GlaxoSmithKline
Consumer Healthcare

CLINICAL PROTOCOL

A single dose, open label, randomized scintigraphic study to investigate the gastrointestinal behavior of 2 triple combination products (Acetaminophen, Phenylephrine and Dextromethorphan) in healthy male volunteers

Compound Name:	Theraflu Daytime Severe Cold & Cough powder for oral solution Theraflu ExpressMax Daytime Severe Cold and Cough Caplets
United States (US) Investigational New Drug (IND) Number:	N/A
European Clinical Trials Database (EudraCT) Number:	NA
Other Regulatory Agency Identified Number:	NA
Protocol Number:	208821
Phase:	I

Sponsor information

Sponsor Legal Registered Address	**GlaxoSmithKline Research & Development Limited** 980 Great West Road Brentford Middlesex, TW8 9GS UK
Sponsor Contact Address	**Clinical Study Manager** PPD GlaxoSmithKline Consumer Healthcare St George's Avenue, Weybridge Surrey, KT13 0DE UK **Clinical Research Scientist** PPD GlaxoSmithKline Consumer Healthcare Novartis Consumer Health S.A. Route de l'Etraz 2, 1269 Nyon Switzerland

Document History

Document	Version Date	Summary of Changes
Clinical Protocol, v2.0 (*Amendment 1*)	25-January-2018	Definition of Medical History added as a footnote to Table 1-1. Clarification made to the following sections to ensure consistency that AEs are collected from Informed Consent. 1. Section 6.2 2. Section 6.2.2 3. Section 6.2.1 4. Section 7.2.2 5. Section 8.2.1 Clarification added to Section 7.2.2 that the *cardio*vascular system will be included in the physical examination. Correction of 'tobacco' spelling in Section 6.1 Clarification in Section 7.2.7 that CRF will capture both results and clinically significant findings of ECG's
Clinical Protocol, v1.0 (*Original Protocol*)	12-December-2017	Not applicable (N/A)

Amendments incorporate all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol and any amendments and according to the current ICH GCP guidelines.

- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure site staff receives all appropriate information throughout the study.

- I agree to conduct this study in full conformance with the laws and regulations of the country in which the research is conducted and the Declaration of Helsinki.

Investigator Name:	Walter J. Doll
Investigator Qualifications:	Ph.D., R.Ph.
Investigator Signature:	PPD
Date of Signature/ Agreement:	PPD DD/MMM/YYYY

Table of contents

List of tables

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Table 1-1 Schedule of Activities

Procedure/Assessment	Screening	Study Period 1	
	Visit 1	Visit 2	
	Day -21 to Day -2	Day -1	Day 1
Informed consent	X		
Inclusion/Exclusion criteria	X	X	
Medical history /smoking history[h]	X	X	
Demographics	X		
Prior medications	X	X	
Physical examination	X[c]	X[c]	X[c]
Laboratory tests	X		X[d]
Urine drug test	X	X	
Height & weight	X	X[e]	
Breath Alcohol test	X	X	
Urine Cotinine test	X	X	
ECG	X		
Scintigraphic imaging[a]			X
Vital signs (BP, PR, RR, oral temperature)	X[f]	X[f]	X[f]
Meals[b]		X	X
Randomization			X
Study treatment administration			X
Concomitant treatments	X	X	X
Adverse events[g]	X	X	X
Study conclusion			X

Abbreviations: ECG = electrocardiogram; BP = blood pressure; PR = pulse rate, RR = respiratory rate

[a] Scintigraphic acquisitions will be taken beginning after dose administration until 10 hours post-dose.

[b] Subjects will be given a standard lunch 4 hours postdose, and a standard dinner at 10 hours post-dose.

[c] Full physical examination, on screening, on day -1, and brief physical examination on day 1 before randomization and another brief physical examination before discharge

[d] After final scintigraphic image is taken prior to dinner.

[e] Only weight.

[f] Vital signs that will be performed at visit 1 and visit 2 (day -1): BP, RR PR and oral temperature. At visit 2 (day 1) vital signs that will be performed are only BP and PR and they will be done before randomization and after the last scintigraphic image.

