

Pharmacokinetics Bridging Study of a 400 Mg Extended Release Formulation of the Novel Fumaric Acid Ester PPC-06 (Tepilamide Fumarate) in Healthy Male Volunteers

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Abstract

Tepilamide fumarate (PPC-06) is a new, patented prodrug of monomethyl fumarate (MMF), belonging to the fumaric acid esters (FAEs) class of drugs. The efficacy and safety of a 400 mg PPC-06 dose administered twice daily, achieved thus far through concomitant intake of two tablets of 200 mg, was demonstrated previously in two Phase 2 clinical trials on patients with moderate to severe chronic plaque-type psoriasis. The present Phase I, open label, block randomized, cross-over, single dose, bridging study was carried out for assessing bioequivalence between a newly developed 400 mg extended release formulation of PPC-06 (Test) and an equal dose of the 200 mg extended release formulation of PPC-06 (2 concomitantly administered tablets, given as Reference), in healthy male subjects (N=18), under fed conditions. Since systemic exposure to the intact PPC-06 is negligible after oral dosing (below 12.5 ng/mL) due to its rapid pre-systemic enzymatic hydrolysis to the therapeutically active moiety MMF, the bioequivalence assessment was based on MMF plasmatic concentrations. A high-throughput, fully validated, HPLC-MS/MS method was used for quantification of MMF in PK samples collected up to 24 hours post dosing. The geometric least squares means Test/Reference ratios (%) and associated 90% confidence intervals (CIs) were 102.17 (84.20 - 123.99) for C_{max} , 105.24 (90.44 - 122.46) for AUC_{0-t} and respectively 102.22 (88.58 - 117.96) for AUC_{0-inf} , thus allowing for the conclusion of bioequivalence based on standard regulatory acceptance limits of 80.00% to 125.00%. Analysis of safety data, including clinical laboratory parameters, indicated that PPC-06 was very well tolerated by the study participants. No treatment emergent adverse events (TEAEs) were reported by any of the eighteen subjects dosed at least once in the present study. The positive outcome of this study provides data in support of the 400 mg extended release tablet as alternative dosing unit intended to reduce the number of tablets per intake in patients on PPC-06 doses of 400 mg or higher.

Keywords: PPC-06 (Tepilamide Fumarate); Fumaric Acid Esters (FAEs); monomethyl fumarate (MMF); Bioavailability; Pharmacokinetics

Introduction

Tepilamide fumarate (PPC-06) is a new prodrug of monomethyl fumarate (MMF), belonging to the fumaric acid esters (FAEs) class of drugs. Fumaric acid esters have been used in patients with psoriasis since the late 1950s, the first member of the FAEs class to be developed clinically being Fumaderm[®], an oral formulation containing dimethyl fumarate (DMF) and the calcium, magnesium and zinc salts of monoethyl fumarate (MEF). More recently developed oral drugs in this class include: Skilarence[®] (containing DMF, indicated in the treatment of moderate to severe plaque psoriasis), Tecfidera[®] (containing DMF) and Vumerity[®] (containing diroximel fumarate as a MMF prodrug), the last two being indicated in the treatment of relapsing forms of multiple sclerosis.

Orally administered DMF undergoes rapid presystemic hydrolysis by esterases, being converted to its primary metabolite, monomethyl fumarate (MMF), which is active and presumed to be mainly responsible for the efficacy in psoriasis and relapsing forms of MS [1] since intact DMF does not reach the systemic circulation after oral dosing [2,3]. The exact mechanism of action has not yet been fully

elucidated but most studies conducted so far propose that the therapeutic benefits of MMF are primarily based on immunomodulatory and antioxidative mechanisms [4]. DMF and the metabolite, MMF, have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway *in vitro* and *in vivo* in animals and humans [5]. *In vivo*, the anti-inflammatory and immunomodulatory effects of DMF and its circulating metabolite MMF are thought to be mainly due to the interaction with the intracellular reduced glutathione of cells directly involved in the pathogenesis of psoriasis [6]. *In vitro*, MMF increases levels of (Nrf2) which upregulates expression of antioxidant enzymes such as NQO1 [7] and inhibits inflammatory cytokine production [8]. *In vitro* and *in vivo* evidence also suggest that MMF can induce type II dendritic cells, which induces Th2 cell populations and increases the production of IL4, IL5 and IL10 and decreases the production of inflammatory cytokines such as IFN γ [2,9]. The immunomodulatory shift in T helper cells (Th) from the Th1 and Th17 profile to a Th2 phenotype, brought about by fumarates, is associated with reduced production of pro-inflammatory cytokines, induction of proapoptotic events, inhibition of keratinocyte proliferation, reduced expression of adhesion molecules, and diminished inflammatory infiltrate within psoriatic plaques [10-12].

