A Single-Dose, Open-label, Randomized, Crossover, Drug-Drug Interaction Study of Nifedipine Extended-release Tablets with or without Multiple-dose Administration of Proton-pump inhibitor Omeprazole/sodium bicarbonate in Healthy Volunteers

PROTOCOL

BPSUSA Protocol Number:	2001
Protocol Version Date:	August 3, 2017
Sponsor:	Foods and Drug Administration, USA.

PROTOCOL APPROVAL SIGNATORY PAGE:

I am aware of, and agree to comply with, all of the procedures contained within this protocol and requirements of applicable regulatory agencies:

_____ _____

Kathleen Doisy, M.D. Date (Mmm dd, yyyy)
Principal Investigator
BioPharma Services USA Inc.

BioPharma SERVICES USA INC.

[redacted]

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_____ _____

Dajun Sun, Ph.D. Date (Mmm dd, yyyy)
Project Officer/Contract Office's Representative

Office of Generic Drugs, Food and Drug Administration

REVISION HISTORY

Amendment 1

Description:

1. Dajun Sun serves both the project officer and Contract Office's Representative.
2. Zegerid is switched to Cipla's generic copy of omeprazole/sodium bicarbonate capsules at the same strength of 40 mg/1100 mg.
3. Dr. Kathleen Doisy serves as the PI to replace Dr. David Moreton.

Rationale:

1. [redacted]

Version Date – April 18, 2017

*(strikethrough represents deletion and underline represents addition)

Description:

1. Protocol version number was deleted and the Protocol version will now be considered from the date of the Protocol – "Protocol Version Date".

2. Section 6.0 – Study Population – The first sentence was changed as follows: A ~~total of 64~~ **required number of** healthy volunteers, male and non-pregnant female, aged between 18 and 55 years of age will be screened according to the inclusion and exclusion criteria listed in Sections 7.3 and 7.4 to be sure that about 62-64 are randomized.

3. Section 7.2 - Inclusion Criteria – Bullet point 1 – following underlined words were added:

Healthy, males and non-pregnant **(excluding nursing and lactating)** female volunteers, 18 to 55 years of age, inclusive.

4. Section 7.6 – Study Restrictions - Bullet point 6 – the number of days of restriction was changed to 14 from previous 30 days.
   Any concomitant medication [prescription medications (e.g., prescription pills, topical systemic creams, inhalants, sprays [except for contraceptives]) or over-the-counter (e.g., acetaminophen, Ricola, oral multivitamins) (except for spermicidal/barrier contraceptive products)], any herbal and/or dietary supplements will not be permitted for ~~30~~ **14** days prior to first study drug administration until the last blood draw in the final study period unless deemed otherwise by the PI/Sub-Investigator for treatment of any adverse events (AEs).

5. Section 8.2 – Food and Fluid Intake – *Study arm C and Study arm D* – The underlined hours were added to the meal times:
   In this study, meals will be served at approximately 4.5, 9.5, 13.5, 24.5, 28.5, 33.5, 37.5, 48.5, 52.5, 57.5, 61.5**, 72.5, 76.5, 81.5, and 85.5** hours after capsules dosing on Day 3. (Section 2.0 – Table of Study Procedures footnote i) was also updated with these timepoints).

6. Section 14.5 – Compensation for Participation – The compensation was re-structured in the table. However, the total compensation remains the same.

7. Similar changes were incorporated in the study ICF.

Rationale:

1. To be version consistent with the changes made after Research Involving Human Subjects Committee (RIHSC)-IRB (FDA) request.
2. RIHSC-IRB (FDA) requested change.
3. RIHSC-IRB (FDA) requested change.
4. RIHSC-IRB (FDA) requested change.
5. RIHSC-IRB (FDA) requested change.
6. The compensation structure was re-aligned to be more subject friendly.
7. For Protocol and ICF to be consistent.

Version Date – May 16, 2017

[redacted]

Version Date – August 3, 2017

Description:

1. In sections 2.0 – Table of Study Procedures – time point for procedure/activity ICF was changed from Period 1 to Screening. Superscript "a" explanation was updated from "at first period check in only" to "at screening and prior to any medical screening procedures"
2. In Sections 1.0, 3.2, 6.0, and 7.1, sample size of ~~64~~ 65-66 subjects will be enrolled (minimum of 52 subjects to complete the study). In Section 6.0, "No replacement will be made after randomization" was deleted.

Rationale:

1. To ensure there is no ambiguity in the protocol as it pertains to obtaining a study ICF.
2. Increasing the number of enrolling subjects to 65-66 and allowing replacement of subjects prior to the first dosing can better ensure a minimum of 52 subjects to complete the clinical study.

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SPONSOR, INVESTIGATORS AND FACILITIES

Principal Investigator:	Kathleen Doisy, M.D. BioPharma Services USA Inc. [redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Sponsor:	Dajun Sun, Ph.D. Staff fellow Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, [redacted]	[redacted]	[redacted]
B[redacted]	[redacted]	[redacted]	[redacted]

INVESTIGATOR CREDENTIALS

Dr. Kathleen Doisy, Principal Investigator

[redacted]

[redacted]

Kathleen Doisy, M.D.
Principal Investigator

Date (Mmm dd, yyyy)

[redacted]

1.0 SYNOPSIS

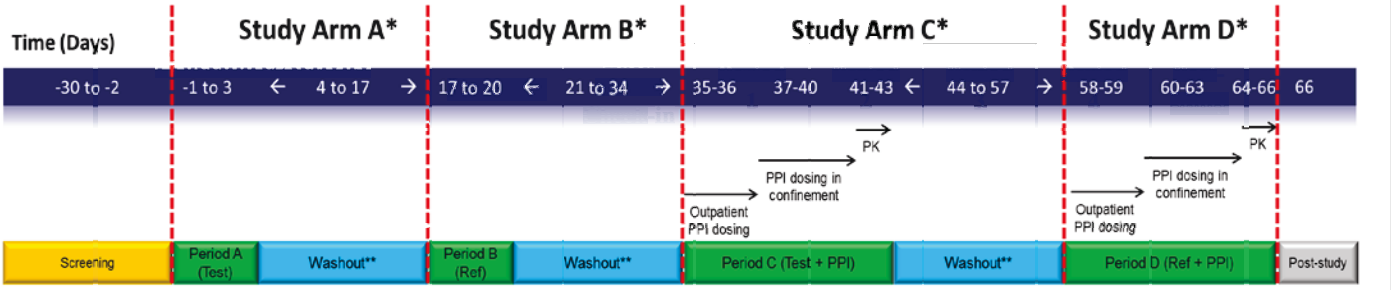
Title:	A Single-Dose, Open-label, Randomized, Crossover, Drug-Drug Interaction Study of Nifedipine Extended-release Tablets with or without Multiple-dose Administration of Proton-pump inhibitor Omeprazole/sodium bicarbonate in Healthy Volunteers.
Objective:	The objective of this study is to compare pharmacokinetics of nifedipine from both generic Nifedipine oral extended-release tablets, 60 mg and reference listed drug PROCARDIA XL (nifedipine; RLD) extended-release tablets, 60 mg when co-administered with or without proton pump inhibitor (PPI)/antacid, omeprazole/sodium bicarbonate 40 mg/1100 mg capsules in healthy males and non-pregnant females under fasting conditions, whose gastric pH will be measured by SmartPill™ technology.
Experimental Design:	A single-dose, randomized, open-label, drug-drug interaction (DDI), 4-way crossover, four-treatment, four-sequence, bioequivalence study.
Study Rationale:	This is an in vivo study to evaluate the test and RLD formulation pharmacokinetics of nifedipine when co-administered with or without PPI/antacid. The outcome of this study will help the Agency advance further understanding about product PK performance of nifedipine in potential patient population co-administered with PPI or with abnormal gastric pH and improve review standards for equivalence of this category of oral ER products if necessary.
Study Population:	65-66 subjects will be enrolled (minimum of 52 subjects to complete the study). The subjects will be dosed in two or more groups. Healthy, non-smoking male and non-pregnant female volunteers, 18-55 years of age, with a body mass index (BMI) within 18.5-35.0 kg/m^2, inclusive.
Test Drug:	Nifedipine extended-release tablets, 60 mg [redacted]
Reference Drug:	PROCARDIA XL extended-release tablets, 60 mg [redacted]
PPI/antacid:	omeprazole/sodium bicarbonate 40 mg/1100 mg capsule
Study arm A (Test Drug):	1 x 60 mg Nifedipine extended-release tablet
Study arm B (Reference Drug):	1 x 60 mg PROCARDIA XL (nifedipine) extended-release tablet
Study arm C (PPI/ antacid + Test Drug)	1 x 40 mg/1100 mg omeprazole/sodium bicarbonate capsule daily over a period of 7 days + 1 x 60 mg Nifedipine extended-release tablet on day 7
Study arm D (PPI/ antacid + Reference Drug)	1 x 40 mg/1100 mg omeprazole/sodium bicarbonate capsule daily over a period of 7 days + 1 x 60 mg PROCARDIA XL (nifedipine) extended-release tablet on day 7
Duration of Confinement:	<u>Study arm A and B:</u> • Day 1: From at least 10 hours prior to dosing

	• Day 2-3: All day confinement. • Day 4: After 48 hours blood draw, subjects will be discharged. A total confinement of at least 58 hours in each study arm. <u>Study arm C and D:</u> • Day 1-2 (walk-in): From at least 1 hour prior to omeprazole/sodium bicarbonate capsules dosing until at least 1 hour post-dose. • Day 3: From at least 1 hour prior to omeprazole/sodium bicarbonate capsules dosing followed by check-in procedure or subjects can check-in the evening. • Day 4-8: All day confinement. • Day 9: After 48 hours blood draw, subjects will be discharged. Total confinement from Day 1 to Day 9 will be of at least 148 hours (approximately 6 days) in each study arm. The total anticipated duration of the clinical part of the study will be approximately 13 to 19 weeks (since signing the ICF by the first subject up to the last planned study procedure of the last subject).
Washout:	At least 14 days after Nifedipine only dosing (Study arms A or B) and for Study arms C and D (e.g., omeprazole/sodium bicarbonate followed with Nifedipine), at least 14 days after the last dose with omeprazole/sodium bicarbonate until the next treatment dose.
Safety Monitoring:	• Vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], and temperature) will be obtained throughout the study. • Laboratory testing (hematology, serum biochemistry and urinalysis) will be conducted at check-in for all study arms. • The PI/Sub-Investigator will be present from approximately 30 minutes prior to SmartPill™ administration until at least 6 hours after the last subject is dosed with nifedipine ER tablets in each study arm. • The PI/Sub-Investigator will remain on-call throughout the duration of the study.
Type of Vacutainer	Pre-chilled K_2EDTA Vacutainer®, 4 mL
Blood Sampling Time points:	Pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36 and 48 hours after nifedipine dosing in each study arm.
Total Blood Volume:	Approximately 345 mL of blood, including ~29 mL for pre- and post- study procedures and ~ 44 mL for laboratory testing at each period check-in.
Gastric pH	Gastric pH using SmartPill™ Technology SmartPill™ capsules will be administered on Day 2 approximately 30 minutes before nifedipine dosing (Study arm A and B), and on Day 7 prior to dosing of nifedipine and omeprazole/sodium bicarbonate capsules (Study arm C and D).

Gastric pH Time-points	The pH will be measured at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours after SmartPill™ administration in each study arm. The pH will be monitored continuously for 24 hours post-dose.
Analyte(s) to be measured:	Plasma samples will be assayed for nifedipine using a validated analytical method according to the principles of Good Laboratory Practice.
Pharmacokinetics and Gastric pH:	Descriptive statistics of pharmacokinetic parameters AUC_t, AUC_{inf} and C_{max}, as well as T_{max}, λ and $T_{1/2}$ will be calculated for each study arm group. The descriptive statistics of the gastric pH and change of gastric pH will be calculated for both test and reference products.
Statistical Analysis:	For Pharmacokinetic Data: Analysis of Variance (ANOVA) for ln-transformed AUC_t, AUC_{inf} and C_{max}, and untransformed T_{max}, λ and $T_{1/2}$. T_{max} will also be analyzed using an additional non-parametric test (Wilcoxon test). The 90% confidence intervals (CI) for the ratios of geometric means for AUC_t, AUC_{inf} and C_{max} will be calculated based on the least square means (LSMEANS) and ESTIMATE of the ANOVA. For Pharmacodynamic Data: Analysis of Variance (ANOVA) for gastric pH and change of gastric pH from baseline will be carried out.

2.0 TABLE OF STUDY PROCEDURES

Procedure/Activity	Time points						
	Screening	Each Period Check-in	Period 1	Period 2	Period 3	Period 4	Post-Study
ICF	X[a]						
Drugs of Abuse	X	X					
Alcohol Test	X	X					
Cotinine	X	X					
Pregnancy (hCG) Test*	X	X					
Vital Signs (BP, HR, RR and Temperature)	X		X[b]	X[b]	X[b]	X[b]	X
Laboratory Testing	X	X[#]					X
Medical History	X						
BMI	X						
ECG	X						
Inclusion/Exclusion Assessment	X						
Restrictions Compliance Check		X	X	X	X	X	
Physical Exam	X						X
SmartPill™ Administration			X[c]	X[c]	X[c]	X[c]	
Nifedipine ER tablets Dosing (Test)			X[d]		X[d]		
PROCARDIA XL (Ref)				X[d]		X[d]	
omeprazole/sodium bicarbonate capsules Dosing					X[e]	X[e]	
pH Measurement			X[f]	X[f]	X[f]	X[f]	
PK Sampling			X[g]	X[g]	X[g]	X[g]	
Adverse Event Reporting		X[h]	X	X	X	X	X
Meals		X	X[i]	X[i]	X[i]	X[i]	



* This is an example of the sequence Period A → B → C → D.
** Set 14 days of a washout period as an example
A (Test) = generic nifedipine extended-release tablets
B (Ref) = Procardia XL tablets
C (PPI+Test) = Omeprazole/sodium bicarbonate capsules (proton pump inhibitor) + generic nifedipine extended-release tablets
D (PPI+Ref) = Omeprazole/sodium bicarbonate capsules (proton pump inhibitor) + Procardia XL tablets
PK = pharmacokinetic study

[#] Laboratory testing (hematology, serum biochemistry, and urine analysis) at each period check-in for Study arm A and B on Day 1 and for Study arm C and D it will be done at check-in on Day 3.

