CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202535Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 202535	Submission Date(s): 09/16/2011
Submission Type; Code	Original submission 505 (b)(1)
Brand Name	PICOPREP
Generic Name	Sodium picosulfate, citric acid and magnesium oxide
Reviewers	Dilara Jappar, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products (DGIEP)
Sponsor	Ferring Pharmaceuticals Inc.
Formulation; Strength(s)	Powder for Oral Solution, consists of 2 pouches of 16.1 g powder. Each pouch contains 10.0 mg of sodium picosulfate, 3.5 g of magnesium oxide and 12.0 g of citric acid
Proposed Indication	Cleansing of the colon as a preparation for colonoscopy in adults
Proposed Dosing Regimen	Split-dose regimen: The first PICOPREP pouch will be taken the night before the colonoscopy, and the second pouch will be taken the next day, in the morning prior to the colonoscopy. Day-before regimen: The first PICOPREP pouch will be taken in the afternoon or early evening and the second pouch will be taken approximately 6 hours later, the night before the colonoscopy.
PDUFA Goal Date:	07/16/2012

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1 Executive Summary

The sponsor is seeking approval of PICOPREP for cleansing of colon as a preparation for colonoscopy in adults through 505(b)(1) approval approach. PICOPREP is powder for oral solution that contains sodium picosulfate, magnesium oxide, and citric acid. It is provided as two pouches, each of which to be dissolved in water. In support of this application, the sponsor has submitted one pharmacokinetic (PK) study in healthy subjects, two *in vitro* inhibition/induction studies in addition to two phase 3 studies to evaluate the safety and efficacy of PICOPREP.

An optional inter-divisional level Clinical Pharmacology Briefing was held on May 22nd, 2012 to discuss this NDA.

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided that a mutual agreement is reached on the labeling languages.

1.2 Phase IV Commitments

- Pediatric studies required by PREA are under discussion.
  - Waiver for patient less than 6 month of age.
  - Deferral for pediatric patient (b) (4)
  - The following 3 studies to be conducted to meet PREA requirement:
    - Multicenter, open label, safety and efficacy assessment of PICOPREP in children ages 9-16
    - Multicenter, open label, safety and efficacy assessment of PICOPREP in children ages 2 to <9, approximately 20 children
    - Multicenter, open label, safety and efficacy assessment of PICOPREP in children ages 6 months to <2 years (Division requested study- not included in Sponsor's submission)
  - We will request PK to be characterized in pediatric patients for all age group.
- The need of a thorough QT study is under discussion Although QT-IRT recommends a TQT study, we have questions regarding the practicality of conducting such a study.
- A study in renal impairment patients: There is a potential for PICOPREP to cause electrolyte imbalance, especially in renally impaired patients. DGIEP is considering a PMR in renally impaired patients to address this safety concern. If such a PMR is requested of the sponsor, we will request pharmacokinetic characterization in this patient

population. However, this PK component in renally impaired patient would not be requested as a stand alone PMC/PMR. (Note that the current proposed label has warnings for its use in renally impaired patients, which is consistent with other cleansing agents.)

The above have been discussed with Dr. Dennis Bashaw, Division Director of DCP III. When the need of Phase IV studies are finalized, all the PMRs/PMCs will be documented in an addendum to this review, which will have the final sign-off by Dr. Dennis Bashaw.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose Selection:

The sponsor did not conduct a dose finding study. The two proposed dosing regimens were studied in two phase 3 trials, which were the same regimens as those approved in Canada. In the Phase 3 trials, HalfLytely was employed as the active control. The primary endpoint in both phase 3 studies was the proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale. According to Dr. Zana Marks, Medical Officer of DGIEP, the phase 3 studies have demonstrated that PICOPREP is non-inferior to HalfLytely with both dosing regimens.

Pharmacokinetics:

One phase 1 PK study was conducted to evaluate the PK parameters of picosulfate, BHPM and magnesium in healthy volunteers following 1 dose (2 pouches separated by 6 hours) of PICOPREP. Following oral administration, both parent drug picosulfate and its active metabolite BHPM had very low systemic exposure.

The mean (± SD) peak plasma concentration (Cmax) of picosulfate was 2.3 ± 1.4 ng/mL and 3.2 ± 2.6 ng/mL following the 1st and 2nd pouches separated by 6 hours, respectively, with Tmax of 1.9 ± 1.0 hours and 7.1 ± 2.1 hours (1.1 hours after the administration of 2nd dose) hours. The mean (± SD) amount of picosulfate recovered in urine was 0.019 ± 0.009 mg, representing approximately 0.19% of the administered dose.

The exposure of the active metabolite BHPM in plasma was even lower compared to the parent drug picosulfate. Only 3 out of 16 subjects had quantifiable levels (above assay lower limit ofuantification of 0.1 ng/mL) of BHPM in plasma. Due to this limited data, a thorough plasma PK analysis was not possible (the reported Cmax was 0.05 ng/mL). For the urine samples, 8 out of 16 subjects has measurable amount of free BHPM in urine, and the estimated percentage of free BHPM recovered in urine was 0.01%.

In addition to picosulfate and BHPM, serum magnesium level was also evaluated in this study. Following the administration of PICOPREP, magnesium level increase by approximately 20% compared to the baseline. Peak magnesium concentration was approximately 1.9 mEq/L with Tmax of 10 hour post first dose. However, the magnesium level stayed within the normal range during this study.

Drug-Drug Interaction (DDI):

In this submission, the sponsor evaluated potential drug-drug interaction of picosulfate by assessing its potential as an inhibitor or inducer of major drug-metabolizing cytochrome P450 enzymes.

Inhibition potential of picosulfate for CYP enzymes were evaluated in human liver microsomes from a pool of 16 individuals with target concentration of picosulfate ranged from 0.018 to 18 μM. Picosulfate does not appear to be a direct, time-dependent or metabolism-dependent inhibitor of any of the CYP enzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) evaluated. Since I_{gut}/IC50 is less than 10, there is no need of further in vivo DDI study. The proposed label has warning about co-administering a drug within one hour of the start of administration of PICOPREP.

Induction potential of picosulfate was evaluated in freshly cultured human hepatocytes from three human donors at picosulfate concentration range of 0.018 to 1.8 μM. Picosulfate does not appear to be an inducer of CYP1A2, CYP2B6 or CYP3A4/5 enzymes at concentrations up to 1.8 μM. Because PICOPREP is intended for one time use for colonoscopy, its induction potential is not considered critical.

In addition to potential DDI via CYP enzymes, PICOPREP may reduce the absorption of co-administered drug by decreasing the GI transit time due to its laxative affect. This potential drug interaction is addressed in the label, as other colonoscopy agents have, by stating that "Oral medication administered within one hour of the start of administration of PICOPREP solution may be flushed from the GI tract and the medication may not be absorbed completely" in drug interaction section.

Although the sponsor has not evaluated picosulfate's potential drug-drug interaction via transporters or chelating potential of Mg, these potential DDIs are minimized by the same warning language in the label about co-administering a drug within one hour of the start of administration of PICOPREP. The primary concern is drug interaction in patients who are on antibiotics or just completed antibiotic therapy as production of the active metabolite, BHPM, depends on the normal gut flora. This point will be reflected in the label.

QT prolongation potential:
The sponsor has requested a waiver of a thorough QT study in this submission. The QT-IRT team, after reviewing the waiver request, concluded that thorough QT assessment should be conducted to exclude effects on QT as PICOPREP has systemic bioavailability. However, we have concerns about the practicality of the study, especially when the systemic exposure at the therapeutic dose is low and a suprartherapeutic dose may not be ethical. This will be further discussed with the clinical division.

2 Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies

Table 1 Overview of Biomaterial and Clinical Pharmacology Studies

Study ID	Design	Treatments	Number of subjects treated with PICOPREP	Population
Clinical Pharmacology Studies				
[FE000017]	Open-label, single-arm study	One dose of PICOPREP (2 pouches administered with a 6-hour interval)	17 (10 females and 7 males) with 16 evaluable subjects	Non-smoking, healthy subjects 22 to 64 years of age with a normal defecation pattern and no history of gastrointestinal disorders

Study ID	Aim	Concentration range	Enzymes	Biomaterial
Human Biomaterial Studies				
[XT115030]	Inhibiting potential of picosulfate on major drug metabolizing CYP450 enzymes	0.018 to 18 µM	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5	Microsomes; pooled from 16 human donors
[XT113031]	Induction potential of picosulfate on major drug metabolizing CYP450 enzymes	0.018 to 1.8 µM	CYP1A2, CYP2B6 and CYP3A4/5	Fresh cultured human hepatocytes from three human donors

In addition to above clinical pharmacology related studies, the sponsor has also conducted two phase 3 clinical trials of PICOPREP, in which plasma levels of picosulfate and BHPM were not measured.

2.2 General Attributes

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug products?

One dose of PICOPREP consists of 2 pouches of 16.1 g white crystalline powder for oral solution. Each pouch contains 10.0 mg of sodium picosulfate, 3.5 g of magnesium oxide, and 12.0 g of citric acid, along with some other expedients.

The components of PICOPREP and their amount per sachet are listed below:

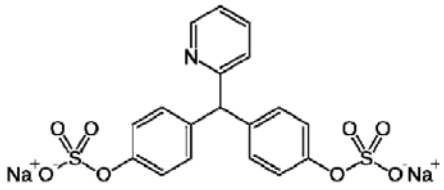
Component	Amount per dosage form	Function	Quality standard
Sodium picosulfate	10 mg	Active	Ph. Eur. current edition
Magnesium oxide (b) (4)	3.5 g	Active	USP current edition
Citric acid, anhydrous	12 g	Active	USP current edition
Potassium hydrogen carbonate (b) (4)	(b) (4)	(b) (4)	USP current edition
Saccharin sodium			USP current edition
Orange flavouring (b) (4) spray dried			FCC

Each pouch is to be dissolved in 5 ounce (150 mL) of cold water prior to administration. When combined in water, magnesium oxide and citric acid form magnesium citrate in solution.

The active ingredient in PICOPREP is picosulfate, which is considered to be an NME, and magnesium citrate. Picosulfate is metabolized in colon to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM, by colonic bacteria.

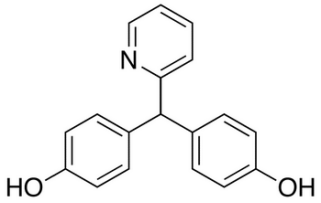
Sodium picosulfate:

- Chemical formula: $C_{18}H_{13}NNa_2O_8S_2$
- Molecular Weight: 499.4 g/mol
- Structural formula:



BHPM:

- Molecular formula: $C_{18}H_{15}NO_2$
- Molecular weight : 277.3 g/mol
- Structural formula:



Magnesium citrate:

- Chemical formula: $Mg_3(C_6H_5O_7)_2$
- Molecular weight: 214.4 g/mol

2.2.2 What is the proposed indication?

The proposed indication for PICOPREP (sodium picosulfate, magnesium oxide and citric acid) powder for oral solution is cleansing of the colon as a preparation for colonoscopy in adults.

2.2.3 What are the proposed mechanisms of actions?

Based on a literature report, the sponsor proposes that sodium picosulfate is metabolized by bacteria in colon to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM that acts directly on the colonic mucosa to stimulate colonic peristalsis.

Magnesium oxide and citric acid react in water to form magnesium citrate, which is an osmotic agent that causes water to be retained within the gastrointestinal tract,

Therefore, magnesium citrate is considered to be an osmotic laxative.

2.2.4 What are the proposed dosage and route of administration?

One dose of PICOPREP consists of 2 pouches of powder for oral solution, each of which to be dissolved in 5 ounces of cold water and administered orally at separate times. The sponsor proposed two dosing regiments:

- Split-Dose regimen: The first PICOPREP pouch will be taken the night before the colonoscopy, and the second pouch will be taken the next day, in the morning prior to the colonoscopy.
- Day-Before regimen: The first PICOPREP pouch will be taken in the afternoon or early evening and the second pouch will be taken approximately 6 hours later, the night before the colonoscopy.

2.2.5 What is the regulatory background?

This product is approved for use for colon cleansing in Europe and Canada under the names of Picolax, PicoSalax or Pico-Salax. In this submission, the sponsor is seeking an approval of this product in the United States for the same indication. Picosulfate, one of the active ingredients in PICOPREP, is considered to be an NME in the United States.

2.2.6 What is the sponsor's dose selection rationale?

In this submission, the sponsor did not conduct a dose ranging study. The two proposed dosing regimens were studied in two phase 3 trials, which were the same regimens as those approved in Canada.

2.3 General Clinical Pharmacology

2.3.1 What are the PK characteristics of parent drug and relevant metabolites in healthy adults?

The sponsor has conducted one PK study (study 000017) where PK parameters of picosulfate, BHPM (the active metabolite) and magnesium were evaluated following administration of 1 dose (2 pouches separated by 6 hours) of PICOPREP powder in solution.

Study 00017 was an open-label, single arm, non-randomized study in 17 healthy subjects (7 males and 10 females) where 1 dose of PICOPREP that comprised of 2 pouches of powder were administered 6 hours apart separately in water under fasting condition (at least 10 hours of overnight fasting). Subjects were dosed with 1 pouch of PICOPREP in the morning of Day 1, followed by a second PICOPREP pouch 6 hours later. The blood and urine samples were collected for 48 hours following the first administration. Of 17 enrolled subjects, 16 of them completed the study as planned receiving full dose (2 pouches). Those 16 subjects were included in the PK analysis. One subject was discontinued from the study early per physician's decision as there was difficulty to access subjects' veins.

The powder from each pouch was reconstituted in 5 ounces (150 mL) of cold water. Following the first administration of PICOPREP, subjects consumed five 8-ounce (240 mL) glasses of clear liquids at the rate of 1 per hour. Following the

second administration of PICOPREP, subjects consumed three 8-ounce glasses of clear liquids at the rate of 1 per hour.