Results from phase 3 clinical trials (DEFINE, CONFIRM) and follow-up study (ENDORSE) have provided good evidence for DMF's efficacy and safety profile. Patient-reported outcomes assessment revealed stabilization or boost in health-related quality of life and work productivity of patients treated with DMF compared to placebo, reflecting a higher patient satisfaction to therapy. However, literature also suggests that intolerance to side effects, especially gastrointestinal adverse effects and flushing is one of the major causes to compromised therapeutic compliance. An increase in the real-world incidence of progressive multifocal leukoencephalopathy and liver abnormality cases is also concerning. While several prevention and mitigation strategies like patient counseling, dose up-titration, pretreatment with aspirin, use of symptomatic therapy and frequent blood monitoring have demonstrated to be effective in tackling the most common adverse effects and promoting adherence to DMF [13], new MMF prodrugs are also emerging as alternative treatment options possibly improving the risk:benefit ratio for patients treated with FAEs.

For instance, Vumerity® (dioximel fumarate or DRF), has shown gastrointestinal tolerability statistically superior to that of dimethyl fumarate in the EVOLVE-MS-2 trial [14].

PPC-06 (tepilamide fumarate) is also a new generation prodrug of MMF, developed by Dr. Reddy's. After oral dosing, it undergoes rapid pre-systemic hydrolysis by non-specific esterases (which are abundant and widely expressed *in vivo*, thus providing a high capacity pathway for conversion to MMF). Systemic exposure to the intact PPC-06 prodrug is negligible (below the 12.5 ng/mL limit of quantitation). PPC-06 is absorbed throughout the gastrointestinal (GI) tract, and is metabolized during absorption to release MMF. The recovery and metabolism of PPC-06 has been fully characterized in a healthy volunteer study with radiolabeled drug. Near complete elimination of the administered drug through urine, feces or expired air was observed.

In vitro metabolism studies have shown that PPC-06 is not a substrate of major human CYP enzymes and does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. No significant induction of CYP1A2, CYP2B6, or CYP3A4 was observed for PPC-06.

Furthermore, it is important to note that for the released MMF itself there is no evidence of interaction with CYP enzymes or the clinically important P-gp transporter and therefore, no interactions are expected with medicinal products metabolized or transported by these systems [15].

The first-in-human pharmacokinetics study conducted in healthy volunteers with a compression coated extended-release tablet (CCT1 prototype) containing 200 mg PPC-06 (107 mg-equivalents of MMF, same as that contained by a single 120 mg dose of Tecfidera) showed sustained MMF exposure that was similar in fasting and fed conditions. The formulation administered as Reference in the present Phase I PK bridging study (CCT2) is an advancement to that prototype, developed for minimal release in the first two hours in order to prevent fumaric acid-induced gastric irritation, followed by a sustained release profile of 14-20 hours.

The efficacy of PPC-06 (CCT1 formulation) was evaluated in a Phase 2 controlled, dose-finding efficacy and safety study in 200 subjects with moderate to severe chronic plaque-type psoriasis, treated for 12 consecutive weeks with either placebo or one of the three distinct dosing regimens of PPC-06 tested (400 mg once a day (QD), 800 mg once a day (QD), 400 mg twice daily (TID)). The primary efficacy endpoint was the mean percent change from Baseline in total PASI (Psoriasis Area and Severity Index) score at Week 12. The least squares mean (LSM) percent reduction from baseline was statistically significant compared with placebo for the 800 mg once daily group (P=0.001) and the 400 mg twice daily group (P<0.001); the difference for 400 mg once daily regimen versus placebo did not reach statistical significance (P=0.066).