[g] AEs (serious and non-serious) will be collected from the time the subject has signed the informed consent form until 5 days following last administration of the investigational product.

[h] Medical History recorded will be any existing or resolved condition that started prior to Informed Consent. Changes in medical history will be assessed at visit 2 (day-1)

1 INTRODUCTION

The common cold is one of the most frequent human illnesses worldwide (Gwaltney 1994) and, although no cure exists, symptoms are treatable. Cold remedies and multi-symptom drug combinations are available in a variety of formats, including a hot drink. Hot drink remedies are associated with greater comfort and provide active ingredients in solution. This may result in reaching the bloodstream faster and being bioavailable quicker than tablet formulations (Hodges 2014).

Theraflu Daytime Severe Cold & Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets are among the commercially available multi-symptom formulations available on the market. Theraflu Daytime Severe Cold & Cough powder for oral solution contains acetaminophen, phenylephrine and dextromethorphan and is available in sachets for reconstitution with hot water.

Given that absorption of these active ingredients from the stomach is negligible but is rapid and significant from the duodenum, (Hengstmann 1982) (Prescott L. 1996) rapid gastric emptying (GE) is a key approach to reducing the delay between drug ingestion and onset of symptom control. This clinical study is designed to characterize the gastrointestinal transit of Theraflu Daytime Severe Cold & Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets using gamma scintigraphy.

External gamma scintigraphy has been used extensively as a noninvasive technique for assessing the *in vivo* performance of drug delivery systems. It provides information on deposition, dispersion and movement of radiolabeled dosage forms. In this study, gamma scintigraphy will be utilized to monitor gastric emptying and intestinal transit of a single radioactive marker by radiolabeling the drug formulation.

1.1 Mechanism of Action/Indication

Acetaminophen is an analgesic and antipyretic, its mechanism of action is believed to include inhibition of prostaglandin synthesis, primarily within the central nervous system. Phenylephrine is a sympathomimetic agent with mainly direct effects on adrenergic receptors producing nasal decongestion. Finally, dextromethorphan has an antitussive action, it controls cough spasms by depressing the medullary cough centre (GSK Global Data Sheet 2017).

1.2 Background and Rationale

This clinical study will be conducted to characterize the gastrointestinal transit of two multi-symptoms formulations by inclusion of a radiolabel marker: Theraflu Daytime Severe Cold & Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets. This study will be the first study to investigate the time of onset and completion of gastric emptying as well as small intestine transit time of Theraflu Daytime Severe Cold &

Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets.

2 STUDY OBJECTIVES AND ENDPOINTS

Objective(s)	Endpoint(s)
Gamma Scintigraphy Imaging	
Characterize time to onset and time to completion of gastric emptying after administration of either Theraflu Daytime Severe Cold & Cough powder for oral solution to be reconstituted with 225 ml of hot water or Theraflu ExpressMax Daytime Severe Cold and Cough caplets using gamma scintigraphic analysis.	Mean time to onset of gastric emptying in healthy male volunteers who did not vomit shortly (within 60 minutes) after study drug administration, who have sufficient data to determine time to onset of gastric emptying and who had no major protocol deviations. Mean time to complete gastric emptying in healthy male volunteers who did not vomit shortly (within 60 minutes) after study drug administration, who have sufficient data to determine time to completion of gastric emptying and who had no major protocol deviations. Further characterize gastrointestinal emptying by calculating additional parameters such as but not limited to: a) GE25%, GE50%, GE90% values, b) the amount remaining in the stomach at 15, 30, 45, 60, 75, 90, 105, 120, 180, 240 min; c) sectional areas under the gastric emptying curve and total AUC; and d) gastric emptying $t_{1/2}$ values. e) Small intestinal transit times which are calculated by determining the arrival time of the radioactive marker at the cecum / colon region and subtracting the gastric emptying value.
Safety	
To evaluate safety of Theraflu Daytime Severe Cold & Cough powder for oral	Safety assessments consists of monitoring and recording adverse events (AEs) and laboratory test

solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets	

3 STUDY DESIGN AND SUBJECT POPULATION

This will be an open label, randomized, single dose, parallel group gamma scintigraphy. Approximately, forty-two healthy male volunteers will be screened to allow a total of 28 healthy male volunteers to be randomized (14 subjects per treatment arm) in order to have 24 evaluable subjects (12 subjects per treatment arm).