Picosulfate:

Following the administration of PICOPREP, Picosulfate had minimal absorption with low plasma concentrations

Graph 1. Mean Picosulfate Plasma Concentrations – Time Profile

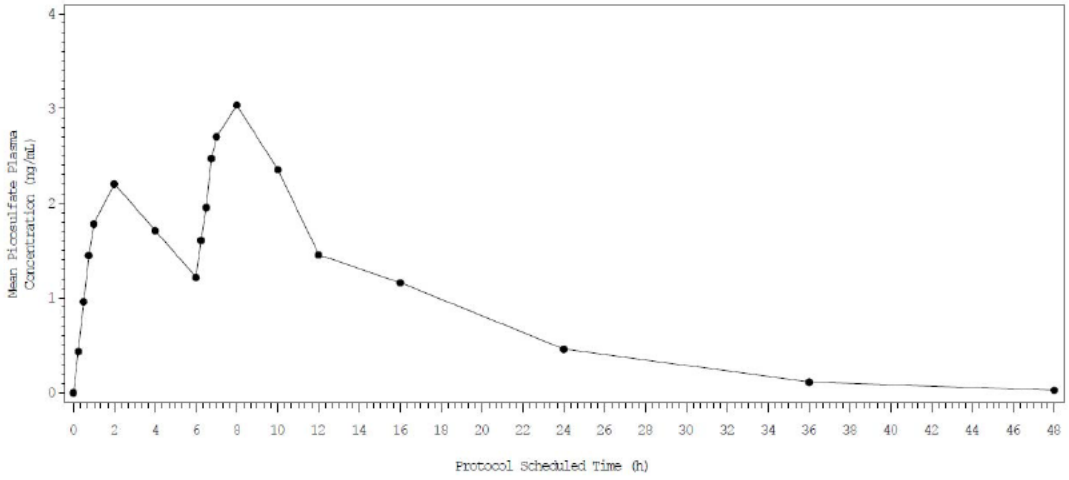


Table 1. Pharmacokinetic Parameters for Picosulfate

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (ng/mL)	16	3.1906	2.57649	80.752	2.7068	56.533	1.240	2.6700	12.400
Cmax6 (ng/mL)	16	2.3221	1.44012	62.019	2.0370	53.663	0.853	2.0550	6.970
Tmax (h)	16	7.07	2.127	30.1	N/A	N/A	2.0	8.00	10.0
Tmax6 (h)	16	1.90	0.988	52.1	N/A	N/A	0.5	2.00	4.0
AUC(0-t) (ng*h/mL)	16	37.8140	32.64991	86.343	31.5236	59.370	13.720	28.7550	154.754
AUC(0-inf) (ng*h/mL)	16	40.0350	32.54143	81.282	33.9514	56.326	14.858	30.8901	156.379
%AUC Extrap (%)	16	7.07	3.950	55.9	N/A	N/A	1.0	6.98	15.3
Lambda_z (1/h)	16	0.1040	0.03065	29.467	N/A	N/A	0.039	0.1074	0.173
t1/2 (h)	16	7.42	3.157	42.5	N/A	N/A	4.0	6.47	17.9

BHPM:

The exposure of the active metabolite BHPM following the picosulfate administration was low with observable levels (above assay LLOQ fo 0.1 ng/mL) in only 3 out of 16 PK-evaluable subjects. Because of this limited exposure of BHPM, the sponsor was not able to characterize the pharmacokinetic of BHPM.

Graph 2. Mean BHPM Plasma Concentrations – Time Profile

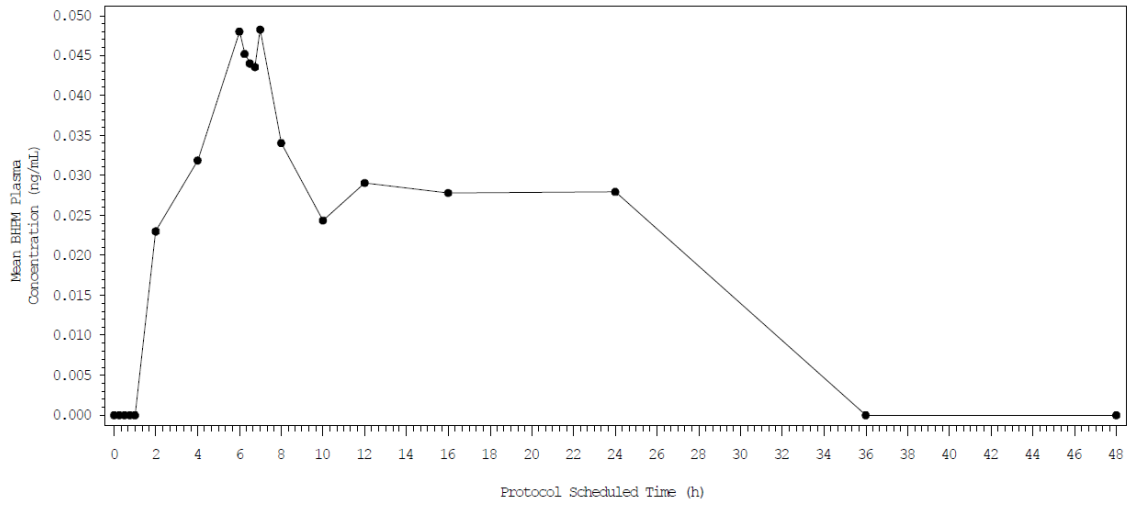
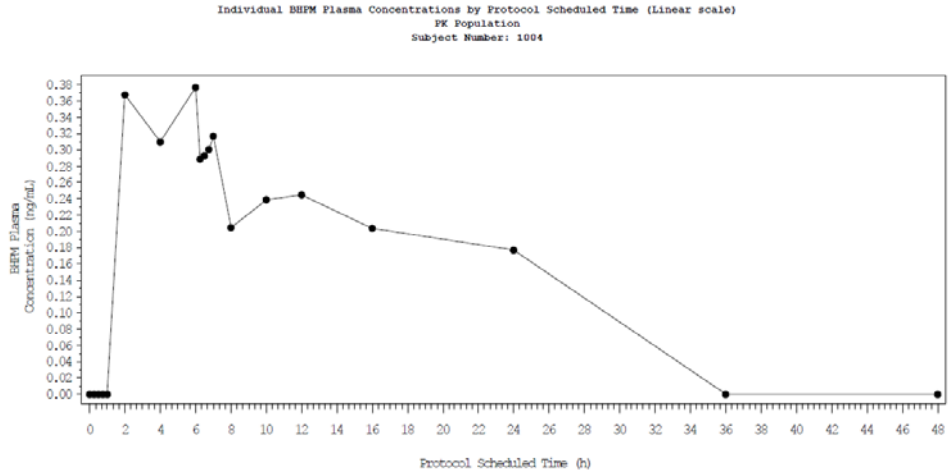
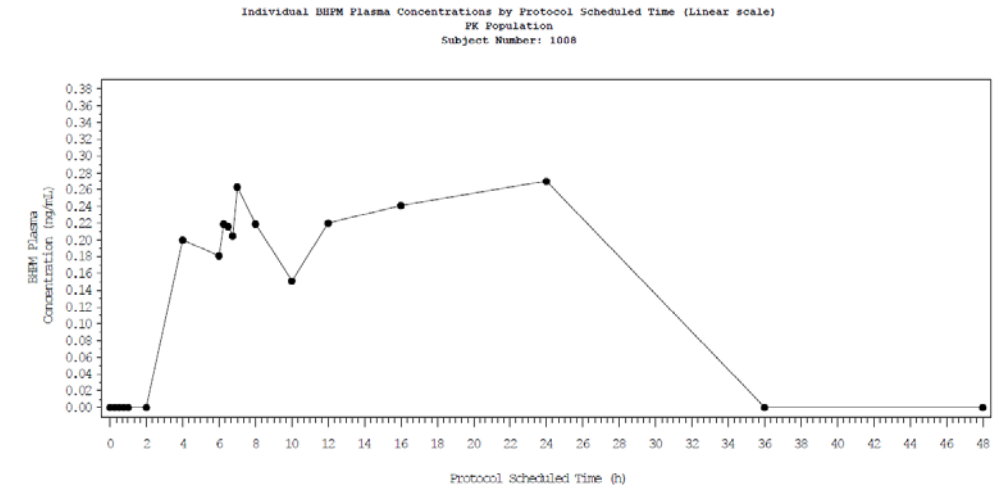


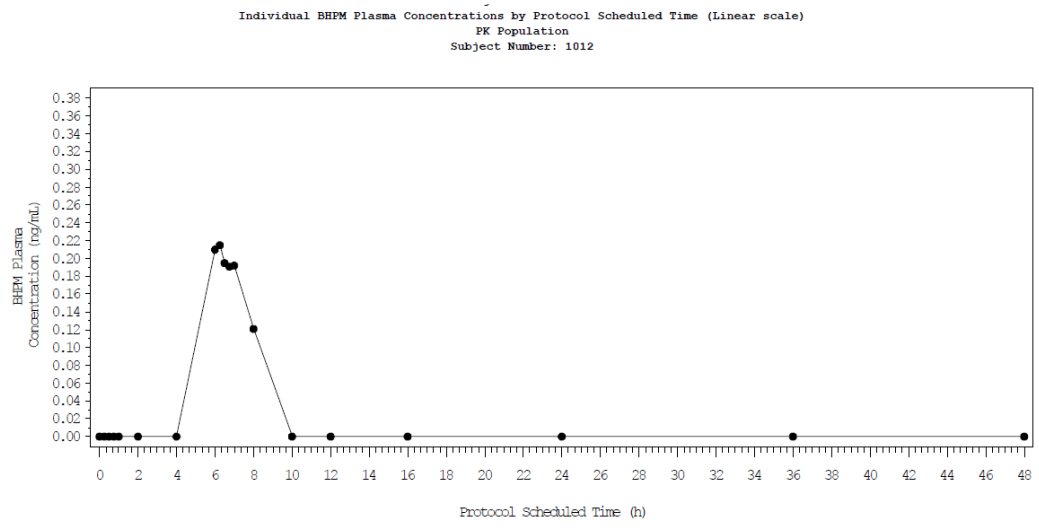
Table 2. Summary of BHPM Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (ng/mL)	16	0.0539	0.11967	222.125	0.2797	28.820	0.000	0.0000	0.377
Cmax6 (ng/mL)	16	0.0492	0.11181	227.312	0.2511	36.402	0.000	0.0000	0.377
Tmax (h)	16	2.26	6.164	272.2	N/A	N/A	0.0	0.00	24.0
Tmax6 (h)	16	0.99	2.167	218.8	N/A	N/A	0.0	0.00	5.9
AUC(0-t) (ng*h/mL)	16	0.6739	1.74013	258.204	2.4600	197.941	0.000	0.0000	5.456
AUC(0-inf) (ng*h/mL)	2	6.9124	8.52895	123.387	3.3778	599.478	0.881	6.9124	12.943
%AUC Extrap (%)	2	46.36	16.243	35.0	N/A	N/A	34.9	46.36	57.8
Lambda_z (1/h)	2	0.2086	0.26159	125.395	N/A	N/A	0.024	0.2086	0.394
t1/2 (h)	2	15.54	19.488	125.4	N/A	N/A	1.8	15.54	29.3

The reported Cmax of 0.05 ng/mL, which was below LLOQ (0.1 ng/mL), was the mean plasma level that includes all 16 subjects. When only these 3 subjects with measurable level of BHPM in plasma are considered, Cmax was 0.54 ng/mL. The following graphs depict the plasma level of BHPM in theses 3 subjects who had measurable level of BHPM in plasma.







Reviewer's Comments:

- *Both picosulfate and its active metabolite BHPM had low systemic exposure (Cmax = 3.2 ng/mL and 0.05 ng/mL, respectively).*

- *All plots and PK parameters estimation were re-analyzed with raw PK data set, and the results were consistent with the sponsor results.*
- *Only 3 out of 16 subjects had detectable levels of BHPM. The first detectable plasma levels of BHPM were 0.368 ng/mL (LOQ 0.100 ng/mL) at 2 hours, 0.200 ng/mL at 4 hours and at 0.210 ng/mL 6 hours. The sponsor stated that picosulfate is metabolized by bacteria in the colon to its active metabolite BHPM. In a response to IR letter dated 03/19/2012, the sponsor contributed this early detection of BHPM in plasma to the variability in gastric transit time and osmotic laxative effect of magnesium citrate. Since the detectable plasma levels only occurred in 3 out of 16 subjects, the sponsor' explanation for early detection of BHPM in plasma is acceptable.*

2.3.2 What are the characteristics of drug excretion in urine?

The above described Study 00017, in addition to evaluating plasma PK profiles, had also evaluated the urine PK profiles of picosulfate and BHPM. Urine samples were collected up to 48 hours following the administration of first pouch.

Table 3. Summary of Picosulfate Urine Concentrations (ng/mL)

Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
0-6 hr	16	5.818	3.1558	54.24	5.107	57.54	1.71	5.050	14.30
6-12 hr	16	21.214	34.6613	163.39	12.842	101.62	3.16	11.350	146.00
12-16 hr	16	31.531	40.2162	127.54	18.505	151.90	1.80	20.450	170.00
Day 2									
16-24 hr	16	13.746	14.3547	104.43	9.626	96.65	3.17	7.810	53.00
24-36 hr	16	2.641	2.7250	103.17	3.301	59.73	0.00	2.260	9.52
Day 3									
36-48 hr	16	1.027	2.4775	241.26	3.173	92.78	0.00	0.000	9.62

Table 4. Summary of Picosulfate Urine Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Ae (0-t) (mg)	16	0.0193	0.00918	47.535	0.0177	43.008	0.009	0.0171	0.046
fe (%)	16	0.19	0.092	47.5	N/A	N/A	0.1	0.17	0.5

Table 5. Summary of BHPM Urine Concentrations (ng/mL)

Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
0-6 hr	16	0.000	0.0000				0.00	0.000	0.00
6-12 hr	16	0.252	1.0075	400.00	4.030		0.00	0.000	4.03
12-16 hr	16	1.669	3.6619	219.36	8.761	22.09	0.00	0.000	11.10
Day 2									
16-24 hr	16	5.234	8.5082	162.56	6.852	136.58	0.00	0.850	28.70
24-36 hr	16	0.678	1.9719	291.06	5.091	54.00	0.00	0.000	7.28
Day 3									
36-48 hr	16	0.000	0.0000				0.00	0.000	0.00

Table 6. Summary of BHPM Urine Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Ae (0-t) (mg)	16	0.0011	0.00179	170.609	0.0013	156.989	0.000	0.0001	0.006
fe (%)	16	0.01	0.018	170.6	N/A	N/A	0.0	0.00	0.1

Reviewer's Comments:

- *Urinary recovery for both picosulfate and BHPM were very low, 0.19% and 0.01% of administered drug, respectively.*
- *8 of 16 subjects had measurable amount of free BHPM in urine. Of theses 8 subjects, 4 subjects had measurable amount of free BHPM only at one time point, while other 4 subject had measurable amount at 2-3 time points out of 5 urine collection time point. The reported urinary recovery for BHPM of 0.01% was the mean recovery that includes all 16 subjects. The urinary recovery for BHPM did not change significantly when only these 8 subjects with measurable level of BHPM in urine were considered (fe= 0.012%).*
- *All subjects had measurable amount of total BHPM which includes glucuronidated BHPM.*
- *The sponsor did not collect fecal samples.*

2.3.3 How is sodium picosulfate metabolized to its active metabolite BHPM?

The sponsor proposes that sodium picosulfate is metabolized by colonic bacteria (microorganism from the flora of large intestine) in colon to its active metabolite bis-(p-hydroxy-phenyl)-pyridyl-2-methane, BHPM that acts directly on the colonic mucosa to stimulate colonic peristalsis. The small amount absorbed picosulfate is reported to be excreted in the urine as a glucuronide-conjugate of BHPM. To support their statement regarding the metabolism, the sponsor had submitted the following literature reference:

- Jauch R, Hankwitz R, Beschke K, Pelzer H. Bis-(p-hydroxyphenyl)-pyridyl-2-methane: the common laxative principle of bisacodyl and sodium picosulfate. Arzneimittelforschung. 1975;25(11):1796-1800.

  In this article, authors concluded that hydrolysis of sodium picosulfate is attributed to the microorganism of the intestinal flora based on the following findings:
  1) After oral administration of sodium picosulfate, germfree rats do not excrete BHPM with the feces. Likewise fecal homogenates from such animals are completely inactive in hydrolysis of picosulfate.
  2) When normal rats that excrete free BHPM in the feces after oral administration of sodium picosulfate are treated with neomycin for several days, they no longer excrete free BHPM. Furthermore fecal homogenates of these animals are unable to hydrolyze picosulfate. When the neomycin treatment is discontinued, hydrolysis of sodium picosulfate to BHPM resumes both after oral administration and in the fecal homogenates of these animals.
  3) In rat and guinea pigs, sodium picosulfate and BHPM were administered directly to small intestine and cecum. Following administration of BHPM, the bile contained solely BHPM glucuronide regardless of whether the drug had been introduced into the small or large intestine. However, for picosulfate, the bile obtained only unchanged picosulfate after administration into the small intestine, but exclusively BHPM glucuronide after administration into the cecum, suggesting that the hydrolysis of sodium picosulfate to BHPM occurs only in the lower segments of the intestine.