[a] At screening and prior to any medical screening procedures.

[b] Vital signs measurements (BP, HR, RR and temperature) to be obtained for Study arm A and B, and on Day 7 for Study arm C and D at pre-dose and at 4, 12 and 24 hours after dosing nifedipine ER tablets in each study period, and at pre-dose and 1 hour after omeprazole/sodium bicarbonate capsules daily dosing (Day 1 to Day 6) in each study period for Study arm C and D.

[c] SmartPill™ capsules will be administered 30 minutes before dosing nifedipine ER tablets (Study arm A and B), and 30 minutes before dosing nifedipine ER tablets and omeprazole/sodium bicarbonate capsules (Study arm C and D) on Day 7.

[d] Study arm A and B:Nifedipine dosing on Day 2 in each study period

Study arm C and D: Nifedipine dosing on Day 7 co-administered with omeprazole/ sodium bicarbonate in each study period.

[e] Study arm C and D: omeprazole/ sodium bicarbonate capsules dosing for 7 days (Day 1 to 7) in each study period.

[f] pH will be measured at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours after SmartPill™ administration in each study period.

[g] PK sampling - Pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36, and 48 hours after nifedipine dosing in each study period.

[h] Pre-dose conditions at Period 1 check-in.

[i] Study arm A and B: Meals will be served at approximately 6.5, 10.5, 14.0, 24.5, 28.5, 33.5 and 37.5 hours after dosing.

Study arm C and D: Meals will be served at approximately 4.5, 9.5, 13.5, 24.5, 28.5, 33.5, 37.5, 48.5, 52.5, 57.5, 61.5, 72.5, 76.5, 81.5 and 85.5 hours after omeprazole/sodium bicarbonate capsules dosing on Day 3. Meals will be served at approximately 6.5, 10.5, 14.0, 24.5, 28.5, 33.5, and 37.5 hours after dosing on Day 7.

3.0 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

3.1 Background Information

Among the top 200 prescription oral drugs in the US, approximately one-third are modified-release (MR) oral drug products (e.g. extended-release, delayed-release) which provide unique clinical benefits compared to their immediate-release (IR) counterparts. The complicated formulation designs and manufacturing processes of MR oral dosage forms have posed regulatory challenges for the evaluation of Abbreviated New Drug Applications (ANDAs). Oral ER dosage forms have been used extensively for long-term therapeutic efficacy, reduced adverse events, and improved patient compliance. Common formulation designs which help achieve an extended release for oral dosage forms can be briefly classified into three types: matrices, coated beads, and osmotic pumps. The mechanisms employed to achieve a controlled release in oral drug delivery systems are based on diverse and complex principles (e.g. dissolution, diffusion, osmosis, swelling, and erosion) among which the development of push-pull osmotic pump systems and diffusion- or dissolution-controlled monolithic devices or reservoir systems has been widely applied to many ER oral dosage forms [1]. In some cases, a generic ER product may employ a completely different release mechanism and/or critical excipients from those of the reference listed drug (RLD) products.

One of the most noted advantages of osmotic drug delivery systems is the ability to maintain a zero-order (i.e. constant) drug release rate, independent of the physical properties of the drug substances and a number of external parameters such as dissolution medium pH and hydrodynamics of mixing [2]. For this reason, a number of oral ER dosage forms have been formulated using osmotic release oral system (OROS) technology (e.g. Invega, Concerta, Procardia XL, Ditropan XL, and Tegretol-XR) (also known as “osmotic pump”) to achieve desired pharmacokinetic (PK) profiles and clinical performance [3]. The generic applicants of oral ER drug products may employ a different controlled-release design from that of the osmotic pump RLD, considering that the manufacturing processes or formulation designs of RLD product may not always be available to the generic applicants (e.g. patent protection).

A question that arises with generic oral ER products is related to pH-dependent dissolution kinetics in comparison with that of their RLD. Depending on the formulation design, poorly water-soluble nifedipine with a pKa in the gastrointestinal (GI) pH range may have pH-dependent solubility. In this case, the in vitro dissolution of matrix-based ER tablets may also be pH-dependent as the drug release is controlled by diffusion driven by a concentration gradient between surface drug concentration and solubility. Bioequivalence (BE) between these

generic products based on a matrix design and their RLDs based on an osmotic pump design is often demonstrated via an in vivo bioequivalence pharmacokinetic study using healthy volunteers whose gastric pH is within the physiological norm (e.g. pH 1.2). In this case, ANDA applicants are not required to employ the same release mechanism and formulation design as the osmotic pump RLD. Whether or not the two products are still bioequivalent in subjects with an elevated gastric pH environment as commonly occurred in patients with achlorhydria or population who take concomitant proton pump inhibitors (PPIs) would require additional evaluation.

Food and Drug Administration performed a comprehensive and systematic analysis on generic MR oral drug products in different therapeutic classes based on in-house data on formulations, clinical studies, and post-market surveillance work. The formulations of 15 osmotic pump MR oral drug products and all their approved and pending generic counterparts were identified and analyzed for potential failure modes related to bioequivalence in a risk analysis. Additional modeling work was used to predict the impact of dissolution variations of carbamazepine, metoprolol succinate, venlafaxine HCl (lag time of drug release) [4], and nifedipine (pH-dependent dissolution behavior) MR oral drugs on the resulting PK profiles. These simulation studies helped identify the range of release curve alterations within which the BE of generic products can be maintained and also help suggest potential *in vivo* predictive dissolution conditions. Based on in-house formulation analysis and dissolution testing, a generic version of nifedipine extended-release (ER) tablets using a matrix design has been identified as having pH-dependent dissolution behaviors compared to its reference product (i.e. Procardia XL) in which the drug release is pH-independent.

Nifedipine is a calcium channel blocker, indicated for the long-term treatment of hypertension and angina. The drug substance is a practically water-insoluble weak acid (pKa 3.9), which has a pH-dependent solubility across physiological pHs in the GI tract [5]. Currently, there is one RLD of oral ER nifedipine tablets based on an osmotic pump design (i.e. Procardia XL) [6] Nifedipine release from Procardia XL is independent of the pH environment of the dissolution medium or gastrointestinal motility according to the drug label [6], whereas the drug label of the generic copy of nifedipine ER tablets based on a matrix design does not mention any drug-drug interaction with PPIs as per required consistent labeling between generic and reference products (See the package insert of generic nifedipine ER tablets). Nevertheless, the generic counterpart of nifedipine ER tablets employing a matrix formulation design may have pH-dependent dissolution profiles in comparison to the RLD, considering that such a pH-dependent dissolution behaviors of similar nifedipine ER products formulated in a matrix design have been reported in literature [5, 7, 8] marketed in Europe. Additional in vivo studies have confirmed

the different PK behaviors of two European nifedipine ER oral drug products using an osmotic pump or matrix design [7-9]. These clinical studies clearly showed that the pharmacokinetic properties and behaviors of two nifedipine ER dosage forms (osmotic pump vs. matrix) have a different sensitivity to concomitant food intake which is known to alter the gastric pH. Nevertheless, the current labeling on generic nifedipine ER tablets referencing Procardia XL does not mention any drug-drug interaction with proton pump inhibitors as the RLD and generic labeling should be consistent.

The generic nifedipine ER product which utilizes a different release mechanism could amplify or reduce such a pH dependence (e.g. osmotic pump RLD vs. matrix generic counterparts). Under the existing regulatory practice, ANDA applicants of oral ER drug products are not required to conduct BE studies comparing the generic products with the RLD in patients chronically taking PPIs or with an abnormal gastric pH. This may render these generic ER products more or less dependent on gastric pH modification, commonly occurred in patients taking concomitant PPIs for the treatment of gastric acid-related disorders. It has been noted that PPIs (e.g. lansoprazole, omeprazole, esomeprazole) and PPIs with antacids (e.g. omeprazole/sodium bicarbonate) can drastically elevate the gastric pH, thus potentially changing the equilibrium solubility of co-administered drug substances or altering their release profiles. In the case of nifedipine, clinical studies have shown that in healthy volunteers receiving a single dose of 10 mg nifedipine IR tablets, AUC and Cmax of nifedipine after pretreatment with omeprazole 20 mg once daily for 8 days were 1.26 and 0.87 times those after pre-treatment with placebo [10-12]. This shows a potential drug-drug interaction between PPIs and nifedipine that is formulated in an immediate-release dosage form.

Whether such a pH-dependent in vitro dissolution behavior can translate into any difference in in vivo pharmacokinetics for generic nifedipine ER tablets based on a matrix design can only be evaluated in subjects with an elevated gastric pH. Additional regulatory requirements in this category of oral drug products may be warranted if such changes in PK profiles as a result of pH-dependent dissolution behaviors for matrix-based nifedipine ER tablets could affect the efficacy and safety profiles. Due to complicated release mechanisms, quality attribute profiles, and *in vivo* pharmacokinetic behaviors of ER products, FDA is assessing the need of a drug-drug interaction study between PPIs/antacids (e.g. omeprazole/sodium bicarbonate) and generic nifedipine ER products based on a formulation design which is different from that of its RLD. In so doing, FDA aims to evaluate formulation dependence of interaction with PPIs/antacids which are known to elevate gastric pH and potentially affect in vivo drug release. The study results will help the Agency gain a better understanding of drug-drug interaction between oral

MR products and PPIs/antacids and establish regulatory standards of bioequivalence approaches for this category of generic oral ER products.

3.2 Rationale

The current research proposal is funded by the FDA via a contract agreement (HHSF 22320161004I) with the purpose of investigating the in vivo performance consistency of oral MR drug products under the effect of an elevated gastric pH environment (e.g. co-administration of PPIs). We have chosen to focus on nifedipine ER tablets (brand name and generic products) because the RLD is an osmotic pump and there is a generic version commercially available as matrix-based formulations. We will evaluate the bioequivalence in an open label, clinical study with and without multiple-dose PPI co-adminsitered with the brand name drug and a generic version. In the current study, clearance, volume of distribution, and absorption, as determined by physiological variables (e.g. gastric emptying, motility, pH), are assumed to have less inter-occasion variability compared to the variability arising from formulation performance within the same subject [6, 12-14]. Therefore, differences between two products because of formulation factors can be determined [15].

This clinical study will be open-label because blood concentration levels cannot be influenced by knowledge of the identity of treatment, however, the laboratory analysts will be unaware of the study product sequences. The period of 48 hours, over which blood samples will be collected, is considered to be sufficiently long to adequately characterize the concentration-time profile of extended-release nifedipine (the mean half-life of nifedipine is less than 10 hours). It has been shown that administering multiple-dose (e.g. 7 days) PPIs (i.e. omeprazole) in healthy volunteers can effectively increase their gastric pH [16, 17]. In the current clinical study, subjects will be dosed with PPIs in the first two days without confinement (i.e. outpatient visits) to reduce their burden. Dosing the subjects with PPIs in confinement for the last 5 days is deemed necessary in order to standardize the food effect (omeprazole administration under fasting conditions) prior to the PK study of nifedipine ER tablets. Since the omeprazole PD effect can be eliminated after 3-5 days of discontinuing the drug, a wash-out period of at least 7 days is sufficient to allow the complete elimination of the drug before subsequent dosing and to avoid carry-over effects. In this study, a wash-out period of at least 14 days is chosen to ensure the scientific and logistic conduct of the study.

Nifedipine (Procardia XL®, Pfizer) is a cardiovascular drug that is used for the long-term treatment of hypertension and angina. Nifedipine is a weak acid (pKa 3.9) which is practically insoluble in water and has a pH-dependent solubility across pH 1-7. According to the Biopharmaceutical Classification System (BCS), it is a Class II compound with an oral bioavailability determined by aqueous solubility.

Nifedipine (Procardia XL®) was approved by the FDA in 1989. After loss of patent protection, the FDA approved several generic nifedipine ER tablets manufactured by Osmotica (2005), Mylan (2010), Matrix Laboratories (2010), and others. Although several *in vivo* and *in vitro* methods are available to measure product bioavailability and bioequivalence for orally administered drug products, the FDA guidelines recommend reliance on pharmacokinetic measures such as the rate (i.e., maximum concentration [C_{max}]) and extent (i.e., area under the concentration-time curve [AUC]) of absorption as these best reflect systemic exposure(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320010.pdf). Nifedipine should be administered orally and may be given with or without food [6]. Omeprazole/sodium bicarbonate should be taken orally on empty stomach at least one hour before meal[2]. Therefore, the investigational medicinal products (IMPs) will be administered orally under fasting conditions to better distinguish possible differences between the IMPs. This is in compliance with the Guidance for Industry [15].