Subjects will be randomized to receive either a single dose of Theraflu Daytime Severe Cold & Cough powder for oral solution (Treatment A) or a single dose of Theraflu ExpressMax Daytime Severe Cold and Cough caplets (Treatment B) under fasted conditions:):

Treatment A – 12 healthy male volunteers will be administered 1 sachet of Theraflu

Daytime Severe Cold & Cough radiolabeled powder for oral solution (acetaminophen 650 mg + phenylephrine 10 mg + 20 mg dextromethorphan) reconstituted with 225 mL of hot water

Treatment B – 12 healthy male volunteers will take 2 radiolabeled caplets of Theraflu ExpressMax Daytime Severe Cold and Cough (2 caplets each containing acetaminophen 325 mg + phenylephrine 5 mg + 10 mg dextromethorphan) with 225 mL of room temperature non-carbonated water.

The study will consist of screening visit (Visit 1), followed by a treatment visit (Visit 2). Visit 2 includes two days: day -1 and day 1.

The screening visit will assess subject eligibility and consist of relevant medical examinations.

On visit 2 (day -1) of the study, study participants will be admitted to the unit at approximately 7 pm on the evening before study drug administration to ensure compliance with fasting conditions and will receive a standardized meal. Subjects are required to fast (nothing to eat or drink except room temperature non-carbonated water) from 10 hours prior until 4 hours after study drug administration. Water is permitted until 1 hour prior to investigational product administration, and no additional fluids until the lunch meal is served at approximately 4 hours post dose.

Subjects will be given a standard lunch at 4h post-dose and a standard dinner at 10h post-dose on day 1. Subjects will be discharged from the unit after the last scintigraphic imaging is performed, blood sample for laboratory test is taken as well as a brief physical examination.

4 SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular subject is suitable for this protocol. Healthy

male volunteers will be recruited. It is essential to ensure they do not suffer from any gastrointestinal disorders which could impact on the validity of the scintigraphy data. Vegetarians will be excluded from this study as there is evidence that the absorption of acetaminophen is impaired in this group of the population (Prescott, 1993). Female subjects will be similarly excluded; it has been observed that the menstrual cycle has been associated with changes in gastric emptying patterns (Wald, 1981). Subjects with allergies or intolerance to one or more ingredients of the standard meal will be excluded. Any subjects with a body mass index (BMI) higher than 30.5 kg/m^2 will be excluded as shielding caused by bone, muscle, other organs and soft tissue will attenuate counts.

4.1 Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study before any assessment is performed.
2. Healthy male subjects who, at the time of screening, are between the ages of 21 and 45 years, inclusive.
3. Subjects who are willing and able to comply with scheduled visits, treatment plan, bio-imaging procedure, laboratory tests and other study procedures.
4. Healthy subjects which is defined as in general good physical health, as judged by the investigator and no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, 12-lead ECG or clinical laboratory tests.
5. Body Mass Index (BMI) of 17.5 to 30.5 kg/m^2; and a total body weight >50 kg (110 lbs).

4.2 Exclusion Criteria

Subjects with any of the following characteristics/conditions will not be included in the study:

1. Subjects who are investigational site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or subjects who are GSK employees directly involved in the conduct of the study.
2. Participation in other studies involving investigational drug(s) within 30 days prior to study entry and/or during study participation.

3. Acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.
4. Known or suspected intolerance or hypersensitivity or contraindication to the study materials (or closely related compounds) or any of their stated ingredients.
5. Subject with known allergy or intolerance to any of the contents of the standard meals.
6. Subject is vegetarian.
7. Unwilling or unable to comply with the Lifestyle guidelines described in this protocol.
8. Use of prescription or non-prescription drugs and dietary supplements within 14 days or 5 half-lives, whichever is longer, prior to the first dose of investigational product that are deemed by the investigator to have a potential impact on the study objectives results.
9. Evidence or history of clinically significant laboratory abnormality, hematological, renal, endocrine, pulmonary, cardiovascular, hepatic, psychiatric, neurologic, or allergic disease within the last 5 years that may increase the risk associated with study participation.
10. A positive urine drug screen, breath alcohol test or urine cotinine test during Screening or on Day -1 of the study.
11. Any condition possibly affecting drug absorption (e.g., gastrectomy)
12. A history of current or relevant previous non-self-limiting gastrointestinal disorders peptic ulcer disease and/or gastrointestinal bleeding.
13. Currently suffering from disease known to impact gastric emptying, e.g. migraine, insulin-dependent diabetes mellitus.
14. The subject has had radiation exposure from clinical trials, including from the present study, and from therapeutic or diagnostic exposure, but excluding background radiation, exceeding a target organ (colon) dose of 50 mSv (5 rems) from a single dose within the last 30 days or a cumulative dose of 150 mSv (15 rems) in the last 12 months. No subject whose occupation requires monitoring for radiation exposure will be enrolled in the study.
15. Subjects who have been exposed to ionising radiation in excess of 10 mSv (whole body effective dose) above background over the previous 3 years period as a result of occupational exposure or previous participation in research studies. Clinically justified (therapeutic or diagnostic) exposures are not included in this calculation.
16. Renal disease or impaired renal function at screening as indicated by abnormal levels of serum creatinine or urea or the presence of clinically significant abnormal urinary constituents (e.g. albuminuria). Minor deviations of laboratory values from the normal range are permitted, if judged by the investigator to have no clinical relevance.
17. History or current evidence of ongoing hepatic disease or impaired hepatic function at screening. A candidate will be excluded if more than one of the following lab value deviations are found: 1) AST/SGOT (≥ 1.2 ULN), ALT/SGPT (≥ 1.2 ULN), 2) GGT (≥ 1.2 ULN), ALP (≥ 1.2 ULN), 3) total bilirubin (≥ 1.2 mg/dL) Minor deviations of laboratory values from the normal range are permitted, if judged by the investigator to

have no clinical relevance. Positive results in any of the virology tests for HIV-Ab, HCV-Ab, HBsAg and HBc-Ab (Total).

18. Diagnosis of long QT syndrome or QTc > 450 msec for males at screening.
19. Subjects who were intending to father a child in the 3 months following the study.
20. Subjects who were unwilling to follow contraception requirements described in section 4.4.4.
21. Subject had any non-removable metal objects such as metal plates, screws etc. in their chest or abdominal area.
22. History of regular alcohol consumption exceeding 14 drinks/week (1 drink = 5 ounces (150 mL) of wine or 12 ounces (360 mL) of beer or 1.5 ounces (45 mL) of hard liquor) within 6 months of Screening.
23. Smokers defined as the use of tobacco products (including but not limited to: electronic-cigarettes, nicotine gums, nicotine lozenges, etc…) during the 6 months prior to screening or a positive urine cotinine test at screening.
24. Subject has consumed (eat or drink) grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos, pawpaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits) 14 days prior to the first dose of investigational product.
25. Subjects who have previously been enrolled in this study.

4.3 Randomization Criteria

Subjects will be randomized into the study provided they have satisfied all subject selection criteria to take 1 sachet of Theraflu Daytime Severe Cold & Cough powder for oral solution or 2 caplets of Theraflu ExpressMax Daytime Severe Cold and Cough. Randomization schedule will be generated by InVentiv Health Clinical (IHC).