  Reviewer's comment:

The sponsor didn't to provide human data to support that picosulfate is converted to BHPM in colon by colonic bacteria.

2.3.4 Did the Magnesium level in serum stayed within normal range following the administration of PIROCPREP?

Yes, all magnesium levels were within the normal range through-out the study period.

In Study 00017, serum magnesium was also evaluated for 48 hours after the administration of first pouch. The raw maximum serum magnesium level was approximately 1.9 mEq/L, which is considered to be within the normal range (~ 1.5-2.5 mEq/L)

Serum magnesium concentrations were corrected by subtracting the baseline concentration from the observed magnesium concentration.

Graph 3. Mean Magnesium Serum Concentrations-Time Profile

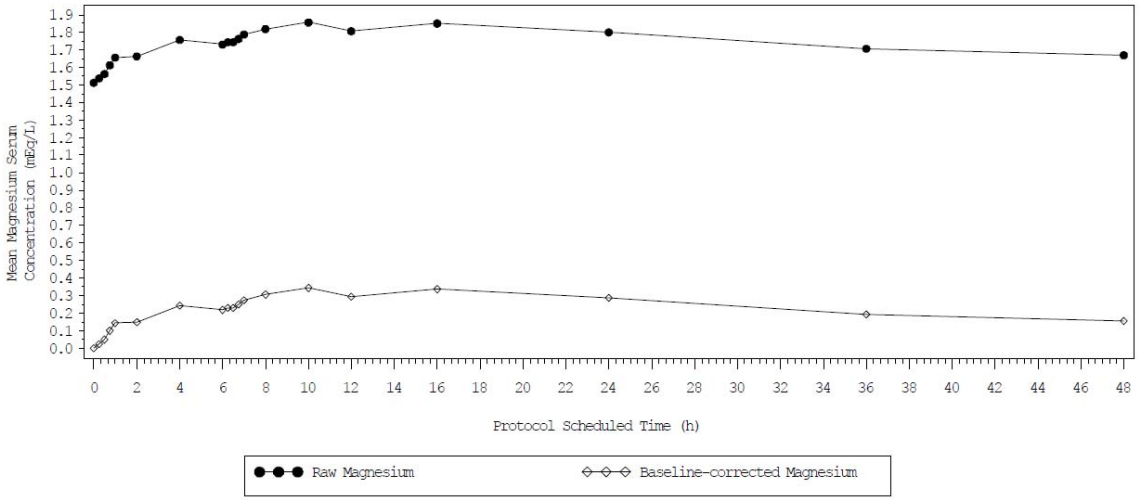


Table 7. Pharmacokinetic Parameters for Magnesium

Pharmacokinetic parameter	Unit	Mean (± SD)	Minimum	Median	Maximum
Raw Magnesium					
C_{max}	mEq/L	1.9 (0.2)	1.6	1.9	2.3
C_{max} (first pouch)	mEq/L	1.8 (0.1)	1.5	1.8	2.1
T_{max}	hr	10.0 (4.0)	4.0	10.0	16.1
T_{max} (first pouch)	hr	3.4 (1.1)	1.0	4.0	4.0
AUC_t	hr*mEq/L	84.2 (5.2)	75.3	83.3	97.2
Baseline corrected Magnesium					
C_{max}	mEq/L	0.4 (0.1)	0.3	0.4	0.6
C_{max} (first pouch)	mEq/L	0.3 (0.1)	0.2	0.2	0.4
T_{max}	hr	10.0 (4.0)	4.0	10.0	16.1
T_{max} (first pouch)	hr	3.4 (1.1)	1.0	4.0	4.0
AUC_t	hr*mEq/L	11.4 (3.0)	5.6	11.1	15.4

Baseline-corrected magnesium exposure was essentially one-fifth that of the uncorrected levels.

2.3.5 Does this drug prolong QT/QTc interval?

The sponsor has requested a waiver of a thorough QT study in this submission. Upon reviewing the waiver request, the QT-IRT team concluded that thorough QT assessment should be conducted per the ICH-E14 Guidelines to exclude small effects on QT as PICOPREP has systemic bioavailability. However, we have concerns about the practicality of the study, especially when the systemic exposure at the therapeutic dose is low and a supratherapeutic dose may not be ethical. This will be further discussed with the clinical division.

2.4 Intrinsic / Extrinsic Factors

2.4.1 Renal and Hepatic Impairment:

Pharmacokinetic of PICOPREP was not evaluated in renally or hepatically impaired patients. The sponsor's rational for not conducting these studies were that PICOPREP is intended for only single-dose administration. Although the Phase 3 trials included, at screening, 379 patients with mild to moderate renal impairment, with creatinine clearance rates of <90 mL/min as determined by Cockcroft-Gault estimation, PK parameters of PICOPREP can not be compared between the renal impairment subjects and healthy subjects as picosulfate and BHPM were not measured in these phase 3 studies. Only magnesium levels were measured in these phase 3 studies.

There is a potential for PICOPREP to cause electrolyte imbalance, especially in renally impaired patients. DGIEP is considering a PMR in renally impaired patients to address this safety concern. If such a PMR is requested of the sponsor, we will request pharmacokinetic characterization in this patient population. However, this PK component in renally impaired patient would not be requested as a stand alone PMC/PMR. (Note that the current proposed label has warnings for its use in renally impaired patients, consistent with other colon cleansing agents.)

2.4.2 What is the drug-drug interaction potential?

The sponsor has evaluated whether picosulfate is an inhibitor or inducer of CYP enzyme to address its potential for drug-drug interaction. It was found that picosulfate is not an inhibitor or inducer of evaluated CYP enzymes.

Inhibition:

To assess whether picosulfate is a direct inhibitor of CYP enzyme, picosulfate, at target concentration ranging from 0.018 to 18 μM, was incubated with human liver microsome from a pool of 16 individuals, marker substrate (at a concentration approximately equal to *K*m or *S*50) and an NADPH-generating system for approximately 5 minutes to measure the CYP activity at 37 ± 1°C, in duplicate. To assess picosulfate's ability to act as a time-dependent and metabolism-dependent inhibitor, picosulfate (at the same concentrations used to evaluate direct inhibition) was pre-incubated with human liver microsomes in the absence and presence of an

NADPH-generating system, respectively, for 30 minutes prior to incubation with the marker substrate at 37 ± 1°C, in duplicate. After the pre-incubation period, the marker substrate (at a concentration approximately equal to *K*m or *S*50) was added, and the incubation continued for 5 minutes to measure the CYP activity. Known direct and metabolism-dependent inhibitors of CYP enzymes were included as positive controls. Incubations that didn't contain picosulfate (0 µM; Solvent Control) and incubations that contained picosulfate but were not pre-incubated, served as negative controls.

Table 8. In vitro evaluation of Picosulfate as an inhibitor of human CYP enzymes

		Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for time-dependent and/or metabolism-dependent inhibition [c]
Enzyme	Enzyme reaction	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	
CYP1A2	Phenacetin *O*-dealkylation	>18	0.70	>18	4.2	>18	NA	Little or no
CYP2B6	Efavirenz 8-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	>18	NA	>18	11	>18	21	Little or no
CYP2C9	Diclofenac 4′-hydroxylation	>18	2.3	>18	1.6	>18	6.4	Little or no
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP2D6	Dextromethorphan *O*-demethylation	>18	5.0	>18	0.60	>18	9.4	Little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP3A4/5	Midazolam 1′-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.

b Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% − Percent solvent control.

c Time-dependent and metabolism-dependent inhibition was determined by comparison of IC_{50} values with and without preincubation and NADPH, by comparison of the maximum inhibition (%) with and without preincubation and NADPH and by visual inspection of the IC_{50} plot.

NA Not applicable. No value was obtained as the rates at the highest concentration of Picosulphate evaluated (18 µM) were higher than the control rates.

Reviewer's Comments:

- Picosulfate does not appear to be a direct, time-dependent or metabolism-dependent inhibitor of any of the CYP enzymes evaluated.
- Due to very little inhibition by picosulfate, IC50 values were not estimated precisely (all > 18 µM). Based on the available data, the possibility of in vivo interaction in systemic circulation is remote as $C_{max}/IC50 < 0.1$ (C_{max} = 3.2 ng/mL = 6.65 nM).
- In gastrointestinal tract, the gut concentration of picosulfate (I_{gut}) is expected to be approximately 140 µM (10 mg/150 mL = 66.7 ug/mL = 140 µM). Base on this estimation, the possibility of in vivo interaction in gut is small as $I_{gut}/IC50 <10$.
- Selection of substrate and substrate concentration used in this study are acceptable.
- The proposed label has warning language about co-administering a drug within one hour of the start of administration of PICOPREP. This labeling language can minimize the potential inhibition effect of picosulfate on other drugs.

Induction:

To assess the induction potential of picosulfate, the isolated hepatocyte cultures from three separate livers were treated once daily for three consecutive days with

one of three concentrations of picosulfate (0.018, 0.18 or 1.8 µM) or one of three know human CYP enzyme inducers, omeprazole (50 µM) for CYP1A2, phenobarbital (750 µM) for CYP2B6 and rifampin (10 µM) for CYP3A4 as positive controls. Following three days of treatment, the microsomal samples were isolated from the hepatocyte culture and incubated with marker substrate at 37°C to measure the CYP enzyme activity. The used marker substrates were phenacetin *O*-dealkylation for CYP1A2, bupropion hydroxylation for CYP2B6 and testosterone 6β-hydroxylation for CYP3A4/5.

Table 9. CYP activity percent positive control: The effects of treating cultured human hepatocytes with Picosulfate or prototypical inducers on microsomal cytochrome P450 (CYP) enzyme activity

Treatment	Concentration	Percent positive control [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	0 ± 0	0 ± 0	0 ± 0
Picosulphate	0.018 µM	0.789 ± 1.488	0.285 ± 0.807	1.83 ± 7.01
Picosulphate	0.18 µM	0.00921 ± 2.26899	-0.144 ± 0.349	2.32 ± 9.28
Picosulphate	1.8 µM	-0.180 ± 2.207	-0.202 ± 0.716	1.48 ± 4.87
Omeprazole	50 µM	100 ± 0	NA	NA
Phenobarbital	750 µM	NA	100 ± 0	NA
Rifampin	10 µM	NA	NA	100 ± 0

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H1034, H1035 and H1036).

NA Not applicable

For CYP1A2, the positive control is omeprazole and the vehicle control is DMSO.

For CYP2B6, the positive control is phenobarbital and the vehicle control is DMSO.

For CYP3A4/5, the positive control is rifampin and the vehicle control is DMSO.

Reviewer's Comments:

- Picosulphate does not appear to be an inducer of CYP1A2, CYP2B6 or CYP3A4/5 activity in cultured human hepatocytes at concentrations up to 1.8 µM.
- Selection of positive control and their concentrations used in this study are acceptable. Positive control inducers resulted in anticipated increase in CYP activities.
- Selection of substrates used in this study to evaluate the enzyme activities are acceptable. However, the substrate concentrations for bupropion-hydroxylation for CYP 2D6 and testosterone 6β-hydroxylation for CYP3A4 were above their respective Km values.
    - testosterone 6β-hydroxylation Km = 52-194 µM
    - testosterone 6β-hydroxylation substrate concentration = 500 µM
    - bupropion-hydroxylation Km = 67-168 µM
    - bupropion-hydroxylation substrate concentration = 250 µM
- Test drug concentrations used in this study well covers the expected therapeutic range for picosulfate.
    - Test drug concentrations used in this study were 0.018, 0.18 and 1.8 µM
    - The expected C_{max} for picosulfate is approximately 3.2 ng/mL = 6.65 nM
- Since PICOPREP is intended for one time use for colonoscopy, its induction potential is not considered critical.

In addition to its potential to inhibit or induce CYP enzymes, PICOPREP may reduce the absorption of co-administerd drug by decreasing the GI transit time. This potential drug interaction is addressed in the proposed label as other colonoscopy agents by stating that "Oral medication administered within one hour of the start of administration of PICOPREP solution may be flushed from the GI tract and the medication may not be absorbed completely" in drug interaction section of the proposed label.

The sponsor has not evaluated picosulfate's potential drug-drug interaction via interaction with transporters. Additionally, the sponsor did not address the chelating potential of Mg either in their proposed label. However, these potential DDIs are minimized by the same warning language about co-administering a drug within one hour of the start of administration of PICOPREP.

The primary drug interaction concern is in patients who are on antibiotics or just completed antibiotic therapy as production of the active metabolite, BHPM, depends on the normal gut flora. This point will be reflected in the label.

2.4.3 What was the clinical endpoint in the Phase 3 trials?

The primary endpoint in both phase 3 studies was the proportion of subjects classified as responders (success) where a responder was a subject with a rating of Excellent or Good according to the Aronchick Scale. Aronchick Scale is a not validated but commonly used assessment scale in clinical trials to assess the overall colon cleansing.

The key secondary endpoint in phase 3 studies was Ottawa Scale, which is a validated and commonly used assessment scale in clinical trials to assess the ascending colon cleansing. For secondary endpoint, a grade of 0, 1, 2 (excellent, good, or fair) were classified as responders.

2.4.4 What was the design and results of phase 3 trials?

The sponsor has conducted 2 randomized, assessor-blinded, active-control, multicenter non-inferiority studies (FE2009-01 and FE2009-02) investigating the efficacy, safety, and tolerability of PICOPREP versus HalfLytely (with 2 x 5-mg tablets of bisacodyl) for colon cleansing in preparation for colonoscopy in 1201 adult subjects in the United States. The two phase 3 studies, FE2009-01 and FE2009-02, have the same study design except for timing of PICOPREP dosing regimen.

According to Dr. Zana Marks, Medical Officer of DGIEP, the phase 3 studies have demonstrated that PICOPREP is non-inferior to HalfLytely with both dosing regimens.

Non-inferiority Analysis for Percentage of Responders Using the Aronchick Scale

Dosing	% responder	PICOPREP (PP)	HalfLytely (HL)	Treatment Diff. (PP - HL)	Lower bound one-sides 97.5 %CI
Split dosing	% (n/N)	84% (256/304)	74% (221/297)	10%	3.4%b
Day-before	% (n/N)	83% (244/294)	80% (239/300)	3%	-2.9%

2.5 Analytical Section

2.5.1 What bioanalytical methods were used to assess the concentration?

Plasma Concentration:

- Plasma picosulfate and its metabolite BHPM concentrations were determined with LC-MS/MS method.

- The calibration standard curve concentration ranged from 0.100 to 20.00 ng/ml for both picosulfate and BHPM.
  - The highest plasma concentrations observed in this study were 3.95 ng/mL for picosulfate and 0.377 for BHPM, respectively, which were all within the calibration standard curve concentration range (0.1 to 20.0 ng/ml).

- LLOQ was 0.100 ng/mL.

- Linear regression equation of $y = a + bx$ with $1/x^2$ weighting were used to calculated the concentration

- Accuracy and precisions of calibration standard curve concentrations ranged from -4.4 % to 3.6 % and from 2.8 % to 9.3 %, respectively for picosulfate, and from -6.2 % to 5.7 % and 1.4 % to7.7 %, respectively for BHPM. Mean R^2 were 0.99377 and 0.99590 for picosulfate and BHPM, respectively.