The specific aim of this research is to conduct a randomized, single-dose, four-treatment, four-period cross-over *in vivo* bioequivalence study in 65-66 healthy adult volunteers (males and non-gravid females) (The sample size is discussed in Section 7.1 of this Study Protocol) to evaluate the *in vivo* performance of brand and generic nifedipine ER tablets with or without co-administration of multiple-dose PPIs. The pharmacokinetics of nifedipine as Procardia XL® and generic nifedipine ER tablets, Procardia XL® with PPIs and generic nifedipine ER tablets with PPIs will be determined and compared in healthy volunteers under fasting conditions.

3.3 Product Information

PROCARDIA XL [6]

Nifedipine is a calcium ion influx inhibitor (slow-channel blocker or calcium ion antagonist) and inhibits the transmembrane influx of calcium ions into cardiac muscle and smooth muscle. The contractile processes of cardiac muscle and vascular smooth muscle are dependent upon the movement of extracellular calcium ions into these cells through specific ion channels. Nifedipine selectively inhibits calcium ion influx across the cell membrane of cardiac muscle and vascular smooth muscle without altering serum calcium concentrations. The indications of nifedipine include:

I. Vasospastic Angina

Procardia XL is indicated for the management of vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm. In those patients who have had angiography, the presence of significant fixed obstructive disease is not incompatible

with the diagnosis of vasospastic angina, provided that the above criteria are satisfied. Procardia XL may also be used where the clinical presentation suggests a possible vasospastic component, but where vasospasm has not been confirmed, e.g., where pain has a variable threshold on exertion, or in unstable angina where electrocardiographic findings are compatible with intermittent vasospasm, or when angina is refractory to nitrates and/or adequate doses of beta blockers.

II. Chronic Stable Angina (Classical Effort-Associated Angina)

Procardia XL is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents.

In chronic stable angina (effort-associated angina), nifedipine has been effective in controlled trials of up to eight weeks duration in reducing angina frequency and increasing exercise tolerance, but confirmation of sustained effectiveness and evaluation of long-term safety in these patients is incomplete.

Controlled studies in small numbers of patients suggest concomitant use of nifedipine and beta-blocking agents may be beneficial in patients with chronic stable angina, but available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely, since severe hypotension can occur from the combined effects of the drugs (See WARNINGS).

III. Hypertension

Procardia XL is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

Omeprazole/sodium bicarbonate **[18]**

Omeprazole/sodium bicarbonate is a proton pump inhibitor (PPI) indicated for,

- Short-term treatment of active duodenal ulcer.
- Short-term treatment (4-8 weeks) of active benign gastric ulcer.
- The treatment of heartburn and other symptoms associated with GERD for up to 4 weeks [*Symptomatic GERD*]
- The short-term treatment (4-8 weeks) of erosive esophagitis which has been diagnosed by endoscopy.
- Maintaining healing of erosive esophagitis.
- Capsules 40 mg/1100 mg (omeprazole/sodium bicarbonate) is indicated for the reduction of risk of upper gastrointestinal bleeding in critically ill patients.

Mechanism of Action:

Omeprazole belongs to a class of anti-secretory compounds, the substituted benzimidazoles, that do not exhibit anticholinergic or H2 histamine antagonistic properties, but that suppress gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell. Because this enzyme system is regarded as the acid (proton) pump within the gastric mucosa, omeprazole has been characterized as a gastric acid-pump inhibitor, in that it blocks the final step of acid production. This effect is dose related and leads to inhibition of both basal and stimulated acid secretion irrespective of the stimulus. Animal studies indicate that after rapid disappearance from plasma, omeprazole can be found within the gastric mucosa for a day or more.

Omeprazole is acid labile and thus rapidly degraded by gastric acid. Capsules are immediate-release formulations that contain sodium bicarbonate which raises the gastric pH and thus protects omeprazole from acid degradation.

Pharmacokinetics:

Absorption

In separate *in vivo* bioavailability studies, when omeprazole/sodium bicarbonate Oral Suspension and Capsules are administered on an empty stomach 1 hour prior to a meal, the absorption of omeprazole is rapid, with mean peak plasma levels (% CV) of omeprazole being 1954 ng/mL (33%) and 1526 ng/mL (49%), respectively, and time to peak of approximately 30 minutes (range 10-90 min) after a single-dose or repeated-dose administration. Absolute bioavailability of omeprazole/sodium bicarbonate Powder for Oral Suspension (compared to I.V. administration) is about 30-40% at doses of 20 – 40 mg, due in large part to pre-systemic metabolism.

When omeprazole/sodium bicarbonate Oral Suspension 40 mg/1680 mg was administered in a two-dose loading regimen, the omeprazole AUC (0-inf) (ng·hr/mL) was 1665 after Dose 1 and 3356 after Dose 2, while Tmax was approximately 30 minutes for both Dose 1 and Dose 2. Following single or repeated once daily dosing, peak plasma concentrations of omeprazole are approximately proportional from 20 to 40 mg doses, but a greater than linear mean AUC (three-fold increase) is observed when doubling the dose to 40 mg. The bioavailability of omeprazole increases upon repeated administration. When omeprazole/sodium bicarbonate is administered 1 hour after a meal, the omeprazole AUC is reduced by approximately 24% relative to administration 1 hour prior to a meal.

Distribution
Omeprazole is bound to plasma proteins. Protein binding is approximately 95%.

Metabolism
Following single-dose oral administration of omeprazole, the majority of the dose (about 77%) is eliminated in urine as at least six metabolites. Two metabolites have been identified as hydroxyomeprazole and the corresponding carboxylic acid. The remainder of the dose was recoverable in feces. This implies a significant biliary excretion of the metabolites of omeprazole. Three metabolites have been identified in plasma – the sulfide and sulfone derivatives of omeprazole, and hydroxyomeprazole. These metabolites have very little or no antisecretory activity.

Excretion
Following single-dose oral administration of omeprazole, little if any, unchanged drug is excreted in urine. The mean plasma omeprazole half-life in healthy subjects is approximately 1 hour (range 0.4 to 3.2 hours) and the total body clearance is 500-600 mL/min.

SMARTPILL™

The SmartPill™ motility testing system is an ingestible capsule that offers a convenient and radiation-free way to assess motility by measuring pressure, pH, and temperature throughout the entire gastrointestinal (GI) tract for patients with unexplained GI symptoms, such as nausea, bloating, constipation, abdominal pain, and vomiting. As it moves through the GI tract, it wirelessly and continuously transmits data to a recorder worn on the belt or lanyard for up to 5 days or when it passes with a regular bowel movement.

In the current study, the SmartPill™ will be used to measure subjects' gastric pH conditions (over a period of 8 hours) under which the nifedipine and co-administered nifedipine and omeprazole/sodium bicarbonate is released in vivo. This direct measurement of gastric pH will confirm a positive pharmacologic response (i.e. increased gastric pH) to proton pump inhibitors in healthy volunteers and determine the extent of gastric pH elevation as a result of 7-day multiple-dose of omeprazole/sodium bicarbonate capsules. In contrast with conventional gastric or nasogastric intubation methods, subjects should feel significantly less pain or discomfort when swallowing the capsule or while the capsule moves through the GI tract. It is naturally passed during a bowel movement, usually within a few days.

SmartPill™ uses MotiliGI® software to display and analyze the data, providing test results in both graphical and report formats. SmartPill™ provides valuable diagnostic information including:

- Gastric emptying time

- Small bowel transit time
- Colonic transit time
- Whole gut transit time
- Pressure patterns from the antrum and duodenum

4.0 STUDY OBJECTIVE

4.1 Study Objective

The objective of this study is to compare pharmacokinetics of nifedipine from both generic Nifedipine oral extended-release tablets, 60 mg and reference listed drug PROCARDIA XL (nifedipine) extended-release tablets, 60 mg when co-administered with or without proton pump inhibitor (PPI)/antacid, omeprazole/sodium bicarbonate capsules 40 mg/1100 mg capsules in healthy males and non-pregnant females under fasting conditions.
The two one-sided t-tests procedure Schuirmann proposed will be used to construct the 90% confidence interval at the alpha=0.05 level of significance for the ratio of geometric mean of PK parameters AUCt, AUCinf and Cmax. The limits of the 90% confidence intervals are 80.00%-125.00% which will be used for the statistical hypothesis testing. Therefore, it consists of decomposing the interval hypotheses into two sets of one-sided hypotheses.

For the drug interaction for both test and reference products, the calculated 90% confidence interval (CI) for the ratios of geometric means for AUCt, AUCinf and Cmax will be used for the following two PK comparisons to assess if the statistical significance of interaction effect between the product type effect (test or reference) and the effect of co-administrating PPI/antacid is or not.

- Test with PPI (Study Arm C)/Test without PPI (Study Arm A)
- Reference with PPI (Study Arm D)/Reference without PPI (Study Arm B)

Hypothesis 1.1: The hypotheses for testing of the interaction effect between Test product and the effect of co-administrating PPI/antacid are as follows:

- The null hypothesis (H01): there is statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than 80.00%.
- The alternative hypothesis (H11): there is no statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than or equal to 80.00%.
- The null hypothesis (H02): there is statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than 125.00%.

- The alternative hypothesis (H12): there is no statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than or equal to 125.00%.

Hypothesis 1.2: The hypotheses for testing of the interaction effect between Reference product and the effect of co-administrating PPI/antacid are as follows:

- The null hypothesis (H03): there is statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than 80.00%.
- The alternative hypothesis (H13): there is no statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than or equal to 80.00%.
- The null hypothesis (H04): there is statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than 125.00%.
- The alternative hypothesis (H14): there is no statistical significance of the interaction effect if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than or equal to 125.00%.

For the relative bioavailability between test and reference products under different conditions (with or without PPI), the calculated 90% confidence interval (CI) for the ratios of geometric means for AUCt, AUCinf and Cmax will be used for the following two PK comparisons to assess if the relative bioavailability is or not.

- Test with PPI (Study Arm C)/Reference with PPI (Study Arm D)
- Test without PPI (Study Arm A)/Reference without PPI (Study Arm B) → Although the generic applicant has already confirmed the bioequivalence between Test and Reference in the absence of PPI, this study will confirm this result.

Hypothesis 2.1: The hypotheses for the assessment of relative bioavailability for Test product with and without PPI are as follows:

- The null hypothesis (H01): there is no comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than 80.00%.
- The alternative hypothesis (H11): there is comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than or equal to 80.00%.
- The null hypothesis (H02): there is no comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than 125.00%.

- The alternative hypothesis (H12): there is comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than or equal to 125.00%.

Hypothesis 2.2: The hypotheses for the assessment of relative bioavailability for Reference product with and without PPI are as follows:

- The null hypothesis (H03): there is no comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than 80.00%.
- The alternative hypothesis (H13): there is comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than or equal to 80.00%.
- The null hypothesis (H04): there is no comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is greater than 125.00%.
- The alternative hypothesis (H14): there is comparable bioavailability if the 90% CI of the ratios of geometric means for AUCt, AUCinf and Cmax is less than or equal to 125.00%.

5.0 STUDY DESIGN

5.1 Discussion of Study Design

This will be a single-dose, randomized, open-label, four-way crossover, four-period, four-sequence, single-center, drug-drug interaction (DDI) study of generic formulation of Nifedipine extended-release tablets, 60 mg and reference listed drug PROCARDIA XL extended-release tablets, 60 mg with or without co-administration multiple-dose of PPI/antacid, omeprazole/sodium bicarbonate capsules 40 mg/1100 mg capsule under fasting conditions.

The generic nifedipine ER tablets based on a matrix design are available at only two strengths (30 and 60 mg), and the higher dose of 60 mg was chosen for its sensitivity of PK metrics in bioequivalence studies as per FDA guidance (Guidance for Industry: Bioequivalence studies with pharmacokinetic endpoints for drugs submitted under an ANDA, Dec 2013). The safety concern of administrating 60-mg single-dose nifedipine is minimal, considering that the existing product-specific bioequivalence guidance recommends generic applicants to conduct fasting and fed single-dose crossover BE studies administering 90-mg nifedipine ER tablets in healthy volunteers. On the other hand, the higher dose of 40mg/1100mg omeprazole/sodium bicarbonate capsules between the two strengths (20 or 40 mg omeprazole) was selected for a more significant gastric pH elevation. Administering 40 mg omeprazole daily for 7 consecutive days in healthy volunteers should be considered safe as shown in the past clinical studies [12, 19, 20]. In addition, omeprazole/sodium bicarbonate at the lower strength (20 mg omeprazole) is an OTC product.

The products will be studied using a crossover design with 65-66 healthy, non-smoking male and non-pregnant female volunteers being administered an oral dose of 1 × 60 mg extended-release tablet with or without co-administration multiple-dose of omeprazole / sodium bicarbonate, 1 x 40 mg/1100 mg once daily for 7 consecutive days under fasting conditions (i.e. subjects are dosed every 24 hrs). There will be at least a 14-day washout after Nifedipine only dosing (Study arms A or B) and for Study arms C and D (e.g., omeprazole/sodium bicarbonate followed with Nifedipine), at least 14 days after the last dose with omeprazole/sodium bicarbonate until the next study arm dose. Blood samples will be collected at pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36, and 48 hours after nifedipine dosing for Study arm A and B on Day 2 and on Day 7 for Study arm C and D in each study period.

5.2 Study Duration and Confinement

Study arm A and B: Subjects will be confined to the clinic from at least 10 hours prior (e.g., 5 pm Friday) to dosing (e.g., 8:00 am Saturday) until at least 48-hours post-dose of nifedipine, for a total of at least 58 hours in each study period.

Study arm C and D:
Subjects will be confined to clinic from at least 1 hour prior to dosing omeprazole/sodium bicarbonate capsules on Day 1 and Day 2 and then the subjects will be discharged 1 hour post-dose.

