laboratory parameters, vital signs, ECG and physical examination data. Moreover, blood samples were taken to measure the concentrations of 2-PPA in serum.
Study endpoints:	Safety: The secondary endpoints for assessment of safety were • the frequency and extent of AEs • the frequency of abnormal haematology and clinical chemistry parameters.
Statistical evaluation:	All safety parameters (AEs, vital signs and laboratory tests) were listed by treatment, centre, and subject and displayed in summary tables. The safety analysis was performed for the safety population. Serum concentrations of 2-PPA were summarized descriptively.

Summary and conclusions:

All subjects, who received at least one dose of study medication, were to be included in the safety population. Due to doubtful clinical data from centre R02, these subjects were not included in the

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combined safety evaluation but are reported separately.

Demography:

Overall (all subjects excluding centre R02) mean age was 36.4 years, mean height 173.0 cm, mean weight 80.2 kg and mean BMI 26.73 cm/kg^2. Differences between the treatment groups were minor and not relevant; mean body weight and BMI were slightly higher in the placebo group compared to the 2-PPA group, however, both parameters showed a very high variability. More male (58.3%) than female (41.7%) subjects were included, differences between genders were higher in the placebo group. All subjects were Caucasians.

Mean demographic characteristics were similar in centre R02 (mean age: 37.0 years, mean height: 172.4 cm, mean weight: 71.2 kg, mean BMI: 23.86 cm/kg^2).

Safety:

Considering all subjects excluding centre R02, 21 subjects (87.5%) reported a total of 109 TEAEs after administration of 2-PPA and 5 subjects (41.7%) reported 11 TEAEs after placebo dosing in the main part of the study. During the extension phase 10 subjects (83.3%) reported a total of 41 TEAEs.

Adverse events reported after active treatment were mainly AEs known to occur after treatment with 2-PPA. The most frequently reported TEAEs were nervous system disorders (mainly tremor, somnolence and dizziness) followed by general disorders (mainly asthenia, fatigue and peripheral oedema) and gastrointestinal disorders (mainly vomiting and nausea).

The majority of TEAEs were of mild to moderate intensity, and nearly all TEAEs were considered drug-related by the investigator.

Nine subjects (37.5%) in the main part of the study (all in the 2-PPA group) and 4 subjects (33.3%) in the extension phase withdrew from the study due to AEs.

Three subjects experienced SAEs: 2 subjects in the 2-PPA group in the main part of the study and 1 subject in the extension part. Serious adverse events were considered unrelated to study drug administration. One subject in the placebo group got pregnant during the study.

In centre R02 (which are separately reported due to doubtful clinical data, 2 subjects (25.0%) randomised to 2-PPA reported 6 TEAEs (all of moderate intensity and judged as drug-related) and 1 subject (20.0%) randomised to placebo experienced 4 TEAEs, which were reported as SAEs (nausea, vomiting and diarrhoea, all of severe intensity and judged as drug-related).

For liver function parameters, especially ALT and AST, a mild transient increase was observed until week 12 after treatment with 2-PPA; thereafter values decreased again and reached the screening level at the follow-up examination. Moreover, some subjects showed a clinically relevant transient decrease in platelets.

There were no clinically relevant time- or treatment-related changes in vital signs or ECGs.

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Frequency table for adverse events reported during the main part of the study by at least 5% of the subjects after active treatment classified by system organ class and preferred term (all causalities, excluding centre R02)

		Treatment	
System organ class	**Preferred Term**	**2-PPA N = 24 x (y, z%)**	**Placebo N = 12 x (y, z%)**
Total		109 (21, 87.5%)	11 (5, 41.7%)
Nervous system disorders	Total	30 (16, 66.7%)	1 (1, 8.3%)
	Tremor	12 (11, 45.8%)	-
	Somnolence	9 (9, 37.5%)	-
	Dizziness	4 (4, 16.7%)	-
	Depressed level of consciousness	2 (2, 8.3%)	-
	Headache	2 (2, 8.3%)	-
General disorders and administration site conditions	Total	24 (15, 62.5%)	1 (1, 8.3%)
	Asthenia	7 (7, 29.2%)	-
	Fatigue	8 (6, 25.0%)	1 (1, 8.3%)
	Oedema peripheral	6 (5, 20.8%)	-
	Face oedema	2 (2, 8.3%)	-
Gastrointestinal disorders	Total	18 (9, 37.5%)	4 (2, 16.7%)
	Vomiting	8 (6, 25.0%)	1 (1, 8.3%)
	Nausea	5 (5, 20.8%)	-
	Diarrhoea	2 (2, 8.3%)	2 (2, 16.7%)
Investigations	Total	13 (9, 37.5%)	-
	Blood amylase increased	3 (3, 12.5%)	-
	Platelet count decreased	3 (3, 12.5%)	-
	ALT increased	2 (2, 8.3%)	-
	Blood pressure decreased	2 (2, 8.3%)	-
Psychiatric disorders	Total	7 (5, 20.8%)	-
	Depression	2 (2, 8.3%)	-
Metabolism and nutrition disorders	Total	4 (4, 16.7%)	-
	Increased appetite	3 (3, 12.5%)	-
Ear and labyrinth disorders	Total	3 (3, 12.5%)	-
	Tinnitus	3 (3, 12.5%)	-

x (y, z%): x = number of adverse events; y = number of subjects with particular adverse event; z = percentage of subjects with particular adverse event who received respective treatment.
Note: only AEs which occurred in >5% of subjects in the active treatment group are displayed, therefore the number of AEs under 'total' per SOC may be higher than the number of AEs presented for this SOC

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Frequency Table for Adverse Events Reported During the Extension Phase by at Least 2 Subjects Classified by System Organ Class and Preferred Term (all causalities, excluding centre R02

		Treatment
System organ class	**Preferred Term**	**2-PPA N = 12 x (y, z%)**
Total		41 (10, 83.3%)
Nervous system disorders	Total	17 (7, 58.3%)
	Tremor	7 (6, 50.0%)
	Somnolence	5 (5, 41.7%)
General disorders and administration site conditions	Total	7 (4, 33.3%)
	Oedema peripheral	3 (3, 25.0%)
	Asthenia	2 (2, 16.7%)
	Face oedema	2 (2, 16.7%)

x (y, z%): x = number of adverse events; y = number of subjects with particular adverse event; z = percentage of subjects with particular adverse event who received respective treatment.

For liver function parameters, especially ALT and AST, a mild transient increase was observed until week 12 after treatment with 2-PPA; thereafter values decreased again and reached the screening level at the follow-up examination. Moreover, some subjects showed a clinically relevant transient decrease in platelets.

There were no clinically relevant time- or treatment-related changes in vital signs or ECGs.

Conclusion

- Safety data showed an AE profile as known for 2-PPA. Most AEs were nervous system, general or gastrointestinal disorders.
- Laboratory data revealed a mild and transient effect on liver function parameters and platelets.
- No clinically relevant time- or treatment-related changes were observed for vital signs and ECGs.
- Incidence of AEs was low in centre R02 which is in line with the not measurable or very low concentrations of plasma 2-PPA in these subjects.
- No efficacy conclusion could be made because the number of evaluable subjects was too low to allow a meaningful evaluation. This was mainly due to the bad data quality of the obtained colonoscopy recordings and the low plasma concentrations in subjects from centre R02 and the high drop-out rate in the other centres.