Table 10. Precision and accuracy of picosulfate and BHPM quality controls:

Nominal QC Conc (ng/mL)		0.30	3.00	18.0
Picosulfate	Precision (%)	9.2	9.0	4.6
	Accuracy (%)	5.7	1.0	-1.7
BHPM	Precision (%)	7.1	5.8	4.5
	Accuracy (%)	-5.9	-2.8	-7.5

- Plasma samples, stored at approximately -70°C, were analyzed within the time period in which the long-term stability of picosulfate and BHPM have been established.
  - Plasma and urine samples were collected between 05/11/2011 to 5/13/2011.
  - Plasma samples for picosulfate and BHPM were analyzed by May 31st, 2011.
  - Stability of picosulfate and BHPM in human plasma at -70 °C were established for at least for 125 days.

- Stock solutions, stored at 4°C, were used within the time period for which stock solution stability was established.
  - The stock solutions for picosulfate and BHPM were prepared on 04/12/2011 and 05/19/2011. Stock solutions of internal standards were prepared on 05/19/2011. All were stored in refrigerator.
  - All plasma concentration analysis was conducted by 05/31/2011.

- Stock solutions of picosulfate and BHPM and their respective internal standards, Picosulfate-D13 and BHPM-D13, were found to be stable for at least 61 day at $5^{o}C \pm 3^{o}C$.

Urine Concentration:

- Urine picosulfate, BHPM (free) and BHPM after glucuronidase treatment (BHPM total) were determined with LC-MS/MS method.
- To evaluate if glucuronidation as an elimination pathway for the picosulfate metabolite BHPM, as suggested by literature, the urine samples underwent treatment with glucuronidase and was re-assayed for BHPM. It was found that the majority of excreted BHPM in urine is in the glucuronide-conjugated form. Majority of free BHPM samples in urine were below detection limit of 1.5 ng/mL while all urine BHPM samples after glucuronidase treatment were well above detection limit.

- The calibration standard curve concentration ranged from 1.50 to 200.0 ng/ml.
  - The highest urine concentrations observed in this study were 170 ng/mL for picosulfate and 28.7 ng/ml for BHPM, which were all within the calibration standard range (1.5 to 300.0 ng/ml).

- LLOQ was 1.50 ng/mL

- Linear regression equation of $y = a + bx$ with$1/x^2$ weighting were used to calculated the concentration

- Accuracy and precisions of calibration standard curve concentrations ranged from -4.9% to 5.8% and from 2.0% to 12.1%, respectively for picosulfate, and from -4.0% to 5.3% and 1.0% to 6.9%, respectively for BHPM. Mean R^2 were 0.99527, 0.99671, and 0.99762 for picosulfate, BHPM, and BHPM (total), respectively.

Table 11. Precision and accuracy of urine picosulfate and BHPM quality controls:

Nominal QC Conc (ng/mL)		4.5	30.0	240
Picosulfate	Precision (%)	10.8	6.6	14.1
	Accuracy (%)	6.1	-6.3	0.8
BHPM (free)	Precision (%)	4.5	13.7	9.0
	Accuracy (%)	2.8	4.5	-1.5
BHPM (total)	Precision (%)	4.2	4.5	5.1
	Accuracy (%)	9.2	5.5	1.7

- Urine samples, stored at approximately $-70^{o}C$, were analyzed within the time period for which the long-term stability of picosulfate and BHPM have been established.
  - Plasma and urine samples were collected between 05/11/2011 and 5/13/2011.
  - Urine samples for picosulfate and BHPM were analyzed by June 1st, 2011.
  - Stability of picosulfate and BHPM in human urine at -70 °C was established for at least for 133 days.

- Stock solutions, stored at 4°C, were not used within the time period for which stock stability was established.
    - The stock solution for picosulfate, BHPM and internal standards were prepared on 02/9/2011, and they were stored in refrigerator.
    - All urine concentration analysis was conducted between 05/19/2011 through 06/01/2011.
    - Stock solutions of picosulfate and BHPM and their respective internal standards, Picosulfate-D13 and BHPM-D13, were found to be stable for at least 61 day at 5°C ± 3°C.

Reviewer's comment: An information Request (IR) was sent to the sponsor on April 23rd, 2012 to address this issue. In response to this IR (dated May 7th, 2012), the sponsor stated the following:
"To provide further assurance of the expected >92 days stability of the stock solutions, a new stability investigation assessing the degradation level at accelerated conditions will be conducted to cover the stability over the longer time period (>92 days) and Ferring commits to provide this in the first Annual Report for the NDA if the NDA is approved by the PDUFA date or an amendment to the pending NDA if the approval of the NDA is extended beyond the PDUFA date."

As picosulfate and BHPM have very low urine recovery, this would not be an approval issue, and sponsor's proposal to address this issue is acceptable.

2.5.2 Were the analytical assay methods adequately validated?

Yes, both analytical methods for plasma concentration and urine concentration for picosulfate and BHPM were adequately validated.

Plasma Concentration:
The LC-MS/MS analytical methods used for above study to determined the plasma concentration of picosulfate and BHPM are considered to be appropriately validated.

- Selectivity:
  Human plasma samples from six different sources were analyzed and those blank plasma samples did not exhibit signal for picosulfate and BHPM.

- Sensitivity:
  The lower limit of quantification (LLOQ) for human plasma picosulfate and BHPM were 0.100 ng/mL, with acceptable accuracy and precisions for both picosulfate and BHPM (less than 15% each).

- Calibration Curve:
  The calibration (standard) curve for both picosulfate and BHPM were in range of 0.1 – 20.0 ng/mL. Linear regression equation of $y = a + bx$ with $1/x^2$ weighting were used to calculated the concentration.

- Accuracy and Precision:
  The accuracy and precision for both picosulfate and BHPM were within acceptable range, less than 15%.

- The inter-run precision and accuracy for picosulfate was less than 9.7 % and 6.5 %, respectively.
- The inter-run precision and accuracy for BHPM was less than 9.3 % and 8.2 %, respectively.
- The intra-run precision and accuracy for picosulfate was less than 7.0 % and 4.9 %, respectively.
- The intra-run precision and accuracy for BHPM was less than 9.0 % and -10.9 %, respectively.

- Matrix Effect
  No significant matrix effects were observed for picosulfate and BHPM in human plasma.

- Stability:
  - Freeze-Thaw Stability:
    Picosulfate and BHPM in plasma were found to be stable for at least 3 freeze-thaw cycles.

  - Long-Term Stability:
    Picosulfate and BHPM in plasma were found to be stable for at least 125 days at -20^{o}C ± 5^{o}C and -75^{o}C ± 15^{o}C.

  - Short-Term Stability:
    Both picosulfate and BHPM in plasma were found to be stable for at least 24 hr in room temperature.

  - Stock Stability:
    - Stock solutions of picosulfate and BHPM were found to be stable for at least 61 day at 5^{o}C ± 3^{o}C.
    - Stock solution for internal standards Picosulfate-D13 and BHPM were found to be stable for at least 61 day at 5^{o}C ± 3^{o}C

  - Post-Preparative Stability:
    - Picosulfate and BHPM in plasma are stable in cooled autosamplers at ~10^{o}C for at least 120 hours (5 days).
    - Picosulfate and BHPM in plasma are stable in refrigerator at 5^{o}C ± 3^{o}C for at least 72 hours.

  - Blood Stability:
    Picosulfate and BHPM were stable in whole blood for at least one hour.

Urine Concentration:
The LC-MS/MS analytical method used for above study to determined the urine concentration of picosulfate and BHPM are considered to be appropriately validated.

- Selectivity:
  Human urine samples from six different sources were analyzed and those blank plasma samples did not exhibit signal for picosulfate and BHPM. The mean peak areas of the blank and spike 0 ng/mL samples are < 20% compared to the peak areas of the LLOQ samples.

- Sensitivity:
  The lower limit of quantification (LLOQ) for human urine picosulfate and BHPM were 1.50 ng/mL, with acceptable accuracy and precisions for both picosulfate and BHPM (less than 15% each).

- Calibration Curve:
  The calibration (standard) curve for both picosulfate and BHPM were in range of 1.5 – 300 ng/mL. Linear regression equation of $y = a + bx$ with $1/x^2$ weighting were used to calculated the concentration.

- Accuracy and Precision:
  The accuracy and precision for both picosulfate and BHPM in urine were within acceptable range, less than 15%.

  - The inter-run precision and accuracy for picosulfate was less than 13.2 % and 6.6 % respectively.
  - The inter-run precision and accuracy for BHPM was less than 7.5 % and 9.4 % respectively.
  - The intra-run precision and accuracy for picosulfate was less than 12.4 % and 7.1 % respectively.
  - The intra-run precision and accuracy for BHPM (free) was less than 3.3 % and 8.9% respectively.
  - The intra-run precision and accuracy for BHPM (total) was less than 4.3 % and 4.9% respectively.

- Matrix Effect
  No significant matrix effects were observed for picosulfate and BHPM in human urine.

- Stability:
  - Freeze-Thaw Stability:
    Picosulfate and BHPM in urine were found to be stable for at least 4 freeze-thaw cycles.

  - Long-Term stability:
    Picosulfate and BHPM in urine were found to be stable for at least 133 days at -75^{o}C ± 15^{o}C.

  - Short-Term Stability:
    Both picosulfate and BHPM in urine were found to be stable for at least 24 hr in room temperature.

  - Post-Preparative Stability:
    - Picosulfate and BHPM in plasma are stable in cooled autosamplers at ~10^{o}C for at least 72 hours (3 days). BHPM (total) is stable in cooled autosamplers at ~10^{o}C for at least 24 hours (1 days).
    - Picosulfate and BHPM in plasma are stable in refrigerator at 5^{o}C ± 3^{o}C for at least 96 hours.

3 Labeling Recommendations

All recommended changes are noted by color font. Specifically, any additions are noted by underlined text in blue and any deletions are identified by ~~strikethrough text in red~~.

12.3 **Pharmacokinetics**

Sodium picosulfate, which is a prodrug, is converted to its active metabolite, BHPM, by colonic bacteria. After administration of 2 pouches of PICOPREP separated by 6 hours~~,~~ in 16 healthy volunteers, picosulfate reached a mean C_{max} of 3.2 ng/mL at approximately 7 hours (T_{max}). After the first (b) (4) the corresponding values were 2.3 ng/mL at 2 hours. The terminal half-life of picosulfate was 7.4 hours. The fraction of the absorbed sodium picosulfate dose excreted unchanged in urine (b) (4) was 0.1(b) (4)%. (b) (4)

Comment:

1. The current proposed label contains warning about co-medication within 1 hour of the start of administration of PICOPREP solution in section 7 drug interaction. However, Adequacy of 1 hour to avoid potential DDI will be further discussed as this product has 2 active ingredients, osmotic laxative activity of magnesium citrate and stimulant cathartic activity of sodium picosulfate.
2. Drug-Drug interaction with antibiotic will need to be addressed. There is a drug interaction concern in patients who are on antibiotics or just completed antibiotic therapy as production of the active metabolite, BHPM, depends on the normal gut flora.

4 Appendices

4.1 Individual Study Review

4.1.1 Study 000017, PK study

TITLE: An Open-Label, Single-Arm Study Investigating the Pharmacokinetic Parameters of Picosulfate, BHPM, and Magnesium in Healthy Subjects Following Administration of PICOPREP™

STUDY SITE:

Sponsor: Ferring International Pharmascience Center Us, Inc.
Parsippany, NJ 07054

Clinical Site: West Coast Clinical Trials (WCCT)
Cypress, CA, US.

Analytical Site: (b) (4)

Statistical Analysis: (b) (4)

PHASE OF STUDY: Phase 1 study

OBJECTIVE:
The primary objective of the study was to investigate the pharmacokinetic (PK) parameters of picosulfate, its active metabolite, bis-(p-hydroxyphenyl)-pyridyl-2-methane (BHPM), and magnesium following administration of 1 dose (2 pouches) of PICOPREP powder in solution.

Secondary objectives of the study were to investigate the fraction of administered dose of picosulfate and BHPM excreted in urine and to investigate the safety and tolerability of PICOPREP.

STUDY DESIGN:

Reference Products:
Not Applicable

Test Products:
PICOPREP (bowel cleansing agent prior to colonoscopy)
1 dose of PICOPREP comprised of 2 pouches of powder taken separately in water solution separated by 6 hours.

Each pouch contains of 16.1 g of powder, including 10.0 mg sodium picosulfate, 3.5 g magnesium oxide and 12.0 g citric acid powder.
When combined in water, magnesium oxide and citric acid form magnesium citrate in solution.

This study was an open-label, non- randomized study of PICOPREP in 17 healthy male and female subjects. Subjects were confined to the clinical research unit starting on the evening of Day -1, at least 10 hours prior to dosing. Subjects were required to fast (nothing by mouth except water) for at least 10 hours before the first PICOPREP pouch administration on Day 1. Subjects were dosed with 1 pouch of PICOPREP in the morning of Day 1, followed by a second PICOPREP pouch 6 hours later. The powder from each pouch was reconstituted in 5 ounces (150 mL) of cold water. Following the first administration of PICOPREP, subjects consumed five 8-ounce (240 mL) glasses of clear liquids at the rate of 1 per hour. Following the second administration of PICOPREP, subjects consumed three 8-ounce glasses of clear liquids at the rate of 1 per hour. Clear liquids could be continued until 12 hours after the time of the first PIOCOPREP pouch (6 hours after the time of the second PICOPREP pouch; approximately 8:00 PM), at which time subjects could be provided a light dinner. Breakfast was provided after the 24-hour blood and urine sample collection. Lunch was served approximately 4 hours after breakfast and dinner was served approximately 5 hours after lunch. While remaining resident in the clinical research unit, blood samples and total urine were collected for 48 hours following the first administration.

Key inclusion criteria:

- Healthy males and non-pregnant, non-lactating females ages between 22-64 with good health with a normal defecation pattern (at least 3 spontaneous bowel movements per week for 1 month prior to dosing) and no history of gastrointestinal disorders and have Body Mass Index between 18-35 kg/m2, were eligible to enroll.

Key exclusion criteria:

- Having presence or a history of clinically significant diseases of the renal, hepatic, gastrointestinal, cardiovascular, musculoskeletal, or gynaecological systems, or presence or history of clinically significant psychiatric, immunological, endocrine, or metabolic diseases
- Having cancer within the last 5 years, except for adequately managed basal cell carcinoma and squamous cell carcinoma of the skin.
- Taking prescribed medication (except hormonal contraceptives) or over-the-counter medication including herbal medicines, with the exceptions of acetaminophen and chromoglycate (according to the labeling), within 1 week of dosing, and St. John's Wort within 2 weeks of dosing
- History of hypersensitivity to component of study medication
- Having high daily consumption of caffeine-containing beverages (e.g., more than 5 cups of coffee or equivalent) with a risk of withdrawal symptoms arising during the study that could have confounded the safety evaluation; consumption of grapefruit juice within 1 week of dosing

Study Population:

This study had 17 healthy volunteers (7 males and 10 females) enrolled and 16 of them completed the study as planned receiving full dose (i.e., 2 pouches). Safety population included all 17 subjects and PK population included 16 subjects who completed the study. One subject was

discontinued from the study early per physician's decision as there was difficulty to access subjects' veins. There were no discontinuations reported due to AEs.