Subjects will be returning to the clinic 1 hour prior to dosing on Day 3 and can check-in after dosing or may check-in the evening to be confined to the clinic until at least 48 hours post-dose (test and reference) nifedipine dosing on Day 7. Total confinement from Day 1 to Day 9 will be of at least 148 hours (approximately 6 days) in each study period.

This study will consist of four study periods with a washout period of at least 14 days after Nifedipine only dosing (Study arms A or B) and for Study arms C and D (e.g., omeprazole/sodium bicarbonate followed with Nifedipine), at least 14 days after the last dose with omeprazole/sodium bicarbonate until the next study arm dose. The total anticipated duration of the clinical part of the study will be approximately 9 weeks (since signing the ICF by the first subject up to the last planned study procedure of the last subject).

5.3 Randomization and Blinding

In this study, the assignment of study arm groups (randomization scheme) will be generated by a computer program designed and run in SAS® Version 9.4 [redacted]. This is an open-label study and subjects as well as clinic staff will not be blinded to the randomization. The bioanalytical laboratory will not have access to the randomization scheme until the bioanalytical analysis is complete.

Subjects who meet the eligibility criteria will be randomly assigned equally into one of the following four sequence groups:

	Period 1	Period 2	Period 3	Period 4
Sequence 1	A	B	C	D
Sequence 2	B	C	D	A
Sequence 3	C	D	A	B
Sequence 4	D	A	B	C

Each subject is scheduled to receive four periods by the end of the study (See Appendix A).

Study arm A (Test): Nifedipine extended-release tablets [redacted] 60 mg

Study arm B (Reference): PROCARDIA XL extended-release tablets [redacted] 60 mg

Study arm C (PPI/antacid + Test): omeprazole/sodium bicarbonate capsules, 40 mg/1100 mg + Nifedipine extended-release tablets [redacted], 60 mg.

Study arm D (PPI/antacid + Reference): omeprazole/sodium bicarbonate capsules, 40 mg/1100 mg + PROCARDIA XL extended-release tablets [redacted] 60 mg.

The trial will be performed as an open-label study as the pharmacokinetic profile should not be expected to be affected by having the knowledge of reference or generic nifedipine ER tablets was administered. Blinding of the subjects as well as clinic staff is not considered necessary. Only the bioanalytical laboratory staff will not have access to the randomization scheme until the bioanalytical analysis is complete.

6.0 STUDY POPULATION

A required number of healthy volunteers, male and non-pregnant female, aged between 18 and 55 years of age will be screened according to the inclusion and exclusion criteria listed in Sections 7.3 and 7.4 to be sure that about 65-66 are randomized. The volunteers will be selected at the participating clinical site.

This study will be conducted in normal, healthy male and non-pregnant female volunteers, as intended for general population[3]. No one racial group will exceed 65% of total enrolled subjects.

To assure subjects' safety, eligibility will be assessed at the time of screening and upon entry into the clinic prior to first drug administration.

7.0 SUBJECT SELECTION AND WITHDRAWAL/TERMINATION

7.1 Sample Size

A sample size of 65-66 subjects (minimum of 52 subjects to complete the study) is estimated to attain at least 80% statistical power to demonstrate 2x2 crossover bioequivalence study with a margin of 80-125% between the Test and Reference products, assuming the mean Test to Reference difference is within 5% Type I error and the geometric mean ratio is 1.08, based on an estimated intra-subject variability of approximately 27%. Subjects who are dosed will not be replaced.

The subjects will be dosed in two or more groups.

7.2 Inclusion Criteria

Potential subjects meeting all of the following criteria may be included in the study:

1. Healthy, males and non-pregnant (excluding nursing and lactating) female volunteers, 18 to 55 years of age, inclusive.
2. Smoking status: Only non-tobacco/nicotine users (for at least 6 months prior to the clinical study) will be eligible to participate in this study.
3. BMI that is within 18.5-35.0 kg/m², inclusive.
4. Healthy, according to the medical history, ECG, vital signs, laboratory results and physical examination as determined by the PI/Sub-Investigator.
5. Ability to comprehend and be informed of the nature of the study, as assessed by BPSI staff. Capable of giving written informed consent prior to receiving any study procedure. Must be able to communicate effectively with clinic staff.
6. Ability to fast for at least 14 hours.
7. Availability to volunteer for the entire study duration and willing to adhere to all protocol requirements.
8. Female subjects must fulfill at least one of the following:
    - Be surgically sterile for a minimum of 6 months;
    - Post-menopausal for a minimum of 1 year;
    - Agree to avoid pregnancy and use medically acceptable method of contraception from at least 30 days prior to the study until 30 days after the study has ended (last study procedure).

Medically acceptable methods of contraception include contraceptives, intrauterine device, or double barrier method (condom with foam or vaginal spermicidal suppository, diaphragm with spermicide). Complete abstinence alone can be used as a method of contraception.

7.3 Exclusion Criteria

Potential subjects meeting any of the following criteria will be excluded:

1. Known history or presence of any clinically significant hepatic, renal/genitourinary, gastrointestinal (e.g., gastrointestinal obstruction, gastrointestinal ulcers), cardiovascular (e.g., severe obstructive coronary artery disease, myocardial infarction, angina, heart failure), cerebrovascular, pulmonary, endocrine, immunological, musculoskeletal, neurological, psychiatric, dermatological or hematological disease or condition unless determined as not clinically significant by the PI/Sub-Investigator.
2. Clinically significant history or presence of any clinically significant gastrointestinal pathology (e.g. chronic diarrhea, inflammatory bowel disease), unresolved gastrointestinal symptoms (e.g. diarrhea, vomiting, swallowing disorder), or other conditions known to interfere with the absorption, distribution, metabolism or excretion of the drug experienced within 7 days prior to first dosing, as determined by the PI/Sub-Investigator.
3. QTc interval > 430 milliseconds for males and > 450 milliseconds for females, unless deemed otherwise by the PI/Sub-Investigator.
4. Abnormal clinical laboratory values, unless values are deemed by the PI/Sub-Investigator as “Not Clinically Significant”.
5. Hemoglobin values less than 11.5 g/dl.
6. Abnormal vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR] and temperature) measurements, unless deemed otherwise by the PI/Sub-Investigator.
7. Presence of any clinically significant illness within 30 days prior to first dosing, as determined by the PI/Sub-Investigator.
8. Presence of any significant physical or organ abnormality as determined by the PI/Sub-Investigator.
9. Individuals who have implanted or portable electro-mechanical medical device such as a cardiac pacemaker, defibrillator or infusion pump.

10. A positive test result for any of the following: HIV, Hepatitis B surface antigen, Hepatitis C, drugs of abuse (marijuana, amphetamines, barbiturates, cocaine, opiates, phencyclidine and benzodiazepines), alcohol test and cotinine. Positive pregnancy test for female subjects.
11. Known history or presence of:
    - Alcohol abuse or dependence within one year prior to first study period;
    - Drug abuse or dependence;
    - Hypersensitivity or idiosyncratic reaction to nifedipine, omeprazole/sodium bicarbonate, its excipients, and/or related substances;
    - Hypotension;
    - Bartter's syndrome;
    - Gastric bezoar;
    - Crohn's disease or diverticulitis;
    - severe dysphagia to food or pills;
    - Food allergies and/or presence of any dietary restrictions;
    - Severe allergic reactions (e.g. anaphylactic reactions, angioedema).
12. History of intolerance to and/or difficulty with blood sampling through venipuncture.
13. Abnormal diet patterns (for any reason) during the four weeks preceding the study, including fasting, high protein diets, vegan, etc.
14. Individuals who have donated, in the days prior to first study period:
    - 50-499 mL of blood in the previous 30 days;
    - 500 mL or more in the previous 56 days.
15. Donation of plasma by plasmapheresis within 7 days prior to first study period.
16. Individuals who have participated in another clinical trial or who received an investigational drug within 30 days prior to first study period.
17. Use of any enzyme-modifying drugs and/or other products, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g. cimetidine, fluoxetine, quinidine, fluconazole, ketoconazole, voriconazole,

itraconazole, clarithromycin, erythromycin, nefazodone, atazanavir, saquinavir, indinavir, and nelfinavir) and strong inducers of CYP enzymes (e.g. barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s Wort and rifampin) in the previous 30 days before first study period.

18. Use of drugs such as, proton pump inhibitors, clopidogrel, tacrolimus, digoxin, cyclosporine, disulfiram, benzodiazepines, diazepam, warfarin, methotrexate, iron salts, erlotinib, and mycophenolate mofetil (MMF) in the previous 30 days before first study period, or individuals with vitamin B-12 deficiency (as long-term dosing (more than 3 years) of omeprazole/sodium bicarbonate may lead to vitamin B-12 deficiency)
19. Individuals having undergone gastrointestinal (GI) surgery within 3 months prior to first study period, unless deemed otherwise by PI/Sub-Investigator.
20. Use of any prescription medication within 14 days prior to first study period (except for contraceptives).
21. Use of any over-the-counter medications (including oral multivitamins, herbal and/or dietary supplements and/or teas) within 14 days prior to first study period (except for spermicidal/barrier contraceptive products).
22. Consumption of food or beverages containing grapefruit and grapefruit juice and/or pomelo within 10 days prior to first study period.
23. Consumption of food or beverages containing caffeine/methylxanthines, poppy seeds and/or alcohol within 48 hours before dosing.
24. Use of diuretics (drugs or food, see Appendix D) within 24 hours before dosing of SmartPill™.
25. Individuals having undergone any major surgery within 6 months prior to the start of the study, unless deemed otherwise by PI/Sub-Investigator.
26. Difficulty with swallowing whole tablets or large capsules.
27. Have had a tattoo or body piercing within 30 days prior to first study period and during the study.

7.4 Informed Consent Procedure

The Investigator is responsible for ensuring that the informed consent is obtained before any protocol specific procedures are carried out. The decision of a subject to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

Subjects must receive adequate oral and written information. The oral explanation to the participant should be performed by the Investigator or a designated person, and must cover all the elements specified in the informed consent form.

The subject must be given every opportunity to clarify any points they do not understand and, if necessary, to ask for more information. The subject must be given sufficient time to consider the provided information. It should be emphasized that the subjects may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The subjects should be informed and agree that their names will not be disclosed outside the site.

The Investigator or delegated member of the trial team and the subject should sign and date the Informed Consent Form to confirm that consent has been obtained. The participant should receive a copy of this document and the original should be filed in the subject binder. In case of a screen failure, it will be filed separately in the designated binder.

7.5 Screening Procedures

Subjects will review and sign the ICF prior to medical screening procedures. Screening procedures will be conducted within thirty (30) days prior to dosing in Period 1. Screening procedures can be performed on the day of check-in prior to conducting check-in procedures. The physician (Principal Investigator (PI) or Sub-Investigator) will review all screening results/data to assess eligibility of each potential subject.

The Screening procedures will include (but is not limited to): demographic data, medical and medication histories, physical examinations, body measurements, vital signs (seated blood pressure [BP], heart rate [HR], respiratory rate [RR] and temperature.), electrocardiogram (ECG), hematology, biochemistry, serology, urinalysis, urine screening for drugs of abuse and cotinine, alcohol test and serum pregnancy test (female subjects only). For a complete listing of all tests to be performed, please refer to Appendix B - Clinical Laboratory Assessment.

7.6 Study Restrictions

If any subject does not comply with these restrictions, at any time prior to or during the study, continued participation will be re-assessed by the PI/Sub-Investigator, BPSI PK Scientist and/or the Sponsor.

1. No food will be allowed from at least 8 hours before dosing until at least 6 hours after dosing (Study arm A and B). Following the administration of omeprazole/sodium bicarbonate capsules on Day 6, subjects will be required

to fast for at least an 8-hour overnight fasting period before dosing of nifedipine together with omeprazole/sodium bicarbonate capsules on Day 7, and will continue to fast for at least 6 hours after dosing (Study arm C and D). Except for water given with study medication (nifedipine, omeprazole/sodium bicarbonate, SmartPill™), no fluid will be allowed from 8 hours before dosing until 6 hours post-dose. Water will be allowed up to ½ cup (4 fl. oz.) during the six (6) hours post-dose and then water will be allowed/provided *ad libitum* at all other times.

2. For Study arm C and D, no food will be allowed from at least 8 hours before dosing of omeprazole/sodium bicarbonate capsules from Day 1 to Day 6 until at least 1 hour after dosing. Except for water given with study medication, no fluid will be allowed from 1 hour before dosing and 1 hour post-dose. Water will be allowed up to ½ cup (4 fl. oz.) during the six (6) hours post-dose and then water will be allowed/provided *ad libitum* at all other times.
3. Subjects will be required to abstain from smoking or use of tobacco products from 6 months prior to the first study period and for the entire duration of the study based on self-reporting and the cotinine test.
4. Use of any enzyme-modifying drugs and/or other products, including strong inhibitors of cytochrome P450 (CYP) enzymes (e.g., cimetidine, fluoxetine, quinidine, fluconazole, itraconazole, clarithromycin, erythromycin, nefazodone, saquinavir, indinavir, and nelfinavir) and strong inducers of CYP enzymes (e.g., barbiturates, carbamazepine, glucocorticoids, phenytoin, St. John´s Wort and rifampicin) within 30 days prior to first study period until the last blood draw in the final study period.
5. Use of drugs such as, proton pump inhibitors, clopidogrel, tacrolimus, digoxin, cyclosporine, disulfiram, benzodiazepines, diazepam, warfarin methotrexate, iron salts, antibiotics containing ampicillin, erlotinib, and mycophenolate mofetil (MMF) in the previous 30 days before first study period until the last blood draw in the final study period.
6. Any concomitant medication [prescription medications (e.g., prescription pills, topical systemic creams, inhalants, sprays [except for contraceptives]) or over-the-counter (e.g., acetaminophen, Ricola, oral multivitamins) (except for spermicidal/barrier contraceptive products)], any herbal and/or dietary supplements will not be permitted for 14 days prior to first study drug administration until the last blood draw in the final study period unless deemed otherwise by the PI/Sub-Investigator for treatment of any adverse events (AEs).

