1 Title Page

Study Title	A randomised, double blind, placebo controlled efficacy and safety trial of different doses/dose regimens of FP187 compared to placebo in moderate to severe plaque psoriasis
Protocol No.	FP187-201
EudraCT No	2010-020168-39
Investigational Product	FP187
Comparator	Active ingredient-free placebo tablets
Indication	Plaque psoriasis
Design:	A multicentre, randomised, double-blind - double dummy, placebo-controlled parallel group phase II study evaluating efficacy and safety of FP187 in male and female subjects aged at least 18 years with moderate to severe plaque psoriasis, assessed by PASI, sPGA, patient global assessment (PaGA), patient Quality of Life scoring (DLQI), patient evaluation of pruritus, Adverse Event (AE) / Serious Adverse Event (SAE) reporting, dermatological examinations and laboratory examination.
Development Phase	II
Sponsor	Forward Pharma GmbH Deutscher Platz 5A 04103 Leipzig Germany
Coordinating Investigator	 Department of Dermatology University Hospital 'Carl Gustav Carus', Dresden Fetscherstrasse 74 01307 Dresden Germany
Author of Report	 SCIderm GmbH Esplanade 6 20354 Hamburg Germany
Study Initiation Date	First patient in (FPI) 07-SEP-2010
Study Completion Date	Last patient out (LPO) 09-JAN-2012
Date of Report	Final version 1.0: 27-AUG-2012
This study was performed in compliance with Good Clinical Practices (GCP) and according to local medicinal products act (AMG), including the archiving of essential documents.	

2 Synopsis

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Name of Finished Product: FP187		
Name of Active Ingredient: Dimethyl Fumarate		
Title of study: A randomised, double blind, placebo controlled efficacy and safety trial of different doses/dose regimens of FP187 compared to placebo in moderate to severe plaque psoriasis		
Investigator(s) and related study site(s):		

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Publication (reference): Not applicable			
Studied period (years): (date of first enrolment) 07-SEP-2010 (date of last completed) 09-JAN-2012	**Phase of development:** II		
Objectives: The primary objective was to evaluate the efficacy of different BID (two times a day) and TID (three times a day) doses of FP187 in subjects with plaque psoriasis compared with placebo as assessed by Psoriasis Area and Severity Index (PASI) after 20 weeks of treatment. Secondary objectives were to evaluate the efficacy and safety as assessed by PASI, static Physician's Global Assessment (sPGA), patient global assessment (PaGA) score, patients' disease-related quality of life score (using DLQI), patient assessed pruritus, Adverse Events (AEs) / Serious Adverse Events (SAEs), dermatological examinations and laboratory investigations.			
Methodology: This was a multicentre, randomised, double-blind - double dummy, placebo-controlled parallel group phase II study evaluating efficacy and safety of FP187 in the oral treatment of moderate to severe plaque psoriasis. Treatment took place over a period of 20 weeks in the **blinded patient arms** and a slow flexible titration for up to 8 weeks in the **open tolerability arm** followed by continuation of treatment on the maximum tolerated dose until week 20.			
Number of subjects (planned and analysed; blinded / open):	planned: 200 / 45 screened: 253 / 60	randomised: 199 / - completed: 100 / 33	analysed efficacy: 192 / 53 analysed safety: 192 / 53

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Diagnosis and main criteria for inclusion:
The study population consisted of patients with moderate to severe plaque psoriasis.

- Male and female, aged at least 18
- Body surface area (BSA) ≥10% and PASI ≥10
- The psoriasis disease had been stable for at least 6 months at randomisation
- Signed and dated informed consent

Test product, dose and mode of administration, batch number:
FP187 Batch numbers: Blinded patient arms: W006223 und W006224
Open tolerability arm: W009775

Oral administration of up to 750 mg of FP187, three tablets thrice daily with the meals (**4 blinded patient arms**) or starting with one tablet and adding one tablet to the dosing every week to up to 6 tablets daily (TID, fasted first if tolerated, then fed) in total in the **open tolerability arm** allowing flexible up-titration during an 8 week period until max tolerated dose.

Name of active ingredient: Dimethyl Fumarate (DMF)

Duration of treatment:
20 weeks treatment and 4 weeks follow-up.

Reference therapy, dose and mode of administration, batch number:
Placebo tablets Batch numbers: W006100 und W006101

Oral administration of placebo tablets, three tablets thrice daily with the meals (only in the **blinded patient arms**).

Criteria for evaluation:
192 out of 199 randomised patients in the **blinded patient arms** and 53 patients in the **open tolerability arm** were evaluated for efficacy and safety.

Efficacy:
The efficacy analysis was performed on the full analysis (FA) and the per protocol (PP) set.
The efficacy parameters were the PASI, sPGA, PaGA score, patient quality of life score (DLQI), patient assessed pruritus and exploratory analysis of a possible effect of FP187 on cholesterol and triglycerides.