Summary of Demographic

Parameters	**Category/statistics**	**All subject (N= 17)**
Gender	Male	7
	Female	10
Race	American Indian or Alaska Native	0
	Asian	0
	Black or African American	4
	White	12
	Others	1
Ethnicity	Hispanic or Latino	7
	Not Hispanic or Latino	10
Age (years)	Mean	39
	SD	10.95
	Range	22-53
Height (cm)	Mean	16.67
	SD	12.03
	Range	150.5-185.9
Weight (kg)	Mean	73.79
	SD	14.377
	Range	53-103.9
BMI (kg/m2)	Mean	26.06
	SD	2.641
	Range	20.7-30.8

Pharmacokinetic Measurements:
PK blood samples (5 mL) were drawn at 0, 0.25, 0.5, 0.75, 1, 2, 4, 6, 6.25, 6.5, 6.75, 7, 8, 10, 12, 16, 24, 36, and 48 hours after the first administration of PICOPREP (19 blood samples).

Urine was collected following the full consumption of the first PICOPREP pouch until study end. Urine was collected continuously from each subject and pooled for analysis according to the following intervals: 0-6 hours; 6-12 hours, 12-16 hours, 16-24 hours, 24-36 hours and 36-48 hours.

Subjects having at least 3 quantifiable plasma concentration measurement of picosulfate were termed as having evaluable samples and qualified to be in the PK analysis (as PK population).

Some PK parameters were not calculated in all subjects depending on the number of timing of missing concentration or concentration below LLOQ.

The pharmacokinetic parameters $AUC_{(0\text{-}t_{last})}$, $AUC_{(0\text{-}\infty)}$, $C_{max,}$, $C_{max6,}$, $T_{max,}$, $T_{max,6}$, $t_{½\,z}$, $K_{el,}$ % AUC_{extrap}, for plasma picosulfate, BHPM, and serum magnesium were estimated from plasma concentrations using the SAS software with non-compartmental method.

Plasma concentrations that were below the quantification limit (BQL) were treated as 0 prior to the first or after the last quantifiable concentration. The BQL values that occurred between quantifiable measurements treated as missing for the purposes of PK parameters calculation. For descriptive summaries of concentrations, all BQL values were treated as 0.

As part of safety assessments, serum magnesium concentration were determined using blood samples collected at each of PK sampling time. Serum magnesium concentrations were corrected by subtracting the baseline concentration from the observed magnesium concentration.

For urine samples, Ae(0-t) values for both picosulfate and BHPM were determined in order to investigate the fraction of administered dose of picosulfate excreted in urine (i.e., fe), The fraction of picosulfate excreted (fe) was calculated as Ae(0-t)/Oral Dose.

Concomitant Medications
No concomitant medications were reported during the study

Bioanalytical Analysis:

Plasma Concentration:

Plasma picosulfate and its metabolite BMPH concentrations were determined with LC-MS/MS method.

Summary of the Performance in the routine analysis	**Picosulfate**	**BHPM**
Calibration range	0.100 – 20.0 ng/mL	0.100 – 20.0 ng/mL
Lower Limit of Quantification	0.100 ng/mL	0.100 ng/mL
r^2 (mean)	0.99377	0.99590
% cv at the LLOQ (n=4)	4.4	2.6
% bias at the LLOQ (n=4)	-0.9	-2.0
% cv at the lowest QC (n=8)	9.2	7.1
% bias at the lowest QC (n=8)	5.7	-5.9

Precision and accuracy of picosulfate and BHPM calibration standards quality controls:

Cal.Std Nominal Conc (ng/mL)		0.10	0.20	0.50	1.00	2.50	5.00	10.0	20.0
Picosulfate	Precision (%)	4.4	9.3	7.1	2.8	5.5	8.2	4.4	7.1
	Accuracy (%)	-0.9	0.8	-4.4	3.5	2.7	-4.3	3.6	-3.0
BHPM	Precision (%)	2.6	4.0	7.7	4.0	1.4	2.4	3.5	4.7
	Accuracy (%)	-2.0	3.9	-2.5	5.7	0.6	-1.0	1.6	-6.2

Precision and accuracy of picosulfate and BHPM quality controls:

Nominal QC Conc (ng/mL)		0.30	3.00	18.0
Picosulfate	Precision (%)	9.2	9.0	4.6
	Accuracy (%)	5.7	1.0	-1.7
BHPM	Precision (%)	7.1	5.8	4.5
	Accuracy (%)	-5.9	-2.8	-7.5

The analytical method used for above study is considered to be appropriately validated.

The highest plasma concentration observed in this study were 3.95 ng/mL for picosulfate and 0.377 for BHPM, which were all within the calibration standard range (0.1 to 20.0 ng/ml).

Linear regression equation of $y = a + bx$ with$1/x^2$ weighting were used to calculated the concentration.

Plasma samples, stored at approximately -70^{o}C, were analyzed within the time period for which the long-term stability of picosulfate and BHPM has been established.

- Plasma and urine samples were collected between 05/11/2011 through 5/13/2011.
- Plasma samples for picosulfate and BMPH were analyzed by May 31st, 2011.
- Stability of picosulfate and BHPM in human plasma at -70 °C was established for at least for 125 days.

Stock solutions, stored at 4^{o}C, were used within the time period for which stock stability was established.

- The stock solution for picosulfate and BHPM were prepared on 04/12/2011 and 05/19/2011. Stock solution of internal standards were prepared on 05/19/2011. All were stored in refrigerator.
- All plasma concentration analysis was conducted by 05/31/2011.
- Stock solutions of picosulfate and BHPM and their respective internal standards, Picosulfate-D13 and BHPM, were found to be stable for at least 61 day at 5^{o}C ± 3^{o}C.

Urine Concentration:

Urine picosulfate, BMPH (free) and BHPM after glucoronidase treatment (BMPH total) were determined with LC-MS/MS method.

Summary of the Performance in the routine analysis	Picosulfate	BHPM	BHPM (total)
Calibration range	1.50 – 300 ng/mL	1.50 – 300 ng/mL	1.50 – 300 ng/mL
Lower Limit of Quantification	1.50 ng/mL	1.50 ng/mL	1.50 ng/mL
r^2 (mean)	0.99527	0.99671	0.99762
% cv at the LLOQ (n=3)	4.0	2.0	1.2
% bias at the LLOQ (n=3)	0.0	-0.7	-1.3
% cv at the lowest QC (n=6)	10.8	4.5	4.2
% bias at the lowest QC (n=6)	6.1	2.8	9.2

Precision and accuracy of urine picosulfate and BHPM calibration standards quality controls:

Cal.Std Nominal Conc (ng/mL)		1.5	3.0	10.0	25.0	50.0	100	200	250	300
Picosulfate	Precision (%)	4.0	8.3	5.3	7.0	2.0	2.1	2.5	5.1	12.1
	Accuracy (%)	0.0	0.2	-1.4	1.1	2.0	-4.2	5.8	1.4	-4.9
BHPM (free)	Precision (%)	2.0	4.8	1.0	4.9	5.3	2.8	1.9	6.9	2.0
	Accuracy (%)	-0.7	-0.5	4.2	5.3	0.9	1.6	-4.0	0.1	-0.7
BHPM (total)	Precision (%)	1.2	4.8	4.7	0.6	6.2	1.8	5.6	3.2	2.8
	Accuracy (%)	-1.3	1.7	3.4	4.1	-2.4	6.4	-1.7	-2.9	-3.9

Precision and accuracy of urine picosulfate and BHPM quality controls:

Nominal QC Conc (ng/mL)		4.5	30.0	240
Picosulfate	Precision (%)	10.8	6.6	14.1
	Accuracy (%)	6.1	-6.3	0.8
BHPM (free)	Precision (%)	4.5	13.7	9.0
	Accuracy (%)	2.8	4.5	-1.5
BHPM (total)	Precision (%)	4.2	4.5	5.1
	Accuracy (%)	9.2	5.5	1.7

The analytical method used for above study is considered to be appropriately validated.

The highest urine concentration observed in this study were 170 ng/mL for picosulfate and 28.7 for BHPM, which were all within the calibration standard range (1.5 to 300.0 ng/ml).

Urine samples, stored at approximately -70°C, were analyzed within the time period for which the long-term stability of picosulfate and BHPM have been established.

- Plasma and urine samples were collected between 05/11/2011 through 5/13/2011.
- Urine samples for picosulfate and BMPH were analyzed by June 1st, 2011.

- Stability of picosulfate and BHPM in human urine at -70 °C was established for at least for 133 days.

Stock solutions, stored at 4°C, were not used within the time period for which stock stability was established.

- The stock solution for picosulfate , BHPM and internal standards were prepared on 02/9/2011, and they were stored in refrigerator.
- All urine concentration analysis was conducted between 05/19/2011 through 06/01/2011.
- Stock solutions of picosulfate and BHPM and their respective internal standards, Picosulfate-D13 and BHPM, were found to be stable for at least 61 day at 5°C ± 3°C.

Reviewer's comment: An information Request (IR) was sent to the sponsor on April 23rd, 2012 to address this issue. In response to this IR (dated May 7th, 2012), the sponsor stated the following: "To provide further assurance of the expected >92 days stability of the stock solutions, a new stability investigation assessing the degradation level at accelerated conditions will be conducted to cover the stability over the longer time period (>92 days) and Ferring commits to provide this in the first Annual Report for the NDA if the NDA is approved by the PDUFA date or an amendment to the pending NDA if the approval of the NDA is extended beyond the PDUFA date."

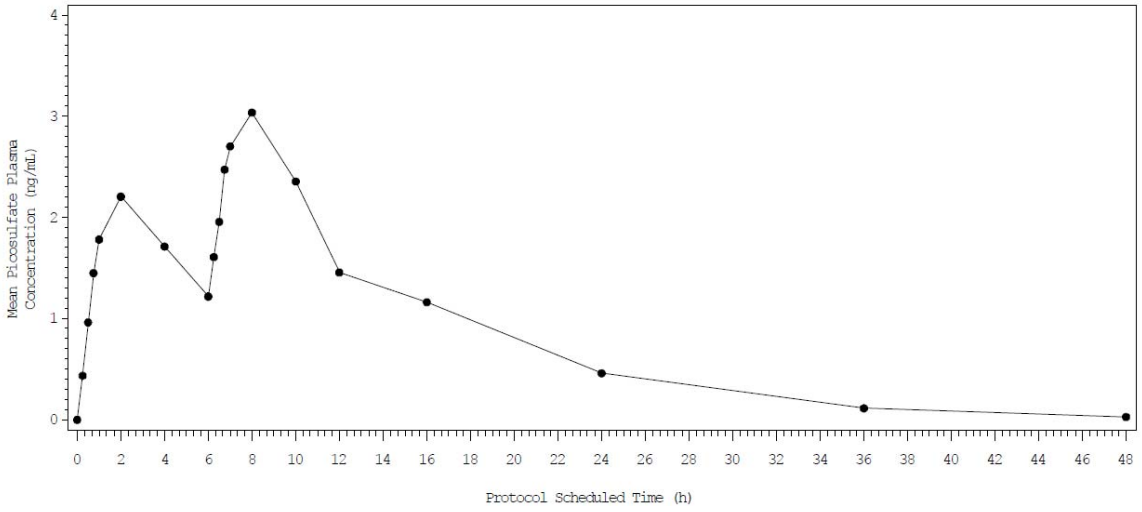
RESULTS:

Of 17 enrolled healthy subjects, 16 subjects completed study as planned receiving full dose (i.e., 2 pouches).

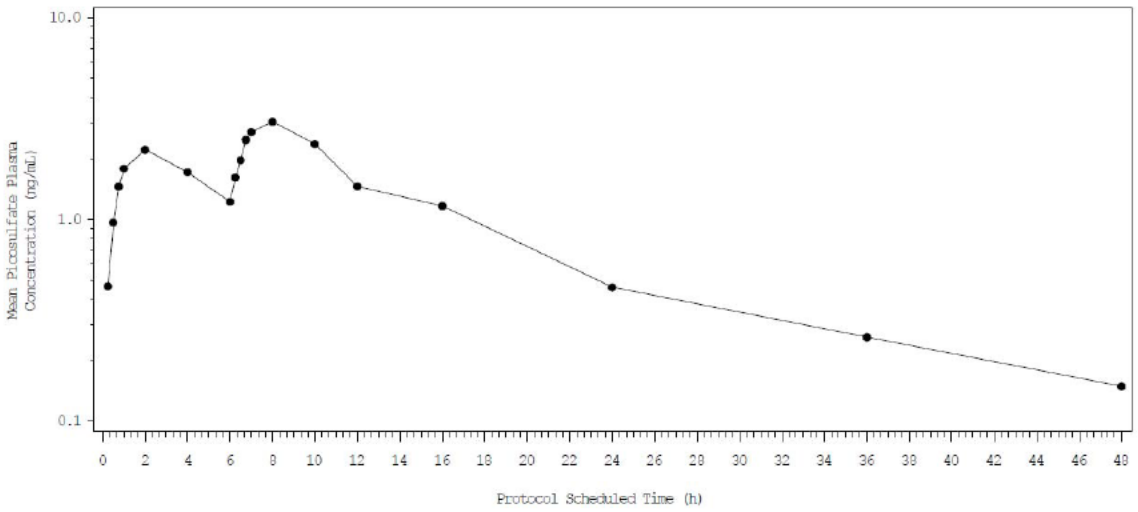
Picosulfate

Picosulfate is absorbed but plasma concentrations following each pouch administration are low.