4.4 Lifestyle Guidelines

4.4.1 Meals and Dietary Restrictions

- Subjects must abstain from all food and drink (except water) at least 4 hours prior to any laboratory test evaluations and 10 hours prior to the administration of the investigational drug. Water is permitted until 1 hour prior to investigational product administration.
- Water may be consumed without restriction beginning 4 hours after dosing. Non-caffeinated drinks (except grapefruit or grapefruit-related citrus fruit juices – see below) may be consumed with meals.
- Lunch will be provided approximately 4 hours after dosing.
- Dinner will be provided approximately 10 hours after dosing after the safety laboratory tests are performed.

- Subjects will not be allowed to eat or drink grapefruit or grapefruit-related citrus fruits (e.g., Seville oranges, pomelos, pawpaw, dragon fruit, kiwi fruit, mango, passion fruit, pomegranate, rambutan, star fruit or products that contain these fruits) from 14 days prior to the first dose of investigational product until collection of the final scintigraphic image.
- While confined, the daily caloric intake per subject should not exceed approximately 3200 kcal.

4.4.2 Alcohol, Caffeine and Tobacco

- Subjects will abstain from alcohol for 72 hours prior to admission to the clinical site and continue abstaining from alcohol until collection of the final scintigraphic image.
- Subjects will abstain from caffeine-containing products for 24 hours prior to admission to the clinical site until collection of the final scintigraphic image.
- Subjects are non-smokers for the last 6 months before the screening date and they will also abstain from the use of tobacco- or nicotine-containing products for 24 hours prior to admission to the clinical site and during confinement at the clinical site.

4.4.3 Activity

- Subjects will not be permitted to assume a fully recumbent position for 4 hours following dosing except during imaging and other required study procedures.
- Subjects will abstain from strenuous exercise (e.g., heavy lifting, weight training, calisthenics, aerobics) for at least 24 hours before admission to the clinical site. Walking at a normal pace will be permitted.

4.4.4 Contraception

Male subjects able to father children and who are sexually active must agree to use a highly effective method of contraception consistently and correctly for the duration of the active study period and for at least 3 months after the last dose of investigational product. Male subjects who are not sexually active but become active, must comply with the contraceptive requirements as described below .The investigator or his or her designee, in consultation with the subject, will confirm that the male subject and female partner of childbearing potential have selected an appropriate method of contraception for the individual subject from the permitted list of contraception methods (see below) and instruct the subject in its consistent and correct use during the informed consent discussion. Subjects need to affirm that they meet the criteria for the correct use of at least 1 of the selected methods of contraception. The investigator or his or her designee will discuss with the subject the need to use highly effective contraception consistently and correctly according to the schedule of activities and document such conversation in the subject's chart. In addition, the investigator or his or her designee will instruct the subject to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the subject's partner.

Male subject or female partner of childbearing potential to use of one of the highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (i.e., perfect use) and include the following:

1. Established use of oral, inserted, injected, transdermal, or implanted hormonal methods of contraception is allowed provided the subject plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness as deemed appropriate by the investigator.
2. Correctly placed copper-containing intrauterine device (IUD).
3. Male condom used WITH a spermicide (i.e., foam, gel, film, cream, or suppository).
4. Male sterilization with documented absence of sperm in the post-vasectomy ejaculate.
5. Bilateral tubal ligation / bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

Female partners of non-childbearing potential must meet at least one of the following criteria (medical documentation must be provided):

a. Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; status may be confirmed by having a serum follicle-stimulating hormone (FSH) level confirming the post-menopausal state;
b. Have undergone a documented hysterectomy and/or bilateral oophorectomy;
c. Have medically confirmed ovarian failure.

All other female partners (including females with tubal ligations) will be considered to be of childbearing potential.

Male subjects should not donate sperm for the duration of the study and for 3 months after the last investigational product dose.

All sexually active male subjects must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom consistently and correctly, beginning with the first dose of investigational product and continuing for at least 3 months after the last dose.

4.5 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. In order to ensure transparent reporting of screen failure subjects, a minimal set of screen failure information will include demography, screen failure details (e.g., withdrawal of consent), eligibility criteria, and any serious adverse events (SAEs).

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened.