   Any use of concomitant medication or herbal/dietary supplement during the restriction period will be reported as soon as possible to the PI/Sub-

Investigator, BPSI PK Scientist and/or the Sponsor. In each case, the decision whether to continue or discontinue the subject's participation in the study will be made by the PI/Sub-Investigator and/or by the BPSI PK Scientist and/or by the Sponsor.

7. The consumption of foods and/or beverages containing grapefruit and/or pomelo (e.g., grapefruit, grapefruit juice, grapefruit candies, pomelo, etc.) will be prohibited for 10 days prior to first study period until the last blood draw in the final study period.
8. The consumption of alcohol of any kind (e.g., wine, beer, liquor, cocktails), products containing caffeine/methylxanthines [e.g., coffee, tea, chocolate, caffeine-containing soft drinks (e.g., Coke, Pepsi, Red Bull)] and poppy seeds containing products (poppy seed cake, cookies, bagels) will be prohibited for 48 hours prior to study period until after the last blood draw in each study period.
9. Use of diuretics (drugs or food, see Appendix D) will be prohibited for 24 hours prior to SmartPill™ administration until after the last blood draw in each study period.
10. Physical activity: For the SmartPill™ administration (Study arm A and B on Day 2) (Study arm C and D on Day 7), subjects will remain awake and seated in an upright position for the first 4 hours following SmartPill™ administration where possible. Subjects are allowed to rise under supervision only for brief periods of time during the first 4 hours post-dose to assure subjects' safety and to use the washroom, after which they will be allowed to ambulate freely within the clinic. However, if a medical event (i.e. AE) occurs, subjects may be placed in an appropriate position at any time. Subjects will be required to abstain from strenuous activities for the duration of the study period(s).
11. For Study arm A and B on Day 2 and for Study arm C and D on Day 7, for 1 hour after each nifedipine administration, subject visits to the washroom will be monitored and recorded by clinic staff. Subjects will be restricted from flushing the toilet to allow staff to inspect the content during this time.

7.7 Withdrawal/Termination

A subject is free to withdraw from participation in the study at any time, for any reason. An Investigator may terminate a study subject's participation in the study if:

- Any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the subject.

- The subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.

The cause, date and time of withdrawal or termination will be documented in the source documents and in the final study report. If a subject's participation is terminated prematurely, the cause for the early termination date and time of the termination will be documented on the source documents and in the final study report.

Subjects experiencing emesis or diarrhea after dosing will be evaluated on a case-by-case basis by the PI/Sub-Investigator (to assess subject safety) and the BPSI Pharmacokinetic Scientist (for assessment of impact on PK) and the Sponsor and a decision on their continued participation will be made. All decisions will be made prior to the bioanalytical laboratory commencing bioanalysis.

Withdrawn and dismissed subjects are not required to adhere to the study specific procedures (e.g., study restrictions). If withdrawn or dismissed following administration of any drug product in the study, these subjects will be asked to adhere to the study restrictions in regards to the safety, prescription medication, over-the-counter medication, dietary and/or herbal supplements and/or teas for the expected duration of the restriction relevant to the study period the subject withdrew or was dismissed from (where that period becomes the subject's last study period).

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the investigator, sponsor and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to subjects.
- Insufficient adherence to protocol requirements.
- Data that are not sufficiently complete and/or evaluable.
- Determination of futility.

Subjects whose participation in the study is discontinued (for any reason) will not be replaced. If a subject withdraws or is dismissed from the study, a post-study symptom-directed physical exam with the possibility for a full physical exam if deemed necessary by the PI/Sub-Investigator will be conducted and post-study testing will be completed, where possible.

8.0 STUDY PROCEDURES

8.1 Study Period Check-in Procedures

At check-in for Period 1, subjects will review the study specific ICF and document their consent by signing the ICF. At check-in for each study period, subjects will be questioned about whether they have complied with the study restrictions.

If drug therapy other than that specified in the protocol was used, a decision to continue or discontinue the subject's participation will be made by the PI/Sub-Investigator and/or by the BPSI PK Scientist and/or by the Sponsor.

Subjects will be required to provide blood and urine samples for laboratory testing (hematology, serum biochemistry and urinalysis) at check-in for each study period. For Study arm C and D blood samples will be taken on Day 3 check-in.

Urine tests for drugs of abuse and cotinine and an alcohol test will be performed on all subjects at each study period check-in. In addition, urine hCG testing will be performed on all female subjects at each study period check-in.

Clinical staff reserves the right to conduct random testing (urine drugs of abuse, cotinine, urine hCG [females only], or alcohol) on any subject at any time during the study to ensure subject compliance and/or safety. Any subjects with a positive test for urine drugs of abuse, cotinine, alcohol or urine hCG (females only) will be withdrawn immediately from the study.

8.2 Food and Fluid Intake

SmartPill™ Administration, Study arm A and Study arm B

Following at least an 8-hour overnight fasting period, subjects will be dosed with nifedipine ER tablets and will be required to continue to fast for at least 6 hours after dosing.

Following the fasting period of at least 6-hours after dosing, subjects will be given standardized meals and caffeine/methylxanthine-free beverages at scheduled times. In this study, meals will be served at approximately 6.5, 10.5, 14.0, 24.5, 28.5, 33.5, and 37.5 hours after dosing. Meals and beverages during confinement will be identical for all study periods.

Except for water given with study medication, no fluid will be allowed from 8 hours before dosing until 6 hours post-dose. Water will be allowed up to ½ cup (4 fl. oz.) during the six (6) hours post-dose and then water will be allowed/provided *ad libitum* at all other times.

Study arm C and Study arm D

No food will be allowed from at least 8 hours before dosing of omeprazole/sodium bicarbonate capsules from Day 1 to Day 6 until at least 1 hour after dosing. Following the administration of omeprazole/sodium bicarbonate capsules on Day 6, subjects will be required to fast for at least an 8-hour overnight fasting period before dosing of nifedipine together with omeprazole/sodium bicarbonate capsules on Day 7, and will continue to fast for at least 6 hours after dosing.

Subjects will be given standardized meals and caffeine/methylxanthine-free beverages at scheduled times during their confinement. In this study, meals will be served at approximately 4.5, 9.5, 13.5, 24.5, 28.5, 33.5, 37.5, 48.5, 52.5, 57.5, 61.5, 72.5, 76.5, 81.5, and 85.5 hours after capsules dosing on Day 3. Following the fasting period of at least 6-hours after dosing of nifedipine together with omeprazole/sodium bicarbonate capsules on Day 7, subjects will be given standardized meals and caffeine/methylxanthine-free beverages at approximately 6.5, 10.5, 14.0, 24.5, 28.5, 33.5, and 37.5 hours after dosing. Meals and beverages during confinement will be identical between each study period.

On dosing Day 1 to Day 6, except for water given with study medication, no fluid will be allowed from 1 hour before dosing and 1 hour post-dose. Water will be allowed/provided *ad libitum* at all other times. On Day 7, except for water given with study medication, no fluid will be allowed from 8 hours before dosing until 6 hours post-dose. Water will be allowed up to ½ cup (4 fl. oz.) during the six (6) hours post-dose and then water will be allowed/provided *ad libitum* at all other times.

8.3 Dosing

Study arm A and Study arm B

Subjects will take their assigned formulation of nifedipine with 8 fl. oz. of ambient temperature water at their scheduled time point after a fast of at least 8-hours.

Study arm C and Study arm D

Subjects will take omeprazole/sodium bicarbonate capsules from Day 1 to Day 6 after a fast of at least 8 hours with 8 fl. oz. of ambient temperature water at their scheduled time point.

Also, subjects will take their assigned formulation of nifedipine together with omeprazole/sodium bicarbonate capsules on Day 7 after a fast of at least 8-hours with 8 fl. oz. of ambient temperature water at their scheduled time point.

Subjects will take their Day 1 to Day 2 doses of omeprazole/sodium bicarbonate capsules at the clinic and will be released 1 hour post-dose.

SmartPill™ Administration

Subjects will take SmartPill™ with 8 fl. oz. of water approximately 30 minutes prior to nifedipine (Study arm A and B) dosing and on Day 7 before omeprazole/sodium bicarbonate capsules and nifedipine dosing (Study arm C and D) to monitor the gastric pH. If subjects cannot swallow SmartPill™ with 8 fl. oz. of water, a maximum of 16 fl. oz. of additional water will be given to the subjects by increments of 4 fl. oz. (i.e. no more than 24 fl. oz. water in total). The total amount of water consumption will be recorded.

Immediately after ingesting a SmartPill™ capsule, subjects are fitted with the wireless Data Recorder to wear on a belt or lanyard until the SmartPill™ capsule passes with a regular bowel movement. The participant will wear the Data Recorder at all time between SmartPill™ dosing and the last pharmacokinetic sampling (i.e., 48 hrs after administering nifedipine ER tablets) in each of the Periods, except while bathing or sleeping. The recorder should be removed while bathing and placed close by where it will not get wet. While sleeping, the participant will be instructed to place the data recorder under the pillow or on a nightstand by the bed. The SmartPill™ is expected to pass within 5 days of ingestion, and participants will be asked to return the Data Recorder before being discharged.

The procedure of dosing and instructions on SmartPill™ will be described in the study directive.

For all periods (Study arms A, B, C, and D), subjects will be instructed not to touch, chew, bite or break the drug products (nifedipine, omeprazole/sodium bicarbonate, SmartPills). If a subject chews, bites or breaks any of the drug products, that subject will be removed from the study. If the subject touches nifedipine or omeprazole/sodium bicarbonate, a replacement dose will be administered. Subjects must consume the drug products and finish the water provided within a few minutes, and the actual time will be recorded.

A hand and mouth check will be conducted by clinic staff immediately following dosing.

8.4 Gastric pH

The gastric pH will be monitored through SmartPill™ Technology. The pH will be measured at 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours in each study period. The pH will be monitored continuously for 24 hours post-dose.

8.5 Safety Monitoring

In the interest of the subject safety the following safety parameters will be conducted on all subjects.

8.5.1 Vital Signs

Vital signs (BP, HR, RR and temperature) will be monitored for Study arm A and B and on Day 7 for Study arm C and D at pre-dose* and at 4, 12 and 24 hours after dosing in each study period and at pre-dose and at 1 hour after omeprazole/sodium bicarbonate capsules dosing from Day 1 to Day 6 in each study period for Study arm C and D.

Pre-Dose and Post-Dose (all periods):
Acceptable Range - systolic blood pressure between 95-140 mmHg, diastolic blood pressure between 55-90 mmHg, inclusive, and heart rate between 50-100 bpm, inclusive.

All subjects with vital signs outside of the acceptable range will have their vital signs repeated up to two times. If vitals are still outside of acceptable range, the PI/Sub-Investigator will determine appropriate course of action.

Additional vital signs measurements will be taken if deemed necessary by the PI/Sub-Investigator. Blood draws at pre-determined time (+/- 5 min) will take precedence over vital signs measurements and other scheduled activities, should a timing conflict arise unless deemed necessary by the PI/Sub-Investigator.

8.5.2 ECG

ECG measurements are not required during this study unless deemed necessary by the PI/Sub-Investigator.

8.5.3 Health Monitoring

For Study arm A and B, the PI/Sub-Investigator will be present approximately 30 minutes prior to SmartPill™ administration until at least 6 hours after the last subject is dosed with nifedipine.

For Study arm C and D, from Day 1 to Day 6, the PI/Sub-Investigator will be present from approximately 30 minutes prior to omeprazole/sodium bicarbonate capsules until at least 1 hour after dosing in each study period. On Day 7, the PI/Sub-Investigator will be present from approximately 30 minutes prior to SmartPill™ administration until at least 6 hours after the last subject is dosed with nifedipine together with omeprazole/sodium bicarbonate capsules in each study period.

*Within 12 hours prior to nifedipine administration.

The PI/Sub-Investigator will remain on-call throughout the duration of the study.

Health monitoring will be conducted throughout the study or as needed. Adverse events will be monitored throughout the study.

8.6 Post-Study Tests

Clinical laboratory tests (hematology, serum chemistry and urinalysis), as per Appendix B – Clinical Laboratory Assessment, will be repeated prior to discharge at the end of the study or after withdrawal/dismissal of a subject from the study.

At exit, a symptom-directed physical exam with the possibility for a full physical exam if deemed necessary by the PI/Sub-Investigator including vital signs (BP, HR, Temperature and RR) will be conducted upon completion of the study or after withdrawal/dismissal of a subject from the study, where possible.

8.7 Sample Collection and Processing

Blood will be obtained by direct venipuncture in the arm, or via an indwelling cannula. Subjects may use up to 1 indwelling cannula in each study period. If the cannula fails to work (i.e. it becomes clogged), the remaining samples will be taken by direct venipuncture. If catheter will be used, the residual volume in the dead space will be washed with saline each time before taking the sample. Subjects who use cannulas will have them removed:

- After the last blood sample collection of confinement (not later than the 24 hour time point);
- If deemed necessary by clinic staff (for any reason);
- If subject requests removal.

Blood sample collection times will be recorded on the appropriate source documents and reported for each subject.