Mean Picosulfate Plasma Concentrations by Protocol Scheduled Time (Linear scale)



Mean Picosulfate Plasma Concentrations by Protocol Scheduled Time (Semi-log scale)



Summary of Picosulfate Plasma Concentrations (ng/mL)

Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
Pre-Dose	16	0.0000	0.00000				0.000	0.0000	0.000
0.25 hr	16	0.4350	0.32303	74.121	0.3854	69.117	0.000	0.3560	1.270
0.5 hr	16	0.9619	0.48322	50.238	0.8528	55.332	0.338	0.7980	2.110
0.75 hr	16	1.4503	0.56900	39.233	1.3489	41.767	0.516	1.3000	2.480
1 hr	16	1.7812	0.95606	53.676	1.6040	47.487	0.739	1.5150	4.470
2 hr	16	2.2039	1.46021	66.254	1.9198	53.712	0.853	1.7550	6.970
4 hr	16	1.7118	1.40357	81.993	1.4422	57.683	0.691	1.3800	6.670
6 hr	16	1.2175	0.91393	75.066	1.0551	51.954	0.527	1.0330	4.480
6.25 hr	16	1.6068	0.96159	59.847	1.4606	41.394	0.874	1.3500	5.010
6.5 hr	16	1.9556	1.28379	65.640	1.7379	47.228	0.903	1.5750	6.430
6.75 hr	16	2.4719	1.51520	61.297	2.2025	48.275	1.200	2.1650	7.580
7 hr	16	2.7013	1.96652	72.800	2.3236	55.385	1.150	2.2350	9.510
8 hr	16	3.0338	2.62719	86.599	2.5090	62.021	1.010	2.5350	12.400
10 hr	16	2.3542	1.95503	83.045	1.9676	60.645	0.739	1.8650	9.300
12 hr	16	1.4542	1.23791	85.127	1.2116	59.901	0.539	1.1150	5.850
Day 2									
16 hr	16	1.1616	1.23731	106.516	0.9003	70.895	0.351	0.8615	5.620
24 hr	16	0.4593	0.43609	94.957	0.3603	73.660	0.122	0.3685	1.960
36 hr	16	0.1138	0.17504	153.879	0.2177	69.027	0.000	0.0000	0.610
Day 3									
48 hr	16	0.0278	0.06025	216.612	0.1474	13.916	0.000	0.0000	0.167

Summary of Picosulfate Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (ng/mL)	16	3.1906	2.57649	80.752	2.7068	56.533	1.240	2.6700	12.400
Cmax6 (ng/mL)	16	2.3221	1.44012	62.019	2.0370	53.663	0.853	2.0550	6.970
Tmax (h)	16	7.07	2.127	30.1	N/A	N/A	2.0	8.00	10.0
Tmax6 (h)	16	1.90	0.988	52.1	N/A	N/A	0.5	2.00	4.0
AUC(0-t) (ng*h/mL)	16	37.8140	32.64991	86.343	31.5236	59.370	13.720	28.7550	154.754
AUC(0-inf) (ng*h/mL)	16	40.0350	32.54143	81.282	33.9514	56.326	14.858	30.8901	156.379
%AUC Extrap (%)	16	7.07	3.950	55.9	N/A	N/A	1.0	6.98	15.3
Lambda_z (1/h)	16	0.1040	0.03065	29.467	N/A	N/A	0.039	0.1074	0.173
t1/2 (h)	16	7.42	3.157	42.5	N/A	N/A	4.0	6.47	17.9

Summary of Picosulfate Urine Concentrations (ng/mL)

Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
0-6 hr	16	5.818	3.1558	54.24	5.107	57.54	1.71	5.050	14.30
6-12 hr	16	21.214	34.6613	163.39	12.842	101.62	3.16	11.350	146.00
12-16 hr	16	31.531	40.2162	127.54	18.505	151.90	1.80	20.450	170.00
Day 2									
16-24 hr	16	13.746	14.3547	104.43	9.626	96.65	3.17	7.810	53.00
24-36 hr	16	2.641	2.7250	103.17	3.301	59.73	0.00	2.260	9.52
Day 3									
36-48 hr	16	1.027	2.4775	241.26	3.173	92.78	0.00	0.000	9.62

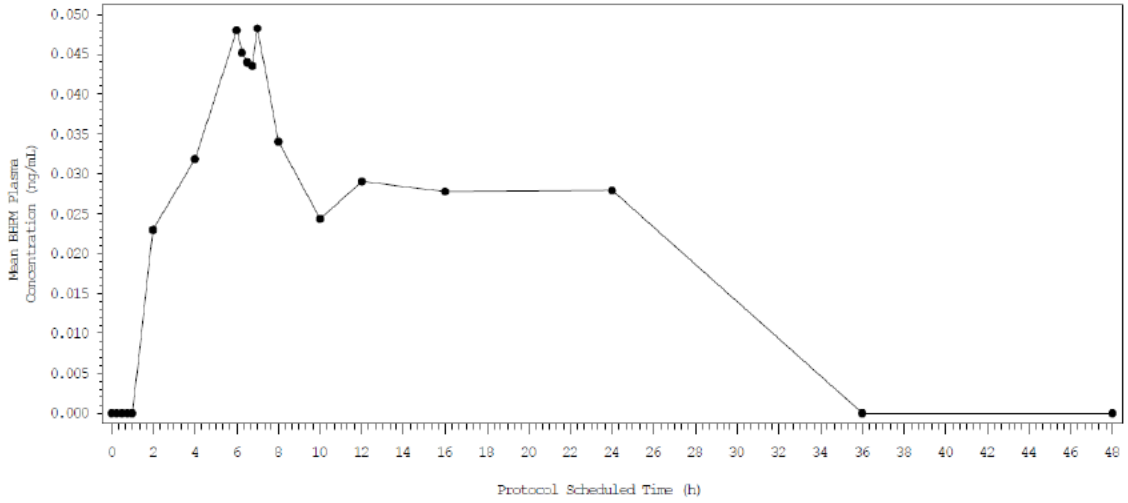
Summary of Picosulfate Urine Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Ae (0-t) (mg)	16	0.0193	0.00918	47.535	0.0177	43.008	0.009	0.0171	0.046
fe (%)	16	0.19	0.092	47.5	N/A	N/A	0.1	0.17	0.5

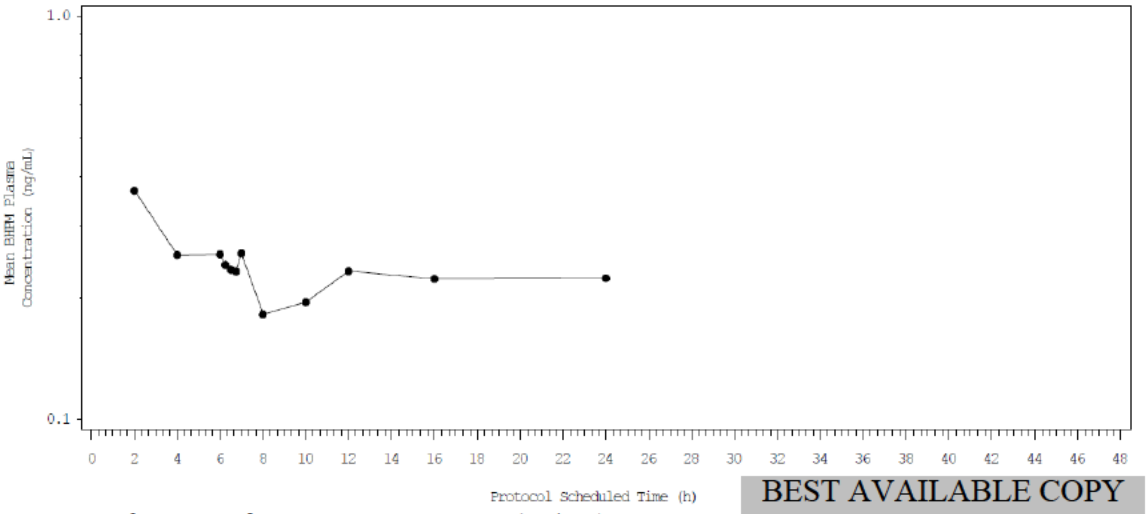
BHPM

The exposure of the active metabolite BHPM following the picosulfate administration was low with observable levels (above assay LLOQ 0.1 ng/mL) in only 3 of 16 PK-evaluable subjects. Because of this limited exposure of BHPM, the sponsor was not able to characterize the pharmacokinetic of BHPM.

Mean BHPM Plasma Concentrations by Protocol Scheduled Time (Linear scale)



Mean BHPM Plasma Concentrations by Protocol Scheduled Time (Semi-log scale)



Summary of BHPM Plasma Concentrations (ng/mL)

Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
Pre-Dose	16	0.0000	0.00000				0.000	0.0000	0.000
0.25 hr	16	0.0000	0.00000				0.000	0.0000	0.000
0.5 hr	16	0.0000	0.00000				0.000	0.0000	0.000
0.75 hr	16	0.0000	0.00000				0.000	0.0000	0.000
1 hr	16	0.0000	0.00000				0.000	0.0000	0.000
2 hr	16	0.0230	0.09200	400.000	0.3680		0.000	0.0000	0.368
4 hr	16	0.0319	0.08938	280.422	0.2490	31.748	0.000	0.0000	0.310
6 hr	16	0.0480	0.11019	229.562	0.2429	40.297	0.000	0.0000	0.377
6.25 hr	16	0.0452	0.09833	217.608	0.2387	16.685	0.000	0.0000	0.289
6.5 hr	16	0.0440	0.09646	219.216	0.2311	21.422	0.000	0.0000	0.293
6.75 hr	16	0.0436	0.09617	220.774	0.2276	24.846	0.000	0.0000	0.301
7 hr	16	0.0483	0.10623	220.166	0.2520	25.753	0.000	0.0000	0.317
8 hr	16	0.0341	0.07575	222.375	0.1758	33.393	0.000	0.0000	0.219
10 hr	16	0.0244	0.06852	281.090	0.1900	33.344	0.000	0.0000	0.239
12 hr	16	0.0291	0.07954	273.703	0.2322	7.622	0.000	0.0000	0.245
Day 2									
16 hr	16	0.0278	0.07630	274.329	0.2217	11.827	0.000	0.0000	0.241
24 hr	16	0.0279	0.07821	279.929	0.2186	30.587	0.000	0.0000	0.270
36 hr	16	0.0000	0.00000				0.000	0.0000	0.000
Day 3									
48 hr	16	0.0000	0.00000				0.000	0.0000	0.000

For the urine samples, 8 out of 16 subjects has measurable amount of free BHPM in urine, and the estimated percentage of free BHPM recovered in urine was 0.01%.

Summary of BHPM Plasma Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (ng/mL)	16	0.0539	0.11967	222.125	0.2797	28.820	0.000	0.0000	0.377
Cmax6 (ng/mL)	16	0.0492	0.11181	227.312	0.2511	36.402	0.000	0.0000	0.377
Tmax (h)	16	2.26	6.164	272.2	N/A	N/A	0.0	0.00	24.0
Tmax6 (h)	16	0.99	2.167	218.8	N/A	N/A	0.0	0.00	5.9
AUC(0-t) (ng*h/mL)	16	0.6739	1.74013	258.204	2.4600	197.941	0.000	0.0000	5.456
AUC(0-inf) (ng*h/mL)	2	6.9124	8.52895	123.387	3.3778	599.478	0.881	6.9124	12.943
%AUC Extrap (%)	2	46.36	16.243	35.0	N/A	N/A	34.9	46.36	57.8
Lambda_z (1/h)	2	0.2086	0.26159	125.395	N/A	N/A	0.024	0.2086	0.394
t1/2 (h)	2	15.54	19.488	125.4	N/A	N/A	1.8	15.54	29.3

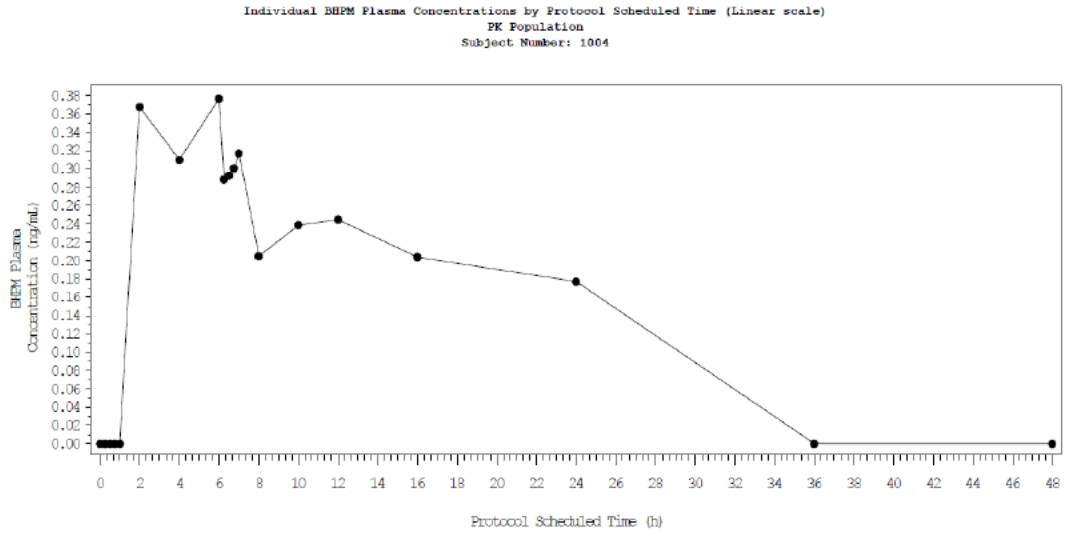
Summary of BHPM Urine Concentrations (ng/mL)

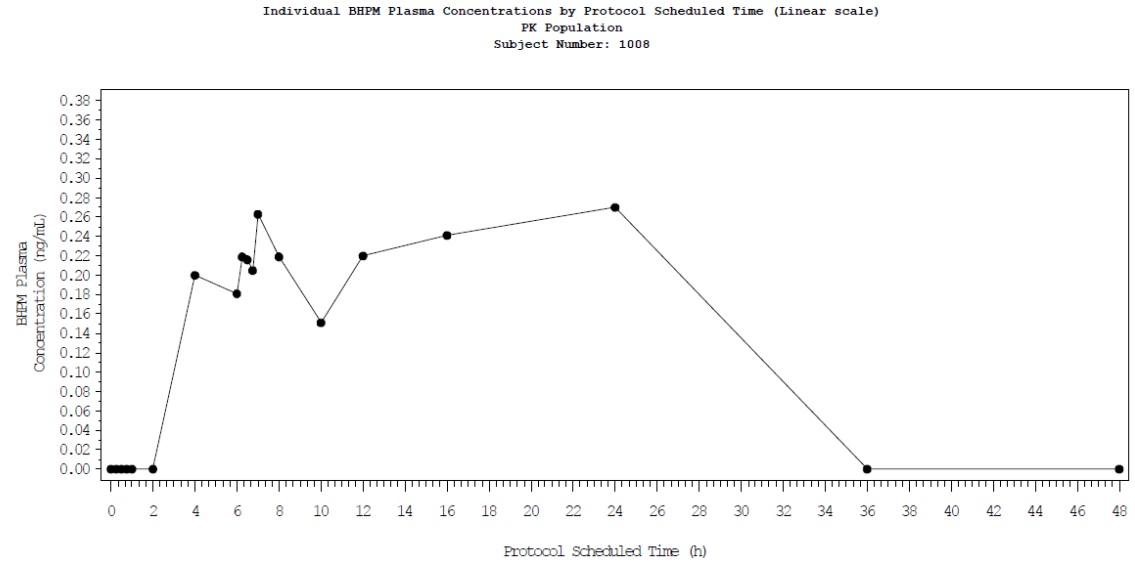
Time Point	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Day 1									
0-6 hr	16	0.000	0.0000				0.00	0.000	0.00
6-12 hr	16	0.252	1.0075	400.00	4.030		0.00	0.000	4.03
12-16 hr	16	1.669	3.6619	219.36	8.761	22.09	0.00	0.000	11.10
Day 2									
16-24 hr	16	5.234	8.5082	162.56	6.852	136.58	0.00	0.850	28.70
24-36 hr	16	0.678	1.9719	291.06	5.091	54.00	0.00	0.000	7.28
Day 3									
36-48 hr	16	0.000	0.0000				0.00	0.000	0.00

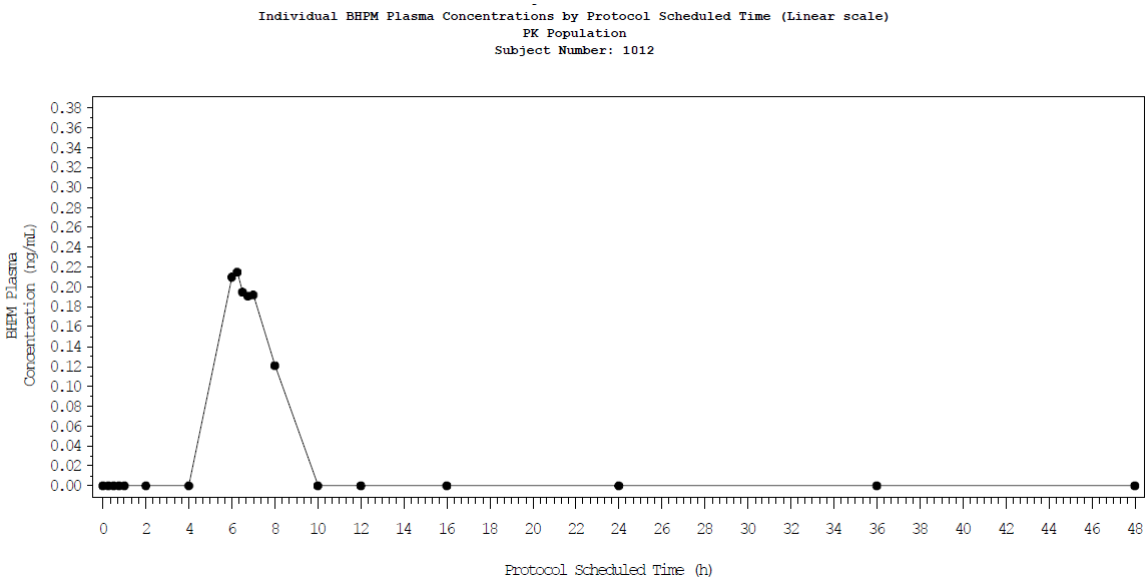
Summary of BHPM Urine Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Ae (0-t) (mg)	16	0.0011	0.00179	170.609	0.0013	156.989	0.000	0.0001	0.006
fe (%)	16	0.01	0.018	170.6	N/A	N/A	0.0	0.00	0.1

Since only 3 subjects had measurable amount of BHPM in plasma, the mean plasma level profile that includes all 16 subjects are below LOQ. The following graphs depict the plasma level of BHPM in theses 3 subjects who had measurable level of BHPM in plasma.