Safety:
The safety analysis was based on the safety analysis population (SA). Safety and tolerability were assessed by AEs / SAEs, their nature, severity, duration, relationship to study medication and frequency, by dermatological examinations and by laboratory parameters (haematology, clinical chemistry, lipids).

Statistical methods:
The Statistical Analysis Plan (SAP; Part I: randomised treatment arms and Part II: open tolerability arm) defined the statistical analyses for all study evaluations.
<u>Blinded patient arms</u>
All continuous variables were summarised descriptively. The frequencies and percentages of observed levels were reported for all categorical measures.
All primary and secondary efficacy endpoints were analysed based on the FA set and the PP set. The results of both analyses were put on an equal footing. For sensitivity analysis,

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the primary endpoint PASI 75 rate was evaluated additionally for the complete intention-to-treat (ITT) population of all randomised patients.
In the efficacy analysis, the two groups with a daily dose of 750 mg were pooled. An additional analysis of the secondary endpoints PASI 75, PASI 75 at any time, PASI 50, PASI 90 and PASI_DLQI at Visits 6 to 11 was performed on the unpooled 750 mg treatment group for the FA and the PP set and in the subgroup of patients with DLQI score at baseline of at least 11 (responder defined as achieving DLQI≤ 5).

Open tolerability arm

All continuous variables were summarised descriptively. The frequencies and percentages of observed levels were reported for all categorical measures.
All primary and secondary efficacy endpoints were analysed based on the FA set and the PP set. The results of both analyses were put on an equal footing. Efficacy analysis for the open tolerability arm included two treatment groups: the open tolerability arm and the placebo group from the blinded patient arms of the study. . The use of the placebo arm data was justified as all examinations, all parameters and the overall treatment schedule was the same. Furthermore the patient population were coming from the same centres. Descriptive evaluation of secondary endpoints was performed for the overall population of the open tolerability arm and separately for low and high dose subgroups defined by the maximum tolerated dose at Visit 7 (low: 125 - 375 mg; high: 500 - 750 mg).

The following methods were used for both parts of the study:

Parameter	Method
PASI 50, PASI 75, PASI 75 at any time, PASI 90 and PASI_DLQI responder rates	Logistic regression, presented by odds ratios (OR) with the 95% Wald confidence intervals together with the corresponding p-values of the Wald-Chi square tests
PASI reduction rel. and abs.	General linear models, presented by adjusted mean differences together with the 95% confidence intervals (CI) and the p-value of the two-sample t-tests
sPGA	Categorical variable and continuous variables by summary statistics, sPGA responder rate: logistic regression
PaGA	Categorical variable and was summarised by frequencies and percentages
DLQI	5-level categorical variable and was summarised by frequencies and percentages and continuous variables by summary statistics, DLQI responder: logistic regression

The analysis of the safety data was based on the safety analysis (SA) population. Safety was analysed including both parts of the study and results were presented separately for the 5 treatment groups (Placebo, 500 mg, 750 mg BID; 750 mg TID, open arm).
The following methods were used:

Parameter	Method
Extent of exposure	Summary statistics
TEAEs	Frequencies and percentages and summary statistics
Safety lab parameters	Frequencies and percentages, further analyses for creatinine clearance, absolute lymphocytes, eosinophils, leucocytes, liver enzymes: shift tables from baseline to Visits 10 and 11, frequencies and percentages for predefined cut-offs
Vital signs	Summary statistics
Dermatological / physical examination	Frequencies and percentages

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Summary - Conclusions:

In this study, adult subjects with moderate to severe plaque psoriasis were treated orally with FP187 over a period of 20 weeks with a one or two week low dose / stepwise dose increase in an initial treatment followed by 18 or 19 weeks of treatment in four treatment groups (Placebo, 500 mg, 750 mg BID, 750 mg TID) in a blinded patient arms and in a slow flexible titration for up to 8 weeks in an open tolerability arm followed by continuation of treatment on the maximum tolerated dose until week 20. Subjects were followed up for 4 weeks.

In the **blinded patient arms**, 199 patients were randomised. Out of these, 192 patients did receive study medication at least once while 7 did not receive any study medication. 92 patients were prematurely discontinued. In the **open tolerability arm**, 53 patients did receive study medication at least once. 20 patients were prematurely discontinued.