4.6 Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list and will be provided by the GSK CH Clinical Study Manager, which should be filed in the Investigator Site File.

The contact number can be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if some subject calls that number, he or she will be directed back to the investigational site.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol identifiers, subject study numbers, contact information for the investigational site, and contact details in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem identified from the subject's healthcare professional other than the investigator.

5 STUDY TREATMENTS

The healthy male individuals will be randomized to take either treatment A: 1 sachet of Theraflu Daytime Severe Cold & Cough powder (Berry flavor) - (acetaminophen 650mg + Dextromethorphan 20mg + Phenylephrine 10mg) or treatment B: 2 caplets of Theraflu ExpressMax Daytime Severe Cold and Cough. (each caplet contains: acetaminophen 325 mg + Dextromethorphan 10mg + Phenylephrine 5mg). Both products will be commercially sourced from local market.

For treatment A: Individual Theraflu doses are prepared by pouring the contents of the sachet into a glass bottle (with cap) and 225 mL of hot, but not boiling water (approximately 90-95°C), will be added to the container and mixed to dissolve the contents of the sachet. The dissolved Theraflu solution will be allowed to cool to approximately 40 – 50°C. After cooling, a small volume (1 to 10 microliters) of ^{99m}Tc-DTPA will be added to the drug solution in the preceding steps to achieve a maximum of 108 µCi (4 MBq) per individual dose at the time of dosing. The container will be capped and maintained at a temperature between 35-45°C until administration.

For Treatment B: Individual caplet doses are prepared by drilling a hole of approximately 1 mm diameter and at a depth of approximately one-half of its thickness (~2-2.5 mm deep) into individual caplets. ^{99m}Tc-DTPA (dissolved in normal saline) will be added into the hole of each caplet as a low volume liquid (0.5-2.0 microliters) to achieve a maximum of 54 µCi (2 MBq) per individual caplet at the time of dosing (two caplets = 108 µCi (4 MBq) dose per assessment visit). The applied liquid will be allowed to air dry and the hole is then filled with the equivalent

powder blend from a crushed caplet such that the drug content will remain constant and the same for all caplets. The small surface area of the caplet that was altered may be sealed with an appropriate material if determined to be necessary. Radiolabeled caplets will be packaged as unit doses (2 caplets per container) and maintained at room temperature until administration.

A document describing the radiolabeling procedure of treatment A and B is detailed in Appendix 13.2

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines, investigational product is defined as a pharmaceutical form of an active ingredient being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 R2 1.33).

5.1 Blinding and Allocation to Treatment/Randomization

Treatments will be provided in an open-label manner. The investigator's knowledge of the treatment should not influence the decision to enroll a particular subject nor affect the order in which subjects are enrolled nor influence the scintigraphy outcomes. Subjects knowing the product they are taking will also not affect the scintigraphy outcomes.
GSK CH will provide a randomization schedule to the investigator and, in accordance with the randomization numbers, the subject will receive the study treatment regimen assigned to the corresponding randomization number.

5.2 Breaking the Blind

Not applicable to this study

5.3 Subject Compliance

Study treatment will be administered under the supervision of investigator site personnel. The emptiness of the mouth/tongue and containers will be checked after drug administration. A record of the administration of study formulations will be kept using the Dosing Accountability Log and the Case Report Form (CRF), any comments on the performance of this procedure should be recorded on the CRF. Any violation of compliance will require evaluation by the investigator and sponsor to determine if the subject will continue in the study.

5.4 Investigational Product Supplies

5.4.1 Dosage Form and Packaging

Treatment A, Theraflu Daytime Severe Cold & Cough sachets (acetaminophen 650 mg + phenylephrine 10 mg + 20 mg dextromethorphan sachet) and treatment B, Theraflu ExpressMax Daytime Severe Cold and Cough caplets (each containing acetaminophen 325 mg +

phenylephrine 5 mg + 10 mg dextromethorphan) used in this study will be sourced commercially and supplied by GSK CH Global Clinical supply (GCS).