The efficacy of PPC-06 (CCT2 formulation) was also explored in another (Phase 2b) randomized double blind placebo-controlled, dose-ranging study, conducted in 76 US sites, in psoriasis patients who had PASI scores ≥ 12 , IGA (Investigator's Global Assessment) Scores ≥ 3 , and BSA (Body Surface Area) $\geq 10\%$. 426 subjects were randomized in a 1:1:1:1 ratio into 1 placebo arm and 3 PPC-06 dose arms: 400 mg once a day (QD), 400 mg twice a day (BID), and 600 mg twice a day (BID). A 5-week titration phase was followed by 19 weeks of treatment. At week 24, PASI-75 response rates were achieved by 44.3%, 47.2% and 39.7% patients in PPC-06 600 mg BID, 400 mg BID and 400 mg QD treatment groups, compared to 20% in the placebo group (p<0.01). Additionally, 44.4%, 41.4% and 35.7% of patients in the PPC-06 600 mg BID, 400 mg BID and 400 mg QD groups, achieved an IGA score of 0 or 1 at week 24, compared to 22% in the placebo group (p <0.0105). PPC-06 showed significant reduction in PASI scores and numerically higher reduction in NAPSI (Nail Psoriasis Severity Index) scores.

In the Phase 2 study on 200 subjects with moderate to severe chronic plaque-type psoriasis, the most common (>5%) treatment emergent adverse events (TEAEs) reported included, in decreasing order of incidence: diarrhea, nausea, abdominal pain, vomiting, headache, flatulence, flushing, upper abdominal pain, and pruritus. Adverse events pertaining to gastro-intestinal tolerability were predominant in the PPC-06 treatment groups in the Phase 2b study as well, with mild to moderate diarrhea being the most common TEAE reported (by 7% to 23% of patients in PPC-06 treatment groups). Flushing was reported by only 1-2% of patients in the PPC-06 groups.

Safety data from the four Phase 1 healthy volunteer studies conducted with PPC-06 indicate that it is generally well tolerated, its common TEAEs profile being consistent with that of DMF (most common TEAEs including flushing and GI symptoms).

The present study aimed to assess the bioequivalence of a newly developed 400 mg extended release formulation of PPC-06 versus an equal dose of the 200 mg extended release formulation of PPC-06 (2 concomitantly administered CCT2 tablets as Reference) in fed conditions.

Methods

Ethical Approval

The study was conducted at the Medical-Sanitary Public Institution “Clinical Hospital of the Ministry of Health, Labour and Social Protection” (located in Chisinau, Moldavia), following approval from the National Ethics Committee for Ethical Expertise of Clinical Trials and the Medicine and Medical Devices Agency of Moldavia. All subjects gave their written informed consent before they underwent any study-related procedures and were free to withdraw from the trial at any time. Clinical investigations were conducted in accordance to the ethical principles described in the Declaration of Helsinki and ICH-Good Clinical Practice.

Investigational Products

The investigational products administered in the study were PPC-06 (tepilamide fumarate) extended release tablets 400mg (manufactured by Steril-Gene Life Sciences Limited, India for Dr. Reddy’s Laboratories, SA, Switzerland) and PPC-06 (tepilamide fumarate) extended release tablets 200mg (manufactured by Piramal Healthcare, United Kingdom for Dr. Reddy’s Laboratories, SA, Switzerland).

Study Design and Subject Profile

An open label, block randomized, cross-over single dose study was carried out for assessing bioequivalence between a newly developed 400 mg extended release formulation of PPC-06 (Test) and an equal dose of the 200 mg extended release formulation of PPC-06 (2 concomitantly administered tablets as Reference) under fed conditions. The enrolled subjects were healthy, adult, male Caucasians, with body mass index within 18.5 to 30.0 kg/m² and without history of significant symptomatic lactose intolerance. An 8 days washout period was maintained between cross-over administrations, and the study treatments were taken orally, with 240 mL of still bottled water, exactly 30 minutes after the subjects started consuming a moderate high fat breakfast (500 Kcals in total, 30% of which came from fat).

The pharmacokinetic parameters calculated were AUC_{0-t} , $AUC_{0-\infty}$, C_{max} , T_{max} , $t_{1/2}$ and MRT and bioequivalence assessment was based on plasma drug levels of monomethyl fumarate.