Efficacy results:

In the blinded patient arms, the proportion of **PASI 75 responders at Visit 10** (primary endpoint), the proportion of **PASI 75 responders from Visit 7 onwards**, the **PASI 75 responder rate at any time**, the proportion of **PASI 50 responders** from Visit 7 onwards and the **PASI 90 rate** from Visit 9 on was highest for the 500 mg treatment group, followed by the 750 mg group and Placebo group. Statistically significant results were observed for the contrast Placebo-500 mg (FA: p=0.01, PP: p<0.01 and ITT: p=0.02) and Placebo-750 mg (PP: p=0.01) for the PASI 75 responders at Visit 10, the contrasts versus Placebo (Placebo-500 mg: Visit 8 (PP: p=0.04) and Visits 9 and 10 (FA: p=0.01, PP: p<0.01), Placebo-750 mg: Visit 8 (PP: p=0.02), Visit 9 (FA: p=0.04, PP: p<0.01) and Visit 10 (PP: p=0.01) and Placebo combined 500 mg / 750 mg: Visit 8 (PP: p=0.02) and Visits 9 and 10 (FA: p=0.01, PP: p<0.01)) for the PASI 75 responders from Visit 7 onwards and the contrasts versus Placebo (Placebo-500 mg and Placebo combined 500 mg / 750 mg: Visit 7 (FA: p=0.03, PP: p=0.01 respectively p<0.01), Visit 8 (FA: p=0.01, PP: p<0.01), Visit 9 (FA: p<0.01 respectively p=0.04, PP: p<0.01) and Visit 10 (FA and PP: p<0.01) and Placebo-750 mg: Visits 9 and 10 (FA: p=0.04 respectively p=0.02) and Visits 7 to 10 (PP: p<0.01 at all of these visits) for the PASI 50 responders. In the open tolerability arm, clearly higher rates occurred compared with the Placebo group from the blinded patient arms with the contrast Placebo-open tolerability arm being significant for the PASI 75 responders at Visit 10 (FA and PP: p<0.001), at Visit 8 (FA: p=0.03, PP: p=0.01), Visit 9 (FA: p<0.001, PP: p<0.001) and Visit 10 (FA: p<0.001, PP: p<0.001) for the PASI 75 responders and at Visit 7 (FA: p=0.02, PP: p=0.001) and Visits 8 to 10 (FA: p<0.001, PP: p<0.001) for PASI 50 responders.

In the blinded patient arms, for the mean and median **relative and absolute PASI reduction** a clear increase was observed from Visit 6 to Visit 10 in the 500 mg and 750 mg treatment groups (FA and PP), whereas variation was only marginally over the study duration in the Placebo group. At Visit 10, contrasts Placebo-500 mg and Placebo-750 mg were significant (FA and PP: p<0.001). In the open tolerability arm, a clear increase was observed from Visit 6 to Visit 10 with the contrast Placebo-open tolerability arm being significant (FA and PP: p<0.001).

In the blinded patient arms, the proportion of mild or absent / very mild **sPGA** was increasing during the study duration within the FP187 treatment groups from Visit 6 to Visit 10 with slightly higher values for the 500 mg treatment group from Visit 9 on, whereas for Placebo this proportion varied only marginally during the study course (FA:

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500 mg: mild 10.4% at V6, mild 16.7% at V7, mild 33.3% at V8, mild 29.2% and absent / very mild 12.5% at V9, mild 35.4% and absent / very mild 10.4% at V10, mild 37.5% and absent / very mild 10.4% at V11; 750 mg: mild 8.3% at V6, Mild 25.0% and absent / very mild 1% at V7, mild 28.1% and absent / very mild 4.2% at V8, mild 25.0% and absent / very mild 7.3% at V9, mild 26.0% and absent / very mild 8.3% at V10, mild 25.0% and absent / very mild 8.3% at V11; Placebo: mild 10.4% at V6, mild 2.1% at V7, mild 12.5% at V8, mild 8.3% and absent / very mild 2.1% at V9, mild 10.4% and absent / very mild 4.2% at V10, mild 6.3% and absent / very mild 4.2% at V11 with significant values at the following time points: FA: p≤0.01 or p=0.02 (only for 500 mg at Visit 7 and 750 mg at Visit 10); PP: p≤0.01). In the open tolerability arm, the proportion of mild or absent / very mild **sPGA** was increasing compared with the Placebo (FA and PP: p<0.01 at Visits 7 to 10).

In the blinded patient arms, the proportion of good or very good **PaGA** was increasing during the study duration for the 500 mg and the 750 mg treatment groups until Visit 8, whereas for Placebo this proportion varied only marginally during the study course. From Visit 9 on, a higher proportion of good or very good assessments were observed for the 500 mg compared with the 750 mg group (FA and PP). In the open tolerability arm, the proportion of good or very good **PaGA** was increasing from Visit 6 on (FA and PP).

In the blinded patient arms, the percentage of patients with small or no effect at all on their life measured by **DLQI** score was increasing from Visit 6 until Visit 9 for the 500 mg treatment group and from Visit 6 until Visit 10 for the 750 mg treatment group, with the highest percentage for the 500 mg treatment group at all time points (FA and PP). In the open tolerability arm, the percentage of patients with small or no effect at all on their life measured by **DLQI** score was higher in the open tolerability arm compared with the Placebo group from Visit 8 on in the FA set and from Visit 7 in the PP population.