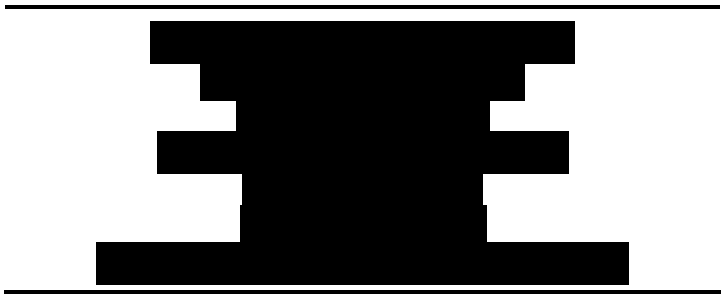
Number of Samples	17 samples from 17 time points in each study period
Total Volume of Blood (for all periods, including approximately 29 mL for pre- and post-study procedures and 44 mL for laboratory testing at check-in for each study period)	Approximately 345 mL of blood
Type of Vacutainer	Pre-chilled K_2EDTA Vacutainer®, 4 mL
Blood Sampling Time Points◆	Pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36 and 48 hours after nifedipine dosing in each study period.

The blood samples collected from each subject will be processed and divided into 2 aliquots. The blood sampling and processing will be performed as per the laboratory directive.

8.8 Sample Shipment

One set of aliquots from all subjects will be shipped to the bioanalytical facility packed on dry ice. Once the initial set has been confirmed to have been received by the bioanalytical facility, the second set of aliquots will then be shipped.

All shipments will be accompanied by an inventory list and delivered to the bioanalytical facility:



Clinic personnel will notify the analytical laboratory prior to shipment by phone, fax or e-mail. The bioanalytical laboratory will notify BPSI by either e-mail or fax of confirmation of receipt of each aliquot.

◆ Pre-dose samples to be obtained within 2 hours prior to nifedipine administration.

9.0 DRUG PRODUCTS

9.1 Drug Information

Treatment Code	A (Test)	B (Reference)	PPI/antacid
Drug Name:	Nifedipine	PROCARDIA XL (nifedipine)	omeprazole/sodium bicarbonate
Strength:	60 mg	60 mg	40 mg / 1100 mg
Dosage Form:	Extended-release tablets	Extended-release tablets	Capsules
[redacted]	[redacted]	[redacted]	[redacted]
Dose:	1 x 60 mg	1 x 60 mg	1 x 40 mg/1100 mg (once daily for 7 consecutive days)

Device Name:	SmartPill™
Dosage Form:	Capsule (26 mm x 13 mm)
Manufactured by/for:	Given Imaging
Dose:	1 capsule 30 minutes prior to SmartPill™ administration

9.2 Labeling, Maintenance, and Retention of Study Drugs (Nifedipine, omeprazole/sodium bicarbonate, SmartPill™)

Each investigational study drug will be labeled (in English) with a statement indicating that the drug is an investigational drug to be used only by a Qualified Investigator and will include but not limited to: Drug Name, Strength, Protocol Number, Sponsor's Name and Address, the recommended storage conditions for the drug, Expiry/Retest Date (when available) and Lot/Batch Number.

9.3 Drug Inventory

The Sponsor will supply sufficient quantities of the study formulation for the following: (1) completion of this study and (2) retention, as per applicable regulations. All drug supplies provided for this study will be stored in a secure area with restricted access, under controlled storage conditions described in the product package labelling, unless otherwise instructed per protocol.

Records will be made of receipt and dispensing of nifedipine, omeprazole/sodium bicarbonate, and SmartPill™ supplied. It is the responsibility of the Sponsor to

ensure that all drug supplies provided for the study are manufactured under current Good Manufacturing Practices (cGMP) and are suitable for human use.

9.4 Disposition of Unused Study Drug (Nifedipine, omeprazole/sodium bicarbonate, SmartPill™)

Upon completion or termination of the study, all remaining study supplies will be retained according to applicable regulations. Once the retention period has elapsed, any remaining unused drug will be returned to the Sponsor in the original containers, or destroyed, as directed in writing by the Sponsor.

10.0 Potential Risks and Benefits

10.1 Potential Risks

Nifedipine

The controlled and open trials with chronic dosing of nifedipine extended-release tablets in hypertension and angina patients were included in the evaluation of adverse experiences. It is noteworthy that these potential risks derived from clinical studies with chronic multiple-dose administration of nifedipine in subjects with cardiovascular (e.g. hypertension and angina) diseases.

- The most common side effect reported with PROCARDIA XL was edema which was dose related and ranged in frequency from approximately 10% to about 30% at the highest dose studied (180 mg).
- Other common adverse experiences reported in patients in a placebo-controlled trials include, headache (15.8%), fatigue (5.9%), dizziness (4.1%), constipation (3.3%), and nausea (3.3%).
- Other adverse reactions were reported sporadically with an incidence of 1.0% or less.
- Gastrointestinal obstruction resulting in hospitalization and surgery, including the need for bezoar removal, has occurred in association with nifedipine extended-release tablets, even in patients with no prior history of gastrointestinal disease.
- Cases of tablet adherence to the gastrointestinal wall with ulceration have been reported, some requiring hospitalization and intervention.

Other serious side effects reported with PROCARDIA XL (nifedipine) use were:

- **Myocardial infarction [heart attack] (4%)**
- Pulmonary edema [fluid accumulation in the lungs] (2%)
- Ventricular arrhythmias [abnormal heartbeat] or conduction disturbances (0.5%)

Omeprazole/sodium bicarbonate

Each capsule contains omeprazole and sodium bicarbonate. Subjects will be asked to consult the Investigator if on a sodium restricted diet or have Bartter's Syndrome (a rare kidney disorder) or at risk of developing congestive heart failure (CHF).

- Omeprazole/sodium bicarbonate may increase risk of getting severe diarrhea caused by an infection (*Clostridium difficile*) in intestines.
- Multiple daily doses of proton pump inhibitor medicines for a long period of time (a year or longer) may
  - Have an increased risk of fractures of the hip, wrist or spine.
  - Increase the risk of inflammation to your stomach lining.
- Possibility of vitamin B-12 deficiency if you have been on omeprazole/sodium bicarbonate for a long time (more than 3 years).
- Low magnesium can happen in some people who take a proton pump inhibitor medicine for at least 3 months.
- The most common side effect reported in patients include, headache, abdominal pain, nausea, vomiting and gas.
- Additional adverse reactions that could be caused by sodium bicarbonate include metabolic alkalosis, seizures, and tetany.
- Other adverse reactions were reported sporadically with an incidence of 1.0% or less.

A long term use of omeprazole/sodium bicarbonate may cause serious side effects including chronic inflammation of the stomach lining (Atrophic Gastritis)**.**

SmartPill™

The risk involved for subjects with the SmartPill™ Capsule Motility procedure is non-passage of the capsule through the intestinal tract. If there is delay in passage of the capsule, and the capsule is located in the stomach, a pro-motility drug could be administered to assist in emptying the capsule from the stomach. Alternatively, endoscopy could be performed in order to retrieve the capsule. If located in the colon, laxative therapy could be administered to facilitate capsule movement, or a colonoscopy could be performed in order to retrieve the capsule. This can occur when a subject has a blockage. Subjects must inform study staff or study doctor in such instance.

Subjects must avoid MRI machines during the SmartPill™ Capsule Motility procedure until 7 days after the study.

10.2 Potential Benefits

While it may not provide direct benefit to subjects, the importance of the knowledge that may result from the study may enhance regulatory review on oral modified-release drug products in which the controlled release rate of drug delivery into the gastrointestinal lumen is a function of gastric pH.

11.0 SAFETY ASSESSMENT

BioPharma Services USA Inc. has established SOPs in conformity with regulatory requirements to ensure the timely, accurate and complete reporting of safety information.

PI/Sub-Investigators at BPSUSA are responsible for monitoring the safety and for providing appropriate medical care for subjects who have entered this trial (i.e., from the signing of ICF onwards). In addition, the PI/Sub-Investigator remains responsible for following-up all AEs.

Each subject will be carefully questioned and/or examined by the PI/Sub-Investigator or a medically qualified delegate (i.e., authorized by the Investigator, in a separate form, to record AEs) to obtain information regarding AEs. All AEs will be reported and documented as stated below

11.1 Definitions

Adverse Event (AE) – is any untoward medical occurrence in clinical trial subject who are administered with any of study drugs (nifedipine, omeprazole/sodium bicarbonate and SmartPill™) and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse Drug Reaction (ADR) of study drug any of study drugs (nifedipine, omeprazole/sodium bicarbonate and SmartPill™) is any untoward and unintended response to any of study drugs (nifedipine, omeprazole/sodium bicarbonate and SmartPill™) related to any dose administered.

Unexpected Adverse (Drug) Reaction – is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Prescribing Information for an authorized product).

Serious Adverse Event (SAE) / Reaction – a serious adverse event (experience) or reaction is any untoward medical occurrence or effect that at any dose can:

- result in death,
- be life-threatening,
- require hospitalization or prolongation of existing inpatient hospitalization,
- result in persistent or significant disability or incapacity,
- cause a congenital anomaly/birth defect,

- be considered to be other medically important event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the participant or may require intervention to prevent one of the above-listed outcomes.

Suspected Unexpected Serious Adverse Reaction (SUSAR) – is all suspected adverse reactions related to PROCARDIA XL, generic nifedipine ER tablets omeprazole/sodium bicarbonate, and SmartPill™, which can occur in the concerned trial, and that are both unexpected and serious.

Unanticipated Problems – The unanticipated problems involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets all of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Subjects will be instructed to inform clinic personnel of any untoward medical symptoms and/or events that may arise during the course of the study.

11.2 Characteristics of an Adverse Event

11.2.1 Relationship to Study Drug

The PI/Sub-Investigator will assess the relationship of all adverse reactions to any of study drugs (nifedipine, omeprazole/sodium bicarbonate and SmartPill™), using the following scale:

Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to drug administration, but which

	could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and which other drugs, chemicals or underlying disease provide plausible explanation.
Unrelated	This category is applicable to AEs which are judged to be clearly and incontrovertibly due to extraneous causes (diseases, environment, etc.) and do not meet the criteria for drug relationship listed for the above-mentioned conditions.

All AEs will be evaluated by the PI/Sub-Investigator, who must approve the subject for subsequent dosing.

Any AEs, whether serious or non-serious, will be monitored throughout the study and followed to resolution, when possible, regardless of whether the subject is still participating in the study.

11.2.2 Expectedness of SAE

The Study PI will be responsible for determining whether an SAE is expected or unexpected as per drug labels. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

11.2.3 Severity Assessment

The term "severe" describes the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as severe headache). This means it is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning[3].

The severity of all AEs will be graded by the PI/Sub-Investigator or a medical qualified delegate according to the following definitions:

Mild	Adverse event resulting in discomfort, but not sufficient to cause interference in normal daily activities.
Moderate	Adverse event resulting in discomfort that is sufficient to cause interference in daily activities.
Severe	Adverse event resulting in discomfort causing an inability to carry

Every effort will be made to obtain an adequate evaluation of the severity. out normal daily activities.

11.3 Adverse Events Reporting

An Adverse Event as defined above generally includes any condition that was:

1) Not present prior to administration of study drugs (nifedipine, omeprazole/sodium bicarbonate, SmartPill™) but appeared after initiation of administration of study drug;
2) Present prior to administration of study drugs (nifedipine, omeprazole/sodium bicarbonate, SmartPill™) but worsened after administration of study drug; or
3) Reported as part of the subject's history, and while not present immediately prior to initiating administration of study drugs (nifedipine, omeprazole/sodium bicarbonate, SmartPill™), reappeared after administration of study drug.

Planned hospital admissions and/or surgical operations/procedures for an illness or disease that existed before the investigational product was given or the participant was enrolled in a clinical trial are not to be considered AEs.

Clinical laboratory data collected during the course of the study, which exceeds or drops below the acceptable limits for the participant population and which, based on baseline values, are considered by the Investigator to be clinically significant, will be reported as an AE. If clinically significant abnormal ECGs and/or laboratory values lead to, or are associated with clinical symptom(s), the diagnosis should be reported as an AE.

If a participant discontinue from the study as a result of an AE, study site personnel must clearly document the circumstances and data leading to the reason for discontinuation.

The investigator/designee is responsible for recording all AEs which have occurred during the study (including clinically important deviations of laboratory values from normal ranges), regardless of their relationship to the study drugs (nifedipine, omeprazole/sodium bicarbonate, SmartPill™). This includes AEs spontaneously reported by the patient, observed by the investigator/designee or elicited by general questioning. All AEs will be determined as Serious or Non-Serious. Treatment of any AEs will be administered under the direction of a physician, either at BPSUSA or at a nearby hospital emergency room

All symptoms will be recorded by clinic staff and will be reviewed by the PI/Sub-Investigator prior to any subsequent dosing. When appropriate, medical tests and examinations will be performed to document resolution of the event(s).

All reported adverse events will be documented in the Clinical Report.

The Investigator will monitor the subject's condition until recovery to a satisfactory state or stabilization. Thus, follow-up visits may be required even after the administration of the study drugs (nifedipine, omeprazole/sodium bicarbonate, SmartPill™) has been discontinued.

Serious Adverse Events

All serious adverse events (SAEs), whether or not the event is deemed study drug-related, will be reported to the Sponsor by telephone within 24 hours of BPSUSA being aware of SAE, followed by a written report within five business days.