The safety parameters analyzed were the adverse events reported and the clinical and laboratory results from the screening and study exit examinations.

Handling and Bioanalysis of Study Samples

Standards and Reagents: The reference standard monomethyl fumarate and the internal standard (IS) monomethyl fumarate-d5 were purchased from Toronto Research Chemicals (North York, Ontario, Canada). Acetonitrile, formic acid, dimethylsulfoxide, methanol and hydrochloric acid were of analytical or high-performance liquid chromatography (HPLC) grade, purchased from either Merck (Darmstadt, Germany) or Sigma-Aldrich (Steinheim am Albuch, Germany).

Equipment: Analyses were carried out on an MPX-2 multiplexing HPLC system (Applied Biosystems-Sciex, Concord, Ontario, Canada) comprised of cooled CTC autosamplers (CTC Analytics, Zwingen, Switzerland) with 2 Rheodyne injection valves coupled with Shimadzu LC-20AD pumps and Shimadzu DGU-20A5 degassers (Shimadzu, Kyoto, Japan). The software MPX-2 controlled all multiplexing functions of the high-throughput HPLC system.

The mass spectrometer utilized was an AB-Sciex model API 5500 QTRAP, equipped with atmospheric pressure chemical ionization interface (AB Sciex, Framingham, Massachusetts).

Data were collected and processed using the Analyst® software (Version 1.7 of AB Sciex, Foster City, California).

Liquid Chromatography and Mass Spectrometric Conditions: Chromatographic separations were carried out using reversed phase Ascentis RP-Amide (15 cm × 2.1 mm, 5 μm) analytical columns, thermostatted at 35 °C nominal, for optimal selectivity. The

injection volume was 50 μ L. Gradient elution was used, at a flow rate of 0.4 mL/min, using as mobile phase formic acid 0.2% in water (A) and acetonitrile (B); the three step composition gradient was: 70:30% AB, 20:80% AB and again 70:30% AB. In order to ensure stability of the plasma extracts throughout the duration of analytical runs, the autosampler temperature was thermostatted at -5 °C nominal. Quantitative data were acquired in negative ions mode using a multiple reaction monitoring method (MRM). The ion transitions monitored were 128.992 > 85.000 for monomethyl fumarate and 134.043 > 90.000 for monomethyl fumarate-d5.

Calibration Curves and Quality Control Samples: The monomethyl fumarate and monomethyl fumarate-d5 stock solutions were prepared in cold conditions at 1.000 mg/mL concentrations in dimethylsulfoxide and methanol, respectively. They were stored at -20 °C nominal. A series of working solutions for preparation of the eight points calibration curves and the plasma QC samples were obtained by mixing and diluting the stock solutions with pooled human plasma from blank blood samples collected in potassium oxalate and sodium fluoride tubes. Spiked QC samples were prepared at 18.000, 360.000, 1200.000 and 2400.000 ng/ml and the range of the calibration curves was 6.000 ng/ml (LLOQ) to 3000.000 ng/ml (ULOQ). Calibration curves and QC samples were analyzed during each analytical sequence.

Study Samples: For the quantification of monomethyl fumarate plasma levels, venous blood samples of 4 mL were drawn in tubes containing potassium oxalate as anticoagulant and sodium fluoride as plasma stabilizer before dosing and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 9, 10, 11, 12, 16 and 24 hours post dose in each study period. The samples were immersed in water and ice baths immediately after collection and then centrifuged under refrigeration (10 minutes at 1500 g and a nominal temperature of 4 °C). The samples were stored at -20 °C or colder until submitted to analysis. Before analysis, plasma samples were thawed in ice-water baths, mixed for 3 minutes and centrifuged for 3 minutes at 2000 g and 10 °C nominal. Aliquots of samples were: spiked with cold internal standard (monomethyl fumarate-d5), extracted in cold conditions (keeping the samples, tubes and solvents on crunched ice), mixed and centrifuged; supernatants were evaporated to dryness under air stream, reconstructed with a methanol/water and formic acid solution, mixed and centrifuged; finally, the samples have been transferred in the autosampler to be injected. The analytical work was performed according to GLP principles and current FDA requirements. The analytical method was fully validated before starting the analysis of study plasma samples. The method was verified for linearity, quantification limits, assay specificity, between-run and within-run precision and accuracy, analyte recovery, and stability in stock solution and biological matrix under processing conditions during the entire period of storage. The potential risk of analyte conversion during sample storage or preparation was tested on samples spiked with monomethyl fumarate or monoethyl fumarate + monomethyl fumarate + dimethyl fumarate + fumaric acid together. The risk of conversion was excluded for the applied plasma handling protocol.