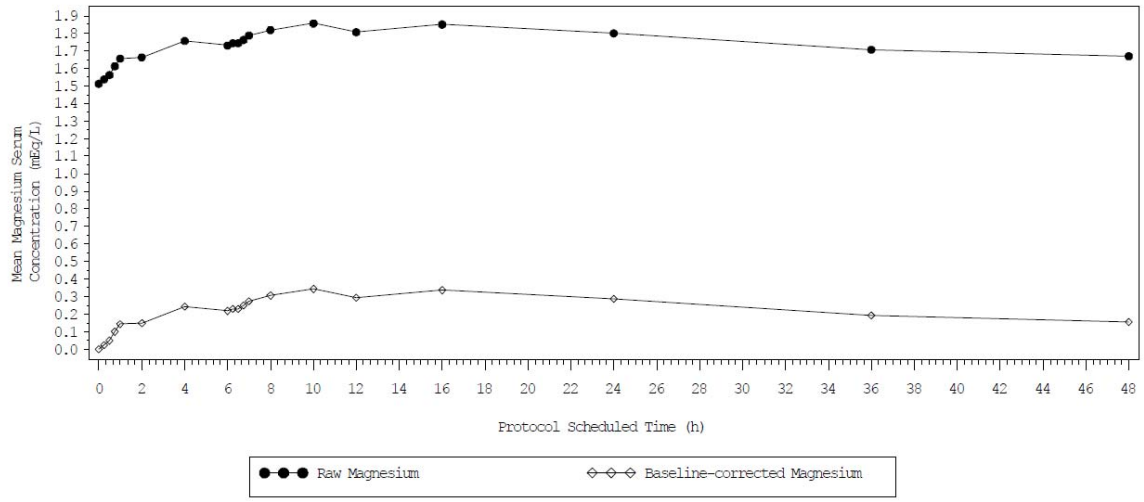




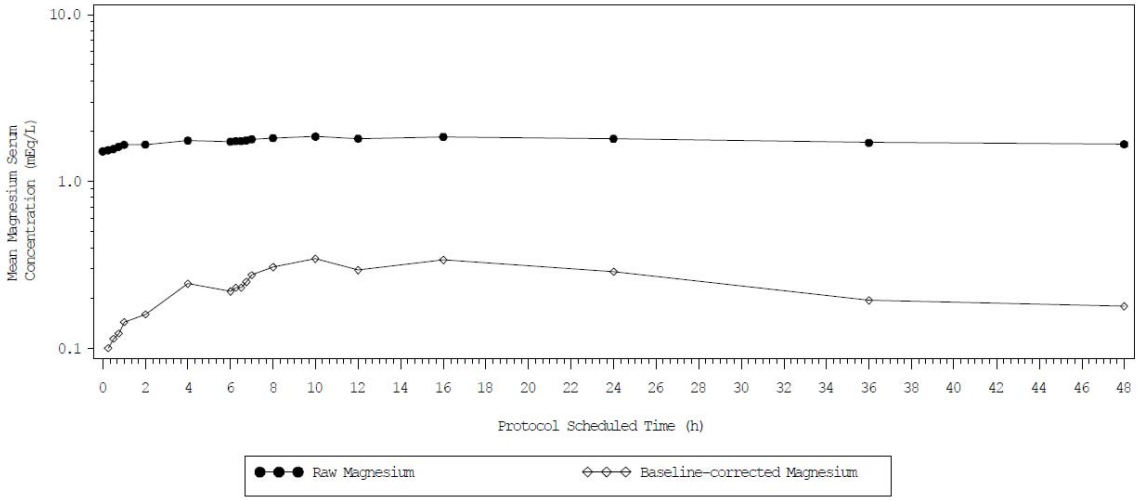
Magnesium Serum

All magnesium levels were within the normal range through-out the study period. (normal range is approximately between 1.5-2.5 mEq/L).

Mean Magnesium Serum Concentrations by Protocol Scheduled Time (Linear scale)



Mean Magnesium Serum Concentrations by Protocol Scheduled Time (Semi-log scale)



Summary of Raw Magnesium Serum Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (mEq/L)	16	1.89	0.159	8.4	1.88	8.3	1.6	1.90	2.3
Cmax6 (mEq/L)	16	1.76	0.131	7.4	1.76	7.4	1.5	1.80	2.1
Tmax (h)	16	10.03	3.953	39.4	N/A	N/A	4.0	10.00	16.1
Tmax6 (h)	16	3.38	1.142	33.8	N/A	N/A	1.0	4.00	4.0
AUC(0-t) (mEq*h/L)	16	84.2320	5.25051	6.233	84.0813	6.163	75.293	83.2745	97.173

Summary of Baseline-corrected Magnesium Serum Pharmacokinetic Parameters

Pharmacokinetic Parameter	n	Mean	SD	Arithmetic CV (%)	Geometric Mean	Geometric CV (%)	Minimum	Median	Maximum
Cmax (mEq/L)	16	0.38	0.093	24.8	0.37	23.3	0.3	0.35	0.6
Cmax6 (mEq/L)	16	0.25	0.063	25.3	0.24	24.2	0.2	0.20	0.4
Tmax (h)	16	10.03	3.953	39.4	N/A	N/A	4.0	10.00	16.1
Tmax6 (h)	16	3.38	1.142	33.8	N/A	N/A	1.0	4.00	4.0
AUC(0-t) (mEq*h/L)	16	11.4206	2.96715	25.981	11.0013	30.326	5.552	11.0627	15.414
AUC(0-inf) (mEq*h/L)	10	18.4901	5.64557	30.533	17.5967	35.749	8.898	19.2905	24.619
%AUC Extrap (%)	10	29.79	16.272	54.6	N/A	N/A	10.1	30.16	53.8
Lambda_z (1/h)	10	0.0353	0.01625	46.012	N/A	N/A	0.015	0.0340	0.058
t1/2 (h)	10	24.70	13.013	52.7	N/A	N/A	12.0	20.47	45.7

Baseline-corrected magnesium exposure was essentially one-fifth that of the raw (uncorrected) levels.

SAFETY:

The safety endpoints evaluated in this study included full blood count, physical examinations, vital signs, clinical chemistry, pregnancy test for female subjects, urinalysis, 12-lead electrocardiogram (ECG), and adverse event (AE) monitoring. According to the sponsor, there were no deaths, SAEs, or TEAEs leading to permanent discontinuations reported during the study. Overall, 2 (11.8%) subjects (Subjects 1006 and 1012) reported experiencing 4 TEAEs during the study. Two of the 4 TEAEs were treatment-related. All the TEAEs were considered mild in intensity.

Overview of Adverse Events (Safety Population)

Category	All Subjects (N=17)
Total number of TEAEs	4
Number of subjects with TEAEs, n (%)	2 (11.8%)
Number of severe TEAEs	0
Number of subjects with severe TEAEs, n (%)	0
Number of serious TEAEs	0
Number of subjects with serious TEAEs, n (%)	0
Number of Adverse Drug Reactions	2
Number of subjects with Adverse Drug Reactions[a], n (%)	2 (11.8%)
Number of subjects with TEAEs leading to treatment discontinuation, n (%)	0
Number of deaths	0

Source: Table [14.3.1.1]
TEAE = treatment emergent adverse event
[a] Adverse Drug Reaction was defined as an AE with possible, probably or unknown relationship to the study drug.

Summary of Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Severity
Safety Population

System Organ Class Preferred Term	All Subjects (N=17) Mild n (%)	 Moderate n (%)	 Severe n (%)
Total number of subjects with Treatment-Emergent Adverse Events	2 (11.8%)	0	0
Gastrointestinal disorders	1 (5.9%)	0	0
Nausea	1 (5.9%)	0	0
Injury, poisoning and procedural complications	1 (5.9%)	0	0
Procedural nausea	1 (5.9%)	0	0
Nervous system disorders	2 (11.8%)	0	0
Presyncope	1 (5.9%)	0	0
Somnolence	1 (5.9%)	0	0

The most commonly affected SOC was nervous system disorders reported in 2 (11.8%) subjects followed by gastrointestinal disorders and injury, poisoning and procedural complications reported in 1 (5.9%) subject, each.

SPONSOR'S CONCLUSION:

- Based on this single dose (two pouches) evaluation, low mean (±SD) peak plasma picosulfate concentrations of approximately 3.2 (±2.6) ng/mL were achieved and a terminal phase half-life of approximately 7.4 (±3.2) hours was observed.
- BHPM levels were consistently low and observed above the assay LLOQ in only 3 of 16 PK-evaluable subjects.
- Urinary recovery of picosulfate is 0.11 % of administered drug.
- All magnesium levels were within the normal range through-out the study period. Peak magnesium concentration was approximately 1.9 mEq/L.
- Baseline-corrected magnesium exposure was approximately one-fifth of the raw magnesium exposure representing administered plus endogenous levels.
- PICOPREP provides minimal picosulfate exposure following single dose (2 pouches) administration.

REVIEWER'S COMMENTS:

- All plots and PK parameters estimations are confirmed with raw PK data set.
- Both picosulfate and its active metabolite BHPM had very low systemic exposure (Cmax = 3.2 ng/mL and 0.05 ng/mL, respectively).
- Urinary recovery for both picosulfate and BHPM were very low, 0.19% and 0.01% of administered drug, respectively.
- 8 of 16 subjects had measurable amount of free BHPM in urine. Of theses 8 subjects, 4 subjects had measurable amount of free BHPM only at one time point, while other 4 subject had measurable mount at 2-3 time points out of 5 urine collection time point.
- All subjects measurable amount of total BHPM which includes glucuronidated BHPM.
- The sponsor did not collect fecal sample.

4.1.2 CYP Inhibition Study

TITLE: *In Vitro* Evaluation of Picosulphate as an Inhibitor of Cytochrome P450 (CYP) in Human Liver Microsomes

STUDY SITE:

Sponsor: Ferring International Pharmascience Center Us, Inc. Parsippany, NJ

Testing Site: (b) (4)

OBJECTIVE:
The primary objective of the study was to evaluate the ability of Picosulphate to inhibit the major CYP enzymes in human liver microsomes (namely CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5 [using two different substrates]) with the aim of ascertaining the potential of Picosulphate to inhibit the metabolism of concomitantly administered drugs.

STUDY DESIGN:

Test Product: Picosulfate (concentrations ranging from 0.018 to 18 µM)

Test System: Human liver microsomes from non-tranplantable, donated livers from a pool of 16 individuals of mixed gender

To assess whether picosulfate is a direct inhibitor of CYP enzyme, picosulfate, at target concentration ranging from 0.018 to 18 uM, was incubated with human liver microsome from a pool of 16 individuals, marker substrate (at a concentration approximately equal to *K*m or *S*50) and an NADPH-generating system for approximately 5 minutes to measure the residual CYP activity at 37 ± 1°C, in duplicate. To assess picosulfate's ability to act as a time-dependent and metabolism-dependent inhibitor, picosulphate (at the same concentrations used to evaluate direct inhibition) was preincubated with human liver microsomes in the absence and presence of an NADPH-generating system, respectively, for 30 minutes prior to incubation with the marker substrate at 37 ± 1°C, in duplicate. After the preincubation period, the marker substrate (at a concentration approximately equal to *K*m or *S*50) was added, and the incubation continued for 5 minutes to measure the residual CYP activity.

Table 1: **IC_{50} determinations: Summary of assay conditions to measure microsomal CYP enzyme activity – Direct, time-dependent and metabolism-dependent inhibition of enzymes by Picosulphate**

Enzyme	Enzyme reaction	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Pre-incubation time (min)	Picosulphate	
							Target concentrations (µM)	Solvent volume [b] (µL)
CYP1A2	Phenacetin *O*-dealkylation	40	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP2B6	Efavirenz 8-hydroxylation	3	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP2C8	Amodiaquine *N*-dealkylation	1.5	200	12.5	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP2C9	Diclofenac 4′-hydroxylation	6	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	40	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP2D6	Dextromethorphan *O*-demethylation	7.5	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP3A4/5	Testosterone 6β-hydroxylation	70	200	100	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8
CYP3A4/5	Midazolam 1′-hydroxylation	4	200	50	5	30	0, 0.018, 0.06, 0.18, 0.6, 1.8, 6, 18	1.8

Assay Control:

Test article interference check:

In order to assess for analytical interference by Picosulphate and/or possible metabolites in the methods used to determine the CYP activities, incubations (with and without preincubation for Picosulphate) that contain the highest concentration of picosulfate, but no probe substrate, were evaluated. According to the sponsor, the addition of Picosulphate to the test system had little or no impact on the validated analytical methods used to measure CYP enzyme activity. (data were not provided)

Negative controls:

Negative controls included incubations containing no Picosulphate (0 µM; Solvent Control) and incubations that contained Picosulphate but were not preincubated.

Positive controls:

For direct inhibition assay, the following table lists the positive control that were used at the normal incubation time in the presence of the marker substrate (approximately equal to *K*m or *S*50)

Enzyme	Positive control	Solvent (v/v, final incubation concentration)	Concentration studied
CYP1A2	α-Naphthoflavone	Methanol (0.1%)	0.5 µM
CYP2B6	Orphenadrine	DMSO (0.2%)	750 µM
CYP2C8	Montelukast	Methanol (0.1%)	0.05 µM
CYP2C9	Sulfaphenazole	Methanol (0.1%)	2.0 µM
CYP2C19	Modafinil	DMSO (0.1%)	250 µM
CYP2D6	Quinidine	Water	0.5 µM
CYP3A4/5	Ketoconazole	Methanol (0.1%)	0.15 / 0.075 µM [a]

a The concentration of ketoconazole was 0.15 µM when testosterone was the marker substrate and 0.075 µM when midazolam was the marker substrate for CYP3A4/5.

For metabolism-dependent assays, additional zero-minute and 30-minute preincubations were conducted in the presence of the following inhibitors.

Enzyme	Positive control	Solvent (v/v, final incubation concentration)	Concentration studied
CYP1A2	Furafylline	DMSO (0.1%)	1.0 µM
CYP2B6	Phencyclidine	Water	30 µM
CYP2C8	Gemfibrozil glucuronide	Acetonitrile with 0.1% v/v formic acid (0.5%)	5.0 µM
CYP2C9	Tienilic acid	Tris base (0.002 mg/mL)	0.25 µM
CYP2C19	*S*-Fluoxetine	Methanol (1%)	20 µM
CYP2D6	Paroxetine	Water	0.3 µM
CYP3A4/5	Troleandomycin	Acetonitrile (0.1%)	25 / 7.5 µM [a]

a The concentration of troleandomycin was 25 µM when testosterone was the marker substrate and 7.5 µM when midazolam was the marker substrate for CYP3A4/5.