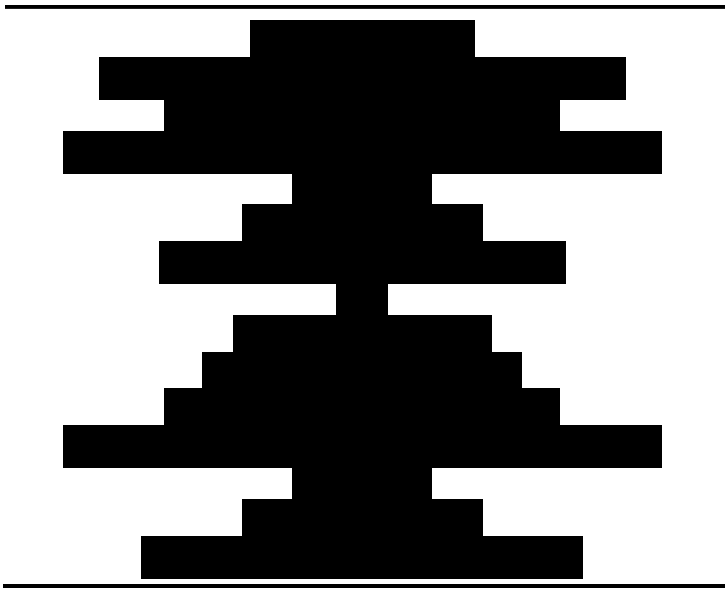
Reports of all SAEs must be communicated as soon as possible to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and/or reported in accordance with local laws and regulations.

Adverse events will be coded into the Preferred Term (PT), classified according to the Medical Dictionary for Regulatory Activities (MedDRA) with System Organ Classification (SOC) and reported with severity, duration, onset time and relationship to study drug (nifedipine, omeprazole/sodium bicarbonate, SmartPill™) and action taken.

The Principal Investigator will report to the RIHSC (FDA IRB) through the FDA Sponsor any unanticipated problems involving risk to human subjects or others 45 CFR 46.103(b)(5)(i). Certain adverse events must be reported to the RIHSC within 10 working days of the discovery of the event. The RIHSC defines these adverse events as including, but not limited to the following:

- An adverse event that is not expected, i.e. not listed in the informed consent document or the investigator’s brochure;
- An expected adverse event that occurs at a greater frequency or duration than expected;
- Any adverse event that would require modification of the protocol and/or informed consent document

The following Sponsor personnel are to be contacted on the occurrence of a SAE:



11.4 Procedures for Reporting Pregnancy

A positive urine pregnancy test or any hCG level ≥ 5 IU/L for females of child-bearing potential and ≥ 8 IU/L for post-menopausal females will be assessed as clinically significant and will result in the immediate dismissal of the subject from the study, unless deemed otherwise by the Investigator. The elevated hCG will be investigated as a potential pregnancy and will be followed up in the same manner as an AE. A confirmatory hCG blood test will be required for any elevated values. If pregnancy is confirmed, any out of range hCG levels will not be considered an adverse event

Once notified that pregnancy has occurred during the course of the study or within 30 days of study completion, clinic personnel will report the pregnancy within 24 hours of the confirmatory hCG blood test, to the PI/Sub-Investigator, the IRB, and appropriate Sponsor representative. A Pregnancy Notification Form will be completed as per BPSUSA internal Standard Operating Procedures and will be included alongside any pertinent information at the time of pregnancy reporting. The confirmed pregnancy will be followed to birth of the child or elective/spontaneous termination of the pregnancy. Follow up will occur at minimum once every three months (i.e. once per trimester) until the end of the pregnancy (birth, termination, etc.).

Elective termination will not be considered an adverse event; however supporting documentation detailing the outcome of the procedure will be required.

Spontaneous termination of the pregnancy will be considered a Serious Adverse Event and will be followed up accordingly (as per Section 11.1).

Although elevated hCG and pregnancy will not be considered adverse events, both will be treated as AEs. As such, for safety purposes, the samples collected from any subject who has elevated hCG levels or is confirmed to be pregnant will be analyzed accordingly. Furthermore, the results will not be included in the pharmacokinetic and statistical analysis, but rather will be presented separately.

12.0 BIOANALYTICAL ANALYSIS

12.1 Analytical Procedures

Data management, quality review and reporting of study data pertaining to laboratory analysis of study data will be the responsibility of the bioanalytical facility.

12.1.1 Samples to be assayed

Samples from subjects fulfilling at least one of the following criteria will be analyzed for drug concentration:

1. Subjects who complete at least two study periods.
2. Subjects who have missed samples that have been pre-determined prior to the start of bioanalytical analysis to not significantly impact the overall outcome of the study, as per BPSI PK Scientist and/or Sponsor recommendation.
3. Subjects who do not complete the study due to AE(s).

The samples from subjects who were dismissed due to non-compliance will not be analyzed.

12.1.2 Analyte(s) in Biological Matrix

Plasma samples will be assayed for nifedipine using a validated analytical method according to the principles of Good Laboratory Practice.

13.0 PHARMACOKINETIC AND STATISTICAL ANALYSIS

13.1 Pharmacokinetic Analysis Data Set

The data from the following subjects meeting one of the criteria will be included in the final PK and statistical analysis:

1. Subjects who complete at least two study periods with both test and reference administered alone; or two study periods with the same product administered with and without PPI.
2. Subjects who have missed samples that have been pre-determined prior to the start of bioanalytical analysis to not significantly impact the overall outcome of the study.

Data from subjects who were dismissed or withdrew due to AE(s) will not be included in the PK and statistical analysis. The data for these subjects will be presented separately.

Any decision for excluding data from the final data set will be provided with a detailed explanation and will be properly recorded and dated.

13.2 Pharmacodynamic (PD) Analysis Data Set

The data from the following subjects meeting one of the criteria will be included in the final PD and statistical analysis:

Subjects who were dosed with SmartPill™ and have collected Gastric pH samples up to 4 hours' time point in any given period.

Any decision for excluding data from the final pharmacokinetic and pharmacodynamics data set will be provided with a detailed explanation and will be properly recorded and dated.

13.3 Analysis of Data

Pharmacokinetic, pharmacodynamic and statistical analysis will be performed on all data from all subjects in the final data set.

The PK, PD and statistical analysis will be performed at BPSI using SAS® Version 9.4. The PK, PD and/or statistical analyses outlined in this protocol may be altered with appropriate justification.

13.3.1 Pharmacokinetic Analysis

Pharmacokinetic parameters will be calculated using non-compartmental analysis (NCA) method. The following PK parameters will be estimated (where possible) for nifedipine and included in the PK and statistical analysis for the subjects in the final data set:

AUC_{inf}:	Area under the concentration-time curve from time zero to infinity, calculated as $AUC_t + C_{last}/\lambda$, where C_{last} is the last measurable concentration.
AUC_t:	Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first. AUC_t is estimated using the trapezoidal method.
C_{max}:	The maximal observed plasma concentration.
$T_{1/2}$:	Terminal elimination half-life, estimated as $\ln(2)/\lambda$.
T_{max}:	Time when the maximal plasma concentration is observed.
λ:	Terminal elimination rate constant, estimated by linear regression analysis of the terminal portion of the ln-concentration vs. time plot.

If nifedipine concentration in the subject's plasma before administering any nifedipine (i.e. pre-dose) in any given period is less than or equal to 5% of the C_{max} value for that subject in the given period, then the subject's data without any adjustments can be included in all PK measurements and calculations. If the pre-dose value is greater than 5% of the C_{max}, data from that subject may be dropped from the PK and statistical analysis based on the assessment of the pharmacokinetic scientist and sponsor. Data for subjects dropped due to higher than 5% of C_{max} pre-dose concentrations will be included in a separate appendix in the final study report.

During PK and statistical analyses, drug concentrations below the lower limit of quantitation (BLQ) of an assay will be considered as zero except when they occur between two non-BLQ concentrations where they will be considered as missing during PK calculations and estimations.

Missed samples and non-reportable concentrations (e.g. quantity not sufficient) from the analytical laboratory will be treated in the pharmacokinetic analysis as if they have not been scheduled for collection.

The λ, $T_{1/2}$, and AUC_{inf} parameters will not be estimated for plasma concentration-time profiles where the terminal linear phase is not clearly defined.

For subjects with missing or non-reportable nifedipine concentrations for three or more of the last samples, only the C_{max} and T_{max} will be presented and included in the statistical analysis. Other PK parameters will not be reported.

13.3.2 Pharmacodynamic Analysis

Pharmacodynamic (PD) parameters of omeprazole/sodium bicarbonate (i.e. proton pump inhibitors) will be evaluated for all subjects with at least 4 hours pH measurement. The PD parameters include gastric pH, change of gastric pH from baseline.

13.3.3 Statistical Analysis

Descriptive statistics (min, max, median, mean, standard deviation and coefficient of variability) of all PK parameters will be provided for nifedipine for all study arm groups.

ANOVA including sequence, subjects nested within sequence, period and study arm will be performed on the ln-transformed data for AUC_t, AUC_{inf} and C_{max} and on the untransformed data for T_{max}, λ and $T_{1/2}$.

T_{max} will be analyzed using an additional non-parametric test (Wilcoxon test).

The 90% CI of the ratios of geometric means for AUC_t, AUC_{inf} and C_{max} will be calculated based on the LSMEANS and ESTIMATE of the ANOVA.

The following PK comparisons will be carried out:

- Test with PPI (Study arm C)/Test without PPI (Study arm A)
- Reference with PPI (Study arm D)/Reference without PPI (Study arm B)
- Test with PPI (Study arm C)/Reference with PPI (Study arm D)
- Test without PPI (Study arm A)/Reference without PPI (Study arm B)

For Pharmacodynamic Data:

The descriptive statistics (min, max, median, mean, standard deviation and coefficient of variability) of the gastric pH and change of gastric pH will be calculated for both test and reference products.

Analysis of Variance (ANOVA) for gastric pH and change of gastric pH from baseline will be carried out.

The following gastric pH comparisons will be carried out:

- Study arm $C_{PPI\ (Day7)}$ – Study arm $A_{(Day2)}$

- Study arm D $_{PPI\ (Day7)}$ – Study arm B $_{(Day2)}$
- The comparison of the change between test and reference can be assessed

Additional statistical and alternate tests will be performed if necessary.

Missing data will not be included in the statistical analysis. There are potential two kinds of unbalanced designs for the analysis: (1) unequal number of subjects across groups, (2) missing cells: there are not available data for some subjects. The Type 3 method will be used for the calculation of sums of squares using SAS software. All the fixed effects will be tested using the Type 3 in the ANOVA to detect statistically significant differences (α=0.05) if applicable. A mixed effects ANOVA model for gastric pH with fixed factors of sequence, period, and study arm and random effects of subject will be fit. A compound-symmetric or other appropriate covariance structure will be used in the analysis.

The null hypotheses for gastric pH comparisons for different study arms are:

- For the comparison of Study Arm A and Study Arm C
- H01: There is no difference between Study Arm A and Study Arm C
- H11: There is a difference between Study Arm A and Study Arm C
- For the comparison of Study Arm D and Study Arm B
- H02: There is no difference between Study Arm D and Study Arm B
- H12: There is a difference between Study Arm D and Study Arm B
- For the comparison of Study Arm A and Study Arm B
- H03: There is no difference for the change of median between Study Arm A and Study Arm B
- H13: There is a difference for the change of median between Study Arm A and Study Arm B

14.0 ETHICAL CONSIDERATIONS / PROTECTION OF HUMAN SUBJECTS

14.1 Basic Principles

This research will be carried out in accordance with Good Clinical Practice (GCP) as set out by the International Conference on Harmonization (ICH), the basic principles defined in the U.S. Code of Federal Regulations (21 CFR Part 312), the Belmont Report, Directive 2001/20/EC (Europe), and the principles enunciated in the most recent version of the World Medical Association Declaration of Helsinki.

14.2 Institutional Review Board

Both Chesapeake IRB and FDA Research Involving Human Subjects Committee (RIHSC) will be the Institutional Review Board (IRB) for this study. This Protocol and the ICF will be reviewed and approved by the IRB prior to the initiation of the study. Termination / suspension of any prior approval / favorable opinion can be done by IEC/IRB.

The board is constituted and operates in accordance with Division 5 of the Food and Drug Regulations, ICH Harmonized Tripartite Guideline (GCP Consolidated Guideline), and 21 CFR Parts 56 and 50.

14.3 Informed Consent Form

Subjects will sign the ICF prior to starting any screening procedures. Each subject will be provided with verbal and written information, in non-technical terms, which will describe the nature of the screening procedures as well as conduct of the study. Prior to signing the ICF, subjects will be allowed adequate time to consider the potential benefits and risks associated with their participation in the study. Signed and dated ICFs will be retained with the study records and a copy will be provided to the subject.

14.4 Confidentiality

The information in this study protocol is confidential. This document contains trade secrets and commercial information that is confidential and may not be disclosed to third parties (except to the IRB, FDA and/or relevant regulatory agencies). These restrictions will apply as well to all future communications if deemed privileged or confidential.

Sponsor, study monitors, auditors, the IRB, FDA and applicable regulatory authorities will be granted direct access to the subject's original medical records for verification of clinical trial procedure and/or data, without violating the confidentiality of the subject, to the extent permitted by applicable laws and

regulations and that, by signing a written informed consent form, the subject or the subjects legally acceptable representative is authorizing such access.

All documentation collected by the Sponsor or by BPSI/BPSUSA Inc. will be kept confidential. The name and identity of the subjects will remain confidential. If documents containing the subjects' names are photocopied, the name will be omitted from the photocopied version.