The intra-day accuracy range was 91.653 to 105.418% and the inter-day accuracy range was 96.265 to 101.843%.

Pharmacokinetic and Statistical Analysis

Non-compartmental PK analysis was performed using SAS® statistical software (SAS Institute Inc., USA). ANOVA was performed on natural logarithm transformed C_{max} , AUC_{0-t} and $AUC_{0-\infty}$ using the Mixed Procedure fitted in SAS® using the method of least squares. Descriptive statistics were performed for all pharmacokinetic parameters.

Results and Discussion

Pharmacokinetic Results

The present Phase I bridging study aimed to assess the bioequivalence between a newly developed 400 mg extended release formulation of PPC-06 (Test) and an equal dose of the 200 mg extended release formulation of PPC-06 (2 concomitantly administered tablets, given as Reference) under fed conditions. A moderate high fat breakfast (with 30% of calories derived from fat out of a total 500 Kcals) was offered to all subjects 30 minutes prior to dosing. The enrolled study population comprised of 18 adult healthy male Caucasians. While 18 subjects were dosed in the first study period, only 17 subjects completed the clinical part of the trial and were included in the Per Protocol PK Population (see Table 1 for mean demographics and body metrics by population).

Study	Age (years) Mean (Range)	Weight (Kg) Mean (Range)	Height (cm) Mean (Range)	BMI (Kg/m ²) Mean (Range)
Enrolled study population (N = 18)	34.56 (21 - 55)	75.89 (53 - 103)	177.33 (162 - 203)	24.06 (18.8 - 29.4)
Per Protocol PK Population (N = 17)	34.83 (21 - 55)	76.53 (53 - 103)	177.47 (162 - 203)	24.23 (18.8 - 29.4)

Table 1: Mean demographic data and body metrics of the study population

After oral dosing, systemic exposure to the intact PPC-06 is negligible (below 12.5 ng/mL) due to its rapid pre-systemic enzymatic hydrolysis to the therapeutically active moiety MMF and therefore, the bioequivalence assessment was based on MMF plasmatic concentrations.

The mean pharmacokinetic parameters are summarized in Table 2 while mean MMF concentration-time curves are shown in Figure 1.

PK parameter	Test	Reference
	1 x 400 mg PPC-06 ER Tablet	2 x 200 mg PPC-06 ER Tablet
C_{max} (ng/ml) Mean (SD)	850.045 (± 422.409)	818.038 (± 343.106)
AUC_{0-t} (ng/ml*h) Mean (SD)	2478.245 (± 870.685)	2350.166 (± 777.509)
$AUC_{0-\infty}$ (ng/ml*h) Mean (SD)	2534.371 (± 878.831)	2471.020 (± 779.901)
T_{max} (h) Mean (SD)	5.235 (± 1.120)	5.353 (± 1.156)
K_{el} (1/h) Mean (SD)	0.506 (± 0.228)	0.584 (± 0.351)
$t_{1/2}$ (h) Mean (SD)	1.718 (± 1.081)	2.010 (± 1.649)

Table 2: Mean monomethyl fumarate pharmacokinetic parameters after a single dose of 400 mg PPC-06 (tepilamide fumarate), given either as one 400mg extended release tablet (Test) or two concomitantly administered 200mg extended release tablets (Reference), under fed condition (N=17)