Treatment A, Theraflu Daytime Severe Cold & Cough powder for oral solution will be supplied to the study site in the commercial secondary package containing 6 individual sachets. The commercial secondary package will be labeled specifically for this study.

Treatment B, Theraflu ExpressMax Daytime Severe Cold and Cough caplets will be supplied to the study site in the commercial secondary package containing 20 caplets, 2-10 count Blister cards. The commercial secondary package will be labeled specifically for this study.

The commercial secondary package labels will include, but not limited to the following information: the study number, Treatment or Product name, Batch number, storage conditions, expiry date, the appropriate regulatory precautionary information, study site name and the sponsor name.

The manufacturers package information on product drug facts, warnings, directions, expiry, lot and storage conditions will not be defaced by the study label.

The study labels will be in accordance with all applicable regulatory requirements. Labeling will be carried out according to cGMP guidelines. Specific study label text for bulk supplies will be reviewed and approved internally by the GSK study team and GSK R&D Quality.

Bulk Packaging and labeling of the study products will be the responsibility of the Clinical Supply Department, GSKCH, Lincoln, NE, USA.

Care should be taken with the supplied products and their labels so that they are maintained in good condition. It is important that all labels remain intact and legible for the duration of the study. The study labels are not to be removed or defaced.

Radiolabeling or individual dose labeling of the study treatments used in this study will be the responsibility of Scintipharma.

5.4.2 Preparation and Dispensing

Radiolabeled Theraflu Daytime Severe Cold & Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets will be prepared, labeled and dispensed by qualified unblinded site personnel and checked by another independent individual at Scintipharma according to the dosage and administration instructions.

5.5 Administration

Following an overnight fast of least 10 hours, subjects will receive investigational product at approximately 8 am (plus or minus 2 hours). Site personnel will administer investigational product as follows:

Treatment A: Hot radiolabeled Theraflu solution (225 mL) that will be prepared as described in section 5, will be allowed to cool sufficiently to be drinkable at a temperature between 35

and 45°C at time of dosing and then subjects will be instructed to consume the hot drink entirely within 30 seconds.

Treatment B: 2 radiolabeled caplets will be swallowed with 225 mL of non-carbonated room temperature water. All the water (225 ml) should be consumed within 30 seconds.

Subjects will swallow the investigational product whole, and will not manipulate or chew the medication prior to swallowing.

In order to standardize the conditions for scintigraphic imaging, all subjects will be required to refrain from lying down (except when required for imaging) and will not be allowed to eat or drink beverages (including water) for the first 4 hours after dosing.

5.5.1 Medication Errors

Medication errors may result, in this study, from the administration or consumption of:

- the wrong product,
- by the wrong subject,
- at the wrong time,
- or at the wrong dosage strength (other examples of concern may be added based on the investigational product administration, such as inadvertent exposure).

Such medication errors occurring to a study participant are to be captured in the CRF. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not a medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on AE CRF page.

5.6 Investigational Product Storage

The investigator, or an approved representative, e.g., pharmacist, will ensure that all investigational products Theraflu Daytime Severe Cold & Cough powder for oral solution and Theraflu ExpressMax Daytime Severe Cold and Cough caplets are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements and product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations (as applicable, including frozen, refrigerated, and/or room-temperature products). This should be

captured from the time of investigational product receipt throughout the study. Even for continuous monitoring systems, a log or site procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature-monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product-label storage conditions should be reported upon discovery. The site should actively pursue options for returning the product to the storage conditions as described in the labeling, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the Sponsor.

Once an excursion is identified, the investigational product must be quarantined and not used until the Sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the investigational product after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation. Specific details regarding information the site should report for each excursion will be provided to the site.

5.7 Investigational Product Accountability

All products supplied are for use only in this clinical study and should not be used for any other purpose.