All of the subject's data obtained through data receiver will not be identified by name and the identity will remain confidential. The data obtained from the data receiver will be transferred to the computer that is password protected and have authorized access to the computer.

14.5 Compensation for Participation

[redacted]

14.6 In Case of an Injury Related to this Research

[redacted]

15.0 ADMINISTRATIVE CONSIDERATIONS

15.1 Revisions and/or Amendments to the Protocol

Revisions and/or amendments to the protocol must be documented and approved by the Principal Investigator and Sponsor. If the revision/amendment will affect subject safety and/or study design, then the amendment will be re-submitted to the IRB for approval. Administrative changes (i.e. change of analytical facility, typographical errors, discrepancies, clarifications) will also be submitted to the IRB, but may not require approval. A copy of the IRB's approval documents will be included in the final report.

For revisions or amendments to the protocol that substantially alter the study design after initiation of the study, the Principal Investigator and Sponsor will decide whether a revised informed consent form will be needed for continued participation.

It is the Sponsor's responsibility to submit, or to assign responsibility to submit, all revisions and amendments to the appropriate regulatory authorities when necessary. If an amended or revised version of the ICF is introduced during the study, each subject's further consent should be obtained.

15.2 Investigator Responsibilities

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, the current revision of the Declaration of Helsinki, ICH - GCP guidelines and applicable regulatory requirements.

15.3 Study Completion/Termination

BioPharma Services USA Inc. and/or the Sponsor reserve the right to terminate the study at any time, and for any reason.

15.4 Sponsor Visits

The Sponsor is encouraged to visit BioPharma Services USA Inc., if desired, and at their convenience. The PI and staff will provide, if requested, all source documents and/or other study-related documents. The PI will maintain regular written and telephone communication with the Sponsor.

16.0 DATA MANAGEMENT/RECORD KEEPING

16.1 Source Data

All data will be recorded in accordance with GCP to ensure accuracy, completeness, legibility, and timeliness of the data reported.

All data will be recorded directly on the source documents and will be considered source data. The source documents will serve as the Case Report Forms.

16.2 Quality of Data

All source documents and laboratory reports will be Quality Control reviewed to ensure accuracy and completeness. Adverse events will be reviewed and assessed for severity and causality by the PI/Sub-Investigator. Specific processes of the study, its source documentation and any reports (if applicable) will be audited by the Quality Assurance (QA) unit of BPSI/BPSUSA.

16.3 Retention of Documents

All records and documents pertaining to the study will be retained by BioPharma Services USA Inc. for at least 5 years from the completion of the study, and will be available for inspection by the Sponsor and/or Regulatory Agencies.

17.0 REFERENCES

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APPENDIX A – SCHEDULE OF EVENTS

	Screening	Study arm A and B				Study arm C and D								
Study Day	**-28 to 0**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Confinement			**X**	**X**	**X[#]**			**X**	**X**	**X**	**X**	**X**	**X**	**X[#]**
Stay overnight		**X**	**X**	**X**				**X**	**X**	**X**	**X**	**X**	**X**	
ICF		X				X								
Check-in		X				X		X						
Demographics	X													
Medical/Medication History	X													
Physical Exam	X				X									X
Body weight	X													
Height	X													
Sitting Vital Signs (BP, HR, PR and temperature)	X	X	X[a]	X[b]	X	X[c]	X[c]	X[c]	X[c]	X[c]	X[c]	X[a]	X[b]	X
Urine Drug Tests	X	X						X						
Alcohol Test	X	X						X						
Cotinine Test	X	X						X						
Pregnancy Test	X[*]	X				X		X						
12-Lead ECG	X													
Hematology	X	X			X			X						X
Serum Chemistry	X	X			X			X						X
Urinalysis	X	X			X			X						X
Serology (HIV, Hepatitis B and C)	X													
Inclusion/Exclusion criteria	X													
Compliance check		X				X		X						
Randomization			X											
SmartPill™ Dosing			X[d]									X[d]		
Nifedipine ER Tablets Dosing			X									X		
Omeprazole/sodium bicarbonate Capsules Dosing						X[e]	X[e]	X[e]	X	X	X	X		
Gastric pH measurement			X[f]									X[f]		
PK Sampling			X[g]									X[g]		
Questioning subjects if use of any concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Meals		X	X	X				X	X	X	X	X	X	

* Serum pregnancy test at screening and urine pregnancy test at each period check-in.
# Study exit at 48 hours post-dose nifedipine
a: 4 and 12 hours post-dose
b: 24 hours post-dose
c: 1 hour post-dose
d: 30 minutes before nifedipine dosing
e: Out-patient visit 1 hour prior to dosing until at least 1 hour post-dose
f: 0, 1, 2, 3, 4, 5, 6, 7, and 8 hours after SmartPill™ administration
g: Pre-dose (0 hour) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 20, 24, 36, and 48 hours after nifedipine dosing

An example of schedule events (note: the sequence of study arms A, B, C, and D may be in a random order).

Study arm	Day	Overnight in clinic?	Example time	Items
	-28 to 0	No		Screening period
A	1	Yes	8:00 PM	Arrive in the evening to check-in for check-in procedure
	2	Yes	(1) 7:00 AM (2) 7:30 AM (3) 7:30 AM →	(1) Administer SmartPill (2) Administer study drug generic nifedipine extended release tablets (3) Draw blood
	3	Yes	Throughout the day	Draw blood
	4	No	→7:30 AM	After the last time point of blood draw, you will be released from the clinical site
	5 to 18	No		Washout period (break), at least 14 days
B	19	Yes	8:00 PM	Arrive in the evening to check-in for check-in procedure
	20	Yes	(1) 7:00 AM (2) 7:30 AM (3) 7:30 AM →	(1) Administer SmartPill (2) Administer study drug brand-name nifedipine extended release tablets (3) Draw blood
	21	Yes	Throughout the day	Draw blood
	22	No	→ 7:30 AM	After the last time point of blood draw, you will be released from the clinical site
	23 to 36	No		Washout period (break), at least 14 days
C	37	No	(1) 6:30 AM (2) 7:30 AM (3) 8:30 AM	(1) Arrive in the clinic (2) Omeprazole/sodium bicarbonate administration (3) Released from the clinic
	38	No	(1) 6:30 AM (2) 7:30 AM (3) 8:30 AM	(1) Arrive in the clinic (2) Omeprazole/sodium bicarbonate administration (3) Released from the clinic
	39	Yes	(1) 6:30 AM (2) 7:30 AM (3) Afternoon	(1) Arrive in the clinic to check-in (2) Omeprazole/sodium bicarbonate administration (3) Check-in procedure
	40	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	41	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	42	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	43	Yes	(1) 7:00 AM (2) 7:30 AM (3) 7:30 AM –	(1) Administer SmartPill (2) Administer Omeprazole/sodium bicarbonate and study drug generic nifedipine extended-release tablets (3) Draw blood

	44	Yes	Throughout the day	Draw blood
	45	No	7:30 AM	After the last time point of blood draw, you will be released from the clinical site
	46 to 59	No		Washout period (break), at least 14 days
D	60	No	(1) 6:30 AM (2) 7:30 AM (3) 8:30 AM	(1) Arrive in the clinic (2) Omeprazole/sodium bicarbonate administration (3) Released from the clinic
	61	No	(1) 6:30 AM (2) 7:30 AM (3) 8:30 AM	(1) Arrive in the clinic (2) Omeprazole/sodium bicarbonate administration (3) Released from the clinic
	62	Yes	(1) 7:00 AM (2) 7:30 AM (3) Afternoon	(1) Arrive in the morning to check-in (2) Omeprazole/sodium bicarbonate administration (3) Check-in procedure
	63	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	64	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	65	Yes	7:30 AM	Omeprazole/sodium bicarbonate administration
	66	Yes	(1) 7:00 AM (2) 7:30 AM (3) 7:30 AM –	(1) Administer SmartPill (2) Administer Omeprazole/sodium bicarbonate and study drug brand-name nifedipine extended-release tablets (3) Draw blood
	67	Yes	Throughout the day	Draw blood
	68	No	7:30 AM	After the last time point of blood draw, you will be released from the clinical site

APPENDIX B – CLINICAL LABORATORY ASSESSMENT

TYPE OF TEST	COMPONENTS			
Hematology	• Hemoglobin • Hematocrit	• RBC • Platelet count	• WBC and differential • Peripheral blood smear†	
Serum Chemistry	• Glucose • Calcium • Sodium • Chloride	• Albumin • Protein • Bilirubin • Lactate Dehydrogenase	• AST • ALT • Potassium • Alkaline Phosphatase	• Urea • Uric Acid • Creatinine • Creatine Kinase
Urinalysis	• Bilirubin • Blood • Glucose	• pH • Ketones • Leukocytes	• Nitrites • Protein	• Specific Gravity • UBG
Additional Tests	Serology (HIV, Hepatitis B surface antigen, Hepatitis C antibody)		Alcohol test Urine Cotinine Serum hCG (only females, at Screening) Urine hCG (only females, at each period check-in)	
Urine Tests for Drugs of Abuse	Marijuana, Amphetamines, Phencyclidine, Barbiturates, Cocaine, Opiates, Benzodiazepines			

† Only if deemed necessary by PI/Sub-Investigator

APPENDIX C – LIST OF COMMON ABBREVIATIONS

AE:	Adverse Event	kg/m^2:	Kilogram/Meter Squared
ALT:	Alanine Aminotransferase	LC/MS/MS:	Liquid Chromatography/Mass Spectrometry/ Mass Spectrometry
ANDA:	Abbreviated New Drug Application	LLOQ:	Lower Limit of Quantitation
ANOVA	Analysis of Variance	LSMEANS:	Least Square Means
AST:	Aspartate Aminotransferase	MedDRA:	Medical Dictionary for Regulatory Activities
AUC_t:	Area under the concentration-time curve from time zero until the last measurable concentration or last sampling time t, whichever occurs first. AUCt is estimated using the trapezoidal method	mg:	Milligram
AUC_{inf}:	Area under the concentration-time curve from time zero to infinity, calculated as AUCt + Clast/λ, where Clast is the last measurable concentration	mL:	Milliliters
BLQ /BQL:	Below the Limit of Quantitation / Below Quantitation Limit	ms:	Millisecond
BMI:	Body Mass Index (kg/m^2)	mmHg:	Millimeter of Mercury
BP:	Blood Pressure	MRI:	Magnetic Resonance Imaging
BPM:	Beats Per Minute	N/A or NA:	Not applicable, Not Available
BPSI:	BioPharma Services Inc.	NOL:	No Objection Letter
BPSUSA:	BioPharma Services USA Inc.	PI:	Principal Investigator
CI:	Confidence Interval	PK:	Pharmacokinetic
C_{max}:	The maximal observed-plasma concentration.	PT:	Preferred Term
CTA:	Clinical Trial Application	QA:	Quality Assurance
CYP:	Cytochrome P450	RBC:	Red Blood Cell
ECG:	Electrocardiogram	RPM:	Revolutions Per Minute
EMA:	European Medicine Agency	RR:	Respiratory Rate
FDA:	Food and Drug Administration	RLD:	Reference Listed Drug
FSH:	Follicle-Stimulating Hormone	SAE:	Serious Adverse Event
g:	Grams	SAS®:	Statistical Analysis System
GCP:	Good Clinical Practice	SD or STD:	Standard Deviation
GLP:	Good Laboratory Practice	SOC:	System Organ Classification
HC:	Health Canada	SOP:	Standard Operating Procedure
hCG:	Human Chorionic Gonadotropin	$T_{1/2}$:	Terminal elimination half-life, estimated as ln(2)/λ
HIV:	Human Immunodeficiency Virus	Temp:	Temperature
ICF:	Informed Consent Form	T_{max} / t_{max}:	Time when the maximal-plasma concentration is observed
ICH:	International Conference on Harmonization	TPD:	Therapeutic Products Directorate
IRB:	Institutional Review Board	UBG:	Urobilinogen
IUD:	Intrauterine Device	WBC:	White Blood Cell
λ:	Terminal elimination rate constant, estimated by linear regression analysis of the terminal portion of the ln-concentration vs. time plot		

APPENDIX D – RESTRICTED LIST OF DIURETICS

Examples of Diuretic Drugs	Examples of Diuretic Foods
Thiazides Diuretics	Lemon
chlorothiazide (Diuril)	Oats
chlorthalidone (Hygroton)	Celery
indapamide (Lozol)	Brussels sprouts
hydrochlorothiazide (Hydrodiuril)	Ginger
methyclothiazide (Enduron)	Beets
metolazone (Zaroxolyn, Diulo, Mykrox)	Apple Cider Vinegar
Loop Diuretics	Cabbage
bumetanide (Bumex)	Cranberry Juice
furosemide (Lasix)	Eggplant
ethacrynate (Edecrin)	Parsley
torsemide (Demadex)	Caffeinated beverages
Potassium sparing Diuretics	Tomatoes
Amiloride hydrochloride	Cucumber
spironolactone (Aldactone)	Watermelon
triamterene (Dyrenium)	Carrots
Carbonic anhydrase inhibitors	Garlic
Acetazolamide Injection/Tablets	Artichokes
Methazolamide	Asparagus
Osmotic diuretics	
glycerin (Glycerol)	
Isosorbide	
Mannitol IV	
Urea	
Nonprescription Diuretics	
Maximum Strength Aqua Ban	

APPENDIX E – NIFEDIPINE LABEL

(See attached)

APPENDIX F – PROCARDIA XL LABEL

(See attached)

APPENDIX G –OMEPRAZOLE/SODIUM BICARBONATE LABEL

(See attached)

APPENDIX H – SMARTPILL™ 510(k) SUMMARY

(See attached)