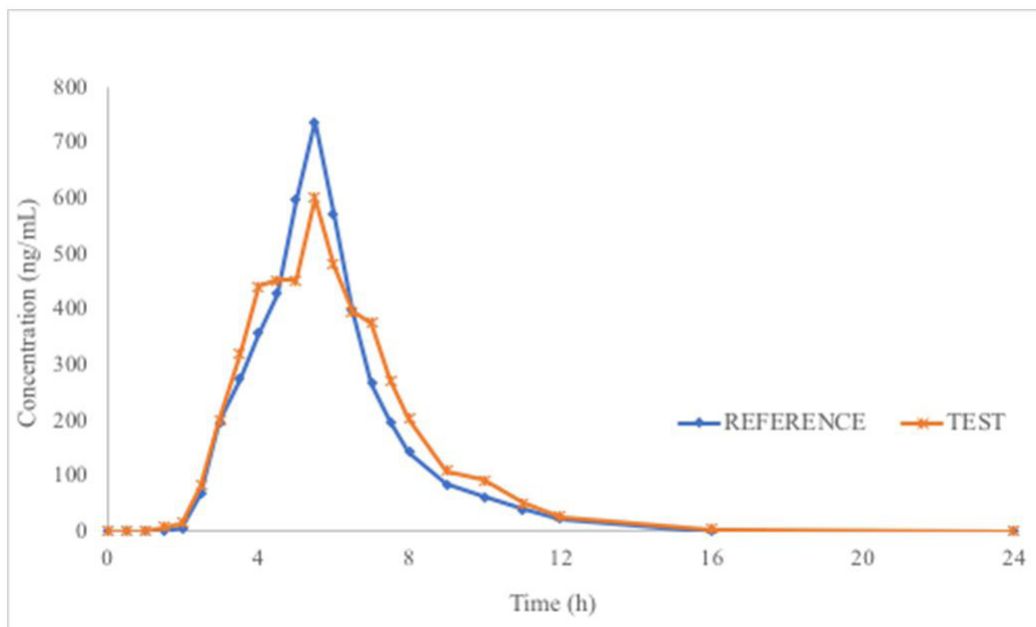


Figure 1: MMF mean pharmacokinetic curves after Test and Reference administered as single dose in fed conditions (N=17)

The point estimates of MMF pharmacokinetic ln-transformed parameters and the 90% confidence intervals for the ratios of the population means, along with the intra-subject CVs registered are shown in Table 3.

PK Parameter	T/R Ratio (%)	90% Confidence Interval	Intra-subject CV (%)
C_{max}	102.17	84.20 - 123.99	32.973
AUC_{0-t}	105.24	90.44 - 122.46	25.560
AUC_{0-inf}	102.22	88.58 - 117.96	24.116

Table 3: Monomethyl fumarate point estimates, 90% CIs and ISCV for the primary PK parameters

The statistical evaluation of pharmacokinetic data showed that the two PPC-06 (tepilamide fumarate) formulations were bioequivalent in fed state as the Test/Reference ratios for the geometric means (%) of the primary parameters (C_{max} , AUC_{0-t} and AUC_{0-inf}) and their corresponding two-sided 90% CIs were contained within the predefined regulatory limits of 80.00% to 125.00%.

Safety Results

No treatment emergent adverse events were reported by any of the eighteen subjects dosed at least once in the present study. There were no abnormal and clinically significant changes from baseline observed during periodic monitoring of individual subject heart

rate or blood pressure during the study period, or in any of the clinical laboratory parameters at the end of the study. The subject who dropped out before the second study period did so due to personal reasons, unrelated to the study medication or procedures. The single doses of 400 mg PPC-06 (tepilamide fumarate), given either as one 400mg extended release tablet (Test) or two concomitantly administered 200mg extended release tablets (Reference), under fed condition, were very well tolerated by all the study participants.

Conclusion

Tepilamide Fumarate (PPC-06) is a new, prodrug of monomethyl fumarate (MMF), to be used for treatment of moderate to severe plaque psoriasis in patients for whom topical therapy is not indicated. The already clinically tested 200 mg extended release formulation of PPC-06 is currently under further clinical development. The present Phase I bridging study assessed the bioequivalence between the newly developed 400 mg extended release formulation of PPC-06 (Test product) and an equal dose of the 200 mg extended release formulation (2 concomitantly administered tablets, given as Reference), under fed conditions. Statistical analysis of the primary PK parameters C_{max} , AUC_{0-t} and AUC_{0-inf} of MMF permitted to conclude that the two drug products are bioequivalent. The positive outcome of this study provides data in support of a 400 mg extended release tablet as alternative dosing unit intended to reduce the number of tablets per intake in patients on PPC-06 doses of 400 mg or higher.

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