In the blinded patient arms, a high variation in **pruritus visual analogue scale (VAS)** was observed for the Placebo and the 750 mg treatment group over the whole study duration. From Visit 6 on, the median and mean VAS was clearly lowest for the 500 mg treatment group, followed by the 750 mg treatment group and Placebo (FA and PP). In the open tolerability arm, the median as well as mean **VAS** was clearly lower for the open tolerability arm compared with the Placebo group in FA and PP population from Visit 6 on.

In both the blinded as well as in the open treatments, no noteworthy changes were observed for the means as well as medians of **cholesterol**, **high density lipoprotein (HDL)**, **low density lipoprotein (LDL)** and **Triglycerides**.

In the blinded patient arms, the **PASI_DLQI responder rate** was highest for the 500 mg treatment group, followed by the 750 mg treatment group and the Placebo group from Visit 7 on. (500 mg: 4.2% at V6, 22.9% at V7, 37.5% at V8, 47.9% at V9 to V11; 750 mg: 6.3% at V6, 15.6% at V7, 22.9% at V8 and V9, 28.1 at V10, 25.0% at V11; Placebo: 6.3% at V6, 10.4% at V7, 16.7% at V8, 10.4% at V9, 14.6% at V10, 12.5% at V11). At Visit 8, the contrast between Placebo-500 mg treatment group was significant (FA: p=0.02) and at Visit 9 and 10 the contrast between Placebo-500 mg (FA. p=<0.01), Placebo-combined 500 mg + 750 mg (FA: p=<0.01) and 500 mg-750 mg treatment group (FA: p=<0.01 at Visit 9 and p=0.02 at Visit 10) were significant. In the open tolerability arm, from Visit 7 on the **PASI_DLQI responder rates** (defined as a patient who both achieved PASI50 response and also achieved a DLQI score of ≤5) were clearly higher for the open tolerability arm compared with the Placebo group (open arm: 1.9% at V6, 13.2% at V7, 32.1% at V8, 39.6% at V9, 37.7% at V10, 45.3% at V11; Placebo: 6.3% at V6, 10.4% at

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V7, 16.7% at V8, 10.4% at V9, 14.6% at V10, 12.5% at V11). At Visit 9 and 10, the contrast between Placebo and the open tolerability arm was significant (FA. p=<0.001 at Visit 9 and p=0.01 at Visit 10).

Overall, the efficacy analysis from both the blinded part as well as from the open flexible arm complements and confirms the efficacy of FP187.

Safety results:

Throughout the study, a total of 805 AEs were evaluated as treatment-emergent adverse event (TEAE) in 203 patients of the SA population with a total of 521 TEAEs in 171 patients rated as related to the study medication with higher numbers in FP187 treatment groups. A total of 129 TEAEs in 67 patients led to the withdrawal. The main reasons for early drop-outs were GI-TEAEs. No deaths were documented. A total of 7 serious TEAEs were reported. Out of these, one was classified as TEAE of mild intensity, 3 of moderate and 3 of severe; 2 were by the investigator judged to be possibly related to study medication. For all FP187 treatment groups, the percentage of patients with at least one GI-TEAE and with at least one Flushing-TEAE was clearly increased. However, the severity of the TEAEs was mainly mild or moderate

Evaluation of the laboratory parameters revealed only single abnormal clinically relevant measurements in the majority of patients within all treatment groups. A mild eosinophilia was observed in all treatment groups, whereas moderate and severe eosinophilia occurred only in FP187 treatment groups (Visit 5 to Visit 7; highest percentages: 750 mg TID group at Visit 6). Almost all eosinophilia cases were normalised within the treatment period or follow-up period. Similarly, a mild lymphopenia was observed in all treatment groups, whereas moderate and severe lymphopenia occurred only in FP187 treatment groups (highest percentages: open tolerability arm and 500 mg group at Visits 8 to 10). Most returned to pre-treatment values during study or were by the investigator considered not clinically relevant at the end of the study.

No relevant abnormal changes in vital signs and no relevant abnormalities in dermatological examination were noticed during the study.

Conclusion:

In conclusion, statistically significant efficacy of FP187 was shown for the primary efficacy endpoint and secondary efficacy parameters with the most effective dose being 500 mg (250 mg BID). Some patients may however benefit from a higher dose during the induction treatment period. Evaluation of the safety parameters revealed that after treatment with FP187 most frequently GI-TEAEs occurred, a well known side effect of fumaric acid ester treatment, but overall the severity of TEAEs was mainly mild to moderate. However, these are not considered a safety issue rather a tolerability issue which can possibly be further improved by the slow up-titration of the dosing regimen even if a part of patients may not tolerate DMF at all and will stop treatment within the first few days to weeks.

Date of report:

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