Bioanalytical Analysis:

All analyses were performed with validated HPLC/MS/MS methods. Zero-time incubations served as blanks.

Enzyme	Metabolite monitored
CYP1A2	Acetaminophen
CYP2B6	8-Hydroxyefavirenz
CYP2C8	*N*-Desethylamodiaquine
CYP2C9	4′-Hydroxydiclofenac
CYP2C19	4′-Hydroxymephenytoin
CYP2D6	Dextrorphan
CYP3A4/5	6β-Hydroxytestosterone
CYP3A4/5	1′-Hydroxymidazolam

Statistical tests and data processing:
Nonlinear regression was used to determine the IC50 values. Levenberg-Marquardt algorithm was used to perform non-linear regression fitting of the data to the following 4-parameter sigmoidal-logistic IC50 equation:

$$Y = Min + (Max - Min) / (1 + (Conc/IC_{50})^{Slope})$$

As percent of control values are utilized, Min is set = 0 and Max is set to 100.

RESULTS:

Table 3: Summary of results: *In vitro* evaluation of Picosulphate as an inhibitor of human CYP enzymes

		Direct inhibition		Time-dependent inhibition		Metabolism-dependent inhibition		
		Zero-minute preincubation		30-minute preincubation without NADPH		30-minute preincubation with NADPH		Potential for time-dependent and/or metabolism-dependent inhibition [c]
Enzyme	Enzyme reaction	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	IC_{50} (µM) [a]	Inhibition observed at 18 µM (%) [b]	
CYP1A2	Phenacetin *O*-dealkylation	>18	0.70	>18	4.2	>18	NA	Little or no
CYP2B6	Efavirenz 8-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP2C8	Amodiaquine *N*-dealkylation	>18	NA	>18	11	>18	21	Little or no
CYP2C9	Diclofenac 4′-hydroxylation	>18	2.3	>18	1.6	>18	6.4	Little or no
CYP2C19	*S*-Mephenytoin 4′-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP2D6	Dextromethorphan *O*-demethylation	>18	5.0	>18	0.60	>18	9.4	Little or no
CYP3A4/5	Testosterone 6β-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no
CYP3A4/5	Midazolam 1′-hydroxylation	>18	NA	>18	NA	>18	NA	Little or no

a Average data (i.e., percent of control activity) obtained from duplicate samples for each test article concentration were used to calculate IC_{50} values.

b Maximum inhibition (%) is calculated with the following formula and data for the highest concentration of test article evaluated (results are rounded to two significant figures): Maximum inhibition (%) = 100% − Percent solvent control.

c Time-dependent and metabolism-dependent inhibition was determined by comparison of IC_{50} values with and without preincubation and NADPH, by comparison of the maximum inhibition (%) with and without preincubation and NADPH and by visual inspection of the IC_{50} plot.

NA Not applicable. No value was obtained as the rates at the highest concentration of Picosulphate evaluated (18 µM) were higher than the control rates.

SPONSOR'S CONCLUSION:

There was little or no evidence of direct, time-dependent or metabolism-dependent inhibition by Picosulphate of any of the CYP enzymes evaluated.

REVIEWER'S COMMENTS:

- Selection of substrate and substrate concentration used in this study are acceptable (according the DDI guidance)
- Due to very little inhibition by picosulfate, IC50 was not estimated precisely (all > 18 uM). Based in the available data, the possibility of in vivo interaction in systemic circulation is remote as Cmax/IC50 < 0.1 (Cmax = 3.2 ng/mL = 6.65 nM).
- In gastrointestinal tract, the gut concentration of picosulfate (I_{gut}) is expected to be approximately 140 µM (10 mg/150 mL = 66.7 ug/mL = 140 uM). Base on this estimation, the possibility of in vivo interaction in gut is smallas I_{gut}/IC50 <10.
- The proposed label has warning language about co-administering a drug within one hour of the start of administration of PICOPREP. This labeling language can minimize the inhibition effect of picosulfate on other drug.
- Since the IC50 value was not estimated precisely with maximum concentration of 18 uM, and estimated gut concentration of picosulfate is approximately 140 uM, the sponsor should have evaluated a concentration higher than 140 uM. However, since I_{gut}/IC50 is less than 10 with current data to eliminate the need for further in vivo DDI study, and current proposed label has proper warning about co-administering a drug within one hour of the start of administration of PICOPREP, inhibition effect of picosulfate on other drug is minimal and the current inhibition study design with maximum of 18 uM inhibitor concentration is acceptable.

4.1.3 CYP Induction Study

TITLE: In Vitro Evaluation of Picosulphate as an Inducer of Cytochrome P450 Expression in Cultured Human Hepatocytes

STUDY SITE:

Sponsor: Ferring International Pharmascience Center Us, Inc.
Parsippany, NJ

Testing Site: (b) (4)

OBJECTIVE:
The objective of this study was to investigate the effects of treating primary cultures of fresh human hepatocytes with Picosulphate on the expression of cytochrome P450 (CYP) enzymes.

STUDY DESIGN:

Test Product: Picosulfate (concentrations ranging from 0.018, 0.18 and 1.8 µM)

Test System: Freshly cultured human hepatocytes from separate livers from three human donors

The isolated hepatocyte cultures from three separate livers were treated once daily for three consecutive days with one of three concentrations of picosulphate (0.018, 0.18 or 1.8uM) or one of three know human CYP enzyme inducers, omeprazole (50 µM) for CYP1A2, phenobarbital (750 µM) for CYP2B6 and rifampin (10 µM) for CYP3A4 as positive controls. Approximately 24 hour after the final treatment, cultures were visualized with microscope to evaluate the morphological integrity of the hepatocype cultures. Following three day treatment, the microsomal samples were isolated from the hepatocyte culture and incubated with marker substrate at 37°C to measure the CYP enzyme activity.

Table 1: Summary of assay conditions to measure microsomal CYP enzyme activity

Enzyme	Substrate	Substrate concentration (µM)	Substrate solvent (v/v, final incubation concentration)	Protein concentration (µg/mL) [a]	Incubation time (min)
CYP1A2	Phenacetin	80	Methanol (0.4%)	40	30
CYP2B6	Bupropion	500	Water	40	30
CYP3A4/5	Testosterone	250	Methanol (2.0%)	40	10

a Incubation volume = 200 µL

The potential of Picosulphate to cause cytotoxicity was evaluated by assessing the release of lactate dehydrogenase (LDH) into the culture medium (a measure of cell membrane integrity).

Bioanalytical Analysis:

All analyses were performed with validated HPLC/MS/MS methods. Zero-time incubations served as blanks.

Enzyme	Metabolite monitored
CYP1A2	Acetaminophen
CYP2B6	Hydroxybupropion
CYP3A4/5	6β-Hydroxytestosterone

Statistical tests and data processing:
Percent positive control was calculated according to the following equation:

$$\text{Percent positive control} = \frac{(\text{activity of test article treated cells} - \text{activity of vehicle control})}{(\text{activity of positive control} - \text{activity of vehicle control})} \times 100$$

Fold increases were calculated by dividing the enzymatic rate for each treatment group by that of the vehicle control.

RESULTS:

Morphology:
Treatment of cultured human hepatocytes with Picosulphate, up to 1.8 µM for 3 days caused little or no change in cellular morphology.

Cytotoxicity:
Treatment of cultured human hepatocytes with Picosulphate, up to 1.8 µM caused little or no change in the release of LDH from the treated hepatocytes into the cell culture media.

Enzyme Induction:
Treatment of cultured human hepatocytes with Picosulphate, up to 1.8 µM caused, on average, little or no change (less than 2-fold increase) in CYP1A2, CYP2B6, and CYP3A4 activities.

Table 3: CYP activity: The effects of treating cultured human hepatocytes with Picosulphate or prototypical inducers on microsomal cytochrome P450 (CYP) enzyme activity

Treatment	Concentration	Enzyme activity (pmol/mg protein/min) [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	29.1 ± 8.3	51.7 ± 5.0	2960 ± 1570
Picosulphate	0.018 µM	31.6 ± 10.1	53.0 ± 8.8	3420 ± 2090
Picosulphate	0.18 µM	29.2 ± 7.6	50.9 ± 2.8	3540 ± 1980
Picosulphate	1.8 µM	28.7 ± 7.5	50.8 ± 1.4	3310 ± 1770
Omeprazole	50 µM	296 ± 75	NA	NA
Phenobarbital	750 µM	NA	784 ± 154	NA
Rifampin	10 µM	NA	NA	19800 ± 3300

Table 4: **CYP activity fold increase: The effects of treating cultured human hepatocytes with Picosulphate or prototypical inducers on microsomal cytochrome P450 (CYP) enzyme activity**

Treatment	Concentration	Fold increase [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	1.00 ± 0.28 [b]	1.00 ± 0.10 [b]	1.00 ± 0.53 [b]
Picosulphate	0.018 µM	1.08 ± 0.15	1.02 ± 0.12	1.13 ± 0.44
Picosulphate	0.18 µM	1.02 ± 0.22	0.987 ± 0.041	1.26 ± 0.49
Picosulphate	1.8 µM	1.00 ± 0.21	0.988 ± 0.090	1.12 ± 0.28
Omeprazole	50 µM	10.2 ± 1.2	NA	NA
Phenobarbital	750 µM	NA	15.4 ± 4.0	NA
Rifampin	10 µM	NA	NA	8.29 ± 4.55

Table 5: **CYP activity percent positive control: The effects of treating cultured human hepatocytes with Picosulphate or prototypical inducers on microsomal cytochrome P450 (CYP) enzyme activity**

Treatment	Concentration	Percent positive control [a]		
		Phenacetin *O*-dealkylation (CYP1A2)	Bupropion hydroxylation (CYP2B6)	Testosterone 6β-hydroxylation (CYP3A4/5)
Dimethyl sulfoxide	0.1% (v/v)	0 ± 0	0 ± 0	0 ± 0
Picosulphate	0.018 µM	0.789 ± 1.488	0.285 ± 0.807	1.83 ± 7.01
Picosulphate	0.18 µM	0.00921 ± 2.26899	-0.144 ± 0.349	2.32 ± 9.28
Picosulphate	1.8 µM	-0.180 ± 2.207	-0.202 ± 0.716	1.48 ± 4.87
Omeprazole	50 µM	100 ± 0	NA	NA
Phenobarbital	750 µM	NA	100 ± 0	NA
Rifampin	10 µM	NA	NA	100 ± 0

a Values are the mean ± standard deviation of three determinations (human hepatocyte preparations H1034, H1035 and H1036).

NA Not applicable

For CYP1A2, the positive control is omeprazole and the vehicle control is DMSO.

For CYP2B6, the positive control is phenobarbital and the vehicle control is DMSO.

For CYP3A4/5, the positive control is rifampin and the vehicle control is DMSO.

SPONSOR'S CONCLUSION:

Picosulphate, at concentrations up to 1.8 µM, is not an inducer of CYP1A2, CYP2B6 or CYP3A4/5 activity in cultured human hepatocytes where the prototypical inducers caused anticipated increases in CYP activities.

REVIEWER'S COMMENTS:

- Selection of positive control and their concentrations used in this study are acceptable. Positive control inducers resulted in anticipated increase in CYP activities.
- Selection of substrates used in this study to evaluate the enzyme activities are acceptable. However, the substrate concentrations for bupropion-hydroxylation for CYP 2D6 and testosterone 6β-hydroxylation for CYP3A4 were above their respective Km values.
    - testosterone 6β-hydroxylation Km = 52-194 uM
    - testosterone 6β-hydroxylation substrate concentration = 500 uM

    - bupropion-hydroxylation Km = 67-168 uM
    - bupropion-hydroxylation substrate concentration = 250 uM

- Test drug concentrations used in this study well covers the expected therapeutic range for picosulfate.
    - Test drug concentrations used in this study were 0.018, 0.18 and 1.8 uM
    - The expected C_{max} for picosulfate is approximately 3.2 ng/mL = 6.65 nM.

- Because PICOPREP is intended for one time use for colonoscopy, its induction potential is not considered critical.

5 OCP Filing/Review Form

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**202535**	**Brand Name**	**PicoPrep**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**sodium picosulfate (an NME), citric acid and magnesium oxide**
Medical Division	**Gastroenterology and Inborn Errors of Metabolism Products**	**Drug Class**	**Bowel Prep**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**cleansing of the colon as a preparation for colonoscopy in adults**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Powder for Oral Solution**
Pharmacometrics Reviewer		**Dosing Regimen**	**16.1 g of powder for oral solution**
Date of Submission	**9-16-2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**05-21-2012**	**Sponsor**	**Ferring Pharmaceuticals Inc**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**07-16-2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		**2 validation reports and 2 bioanalytical report**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	**X**	**2**		
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	**X**	**1**		
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				

In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**0**	**7**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The clinical studies were conducted with to-be-marketed product.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		CYP inhibition and induction studies were conducted.
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			Picosulfate, BHPM, and magnesium levels were measured. However, magnesium citrate level

					was not measure.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?		X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No PK information about magnesium citrate
	General				
18	Are the clinical pharmacology and	X			

	biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

The NDA is **filelable** from clinical pharmacology perspective.

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Dilara Jappar — Oct 6th, 2011
Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee
Team Leader/Supervisor — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DILARA JAPPAR
05/22/2012

SUE CHIH H LEE
05/22/2012

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**202535**	**Brand Name**	**PicoPrep**
OCP Division (I, II, III, IV, V)	**III**	**Generic Name**	**sodium picosulfate (an NME), citric acid and magnesium oxide**
Medical Division	**Gastroenterology and Inborn Errors of Metabolism Products**	**Drug Class**	**Bowel Prep**
OCP Reviewer	**Dilara Jappar**	**Indication(s)**	**cleansing of the colon as a preparation for colonoscopy in adults**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Powder for Oral Solution**
Pharmacometrics Reviewer		**Dosing Regimen**	**16.1 g of powder for oral solution**
Date of Submission	**9-16-2011**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review	**05-21-2012**	**Sponsor**	**Ferring Pharmaceuticals Inc**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**07-16-2012**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**4**		**2 validation reports and 2 bioanalytical report**
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:	**X**	**2**		
Transporters characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:	**X**	**1**		
Patients- (non- C IBS)				
single dose:				
multiple dose:				
Other disease patients				
Dose proportionality – (Dose-Response)				
fasting / non-fasting single dose:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**0**	**7**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		The clinical studies were conducted with to-be-marketed product.
2	Has the applicant provided metabolism and drug-drug interaction information?		X		CYP inhibition and induction studies were conducted.
3	Has the sponsor submitted bioavailability data	X			Picosulfate, BHPM, and

	satisfying the CFR requirements?				magnesium levels were measured. However, magnesium citrate level was not measure.
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?		X		
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?		X		
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?		X		
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No PK information about magnesium citrate
	General				
18	Are the clinical pharmacology and biopharmaceutics	X			

	studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?				
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

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Dilara Jappar — Oct 6th, 2011
Reviewing Clinical Pharmacologist — Date

Sue-Chih Lee
Team Leader/Supervisor — Date

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/s/

DILARA JAPPAR
11/10/2011

SUE CHIH H LEE
11/10/2011