Study treatments must be received by a designated person at the study sites, handled and stored safely and properly, and kept in a secured location to which only the staff have access. Upon receipt, all study treatments should be stored according to the instructions specified on the treatment labels. Clinical supplies are to be dispensed only in accordance with the protocol. Documentation provided with the shipment of study treatments is to be completed by the site designated receiver and must be completed and returned to the clinical supplies department as specified on the documentation. This documentation consists of a GSK shipping manifest and an environmental condition data logger and instruction sheet.

The investigative site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All study drugs will be accounted for using a drug accountability form/record.

The inventory must be available for inspection by the study monitor during the study. Monitoring of treatments accountability will be performed by the field monitor during site visits and at the completion of the study.

5.7.1 Destruction of Investigational Product Supplies

At the termination of the study, all investigational study treatments shipped for this clinical trial will be sent by the site to a third-party vendor which will provide a record or certificate of destruction. At the conclusion of the study, the Principal Investigator or an appropriate designee, and a representative of GSK CH will inventory all used and unused investigational study treatment.

5.8 Concomitant Treatment(s)

Subjects will abstain from all concomitant treatments, except for those used for the treatment of AEs.

All concomitant treatments taken during the study must be recorded with indication, unit dose, daily dose, and start and stop dates of administration. All subjects will be questioned about concomitant treatment at each clinic visit.

Treatments taken within 30 days before the first dose of study investigational product will be documented as a prior treatment. Treatments taken after the first dose of study investigational product will be documented as concomitant treatments.

5.9 Rescue Medication

Not applicable to this study.

6 STUDY PROCEDURES

6.1 Screening

Subjects will be screened within 21 days prior to administration of the investigational product to confirm that they meet the subject selection criteria for the study.

The following procedures will be completed:

- Obtain written informed consent and record in the CRF.
- Review Inclusion and Exclusion criteria and record in the CRF.
- Collect demography, including year of birth and record in the CRF.
- Collect height and weight. The results for each measurement will be recorded in the CRF.
- Obtain medical history as related to the inclusion/exclusion criteria, including any relevant medical or surgical history, allergies or drug sensitivity, history of illegal drug, tobacco and alcohol use. Significant findings that are present from Informed Consent must be included in the CRF.
- Obtain complete medication history of all prescription or nonprescription drugs, and dietary and herbal supplements taken within 30 days prior to the planned first dose, and record in the CRF.
- Obtain supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and oral body temperature. The results for each measurement will be recorded in the CRF.
- Conduct full physical examination. Any clinically relevant findings will be noted in the medical history CRF page and enrollment will be based upon investigator judgement.
- Collect single 12-lead electrocardiogram (ECG). Results and any clinically significant abnormalities found will be recorded on the CRF.

- Following at least a 4-hour fast, collect blood and urine specimens for the following, and record in the CRF:
  - Collect urine for drug screening test. Result will be recorded in the CRF.
  - Collect urine for cotinine test. Result will be recorded in the CRF.
  - Perform alcohol breath test. Result will be recorded in the CRF
  - Laboratory test (hematology, clinical chemistry, urinalysis, virology (HIV antibodies, HBsAg, anti-HBc (Total), anti-HCV)).
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?" Any finding will be recorded on CRF

To prepare for study participation, subjects will be instructed on the use of the Lifestyle Guidelines and Concomitant Treatment(s) sections of the protocol.

6.2 Study Period 1

For the study visits described below, when multiple procedures are scheduled at the same time point(s) relative to dosing, the following chronology of events should be adhered to, where possible.

6.2.1 Visit 2: Day -1

Subjects will be admitted to the clinical site at approximately 7 pm prior to Day 1. The following procedures will be completed following admission to the clinical site:

- Review Inclusion and Exclusion criteria and record in the CRF.
- Collect weight. The results for each measurement will be recorded in the CRF.
- Obtain supine blood pressure (BP), pulse rate (PR), respiratory rate (RR) and oral body temperature. The results for each measurement will be recorded in the CRF.
- Conduct full physical examination by trained medical personnel at the investigator site. Any clinically relevant findings will be noted in the CRF, in the AE section.
- Collect urine for drug screening test. Results will be recorded on the CRF.
- Collect urine for cotinine test. Result will be recorded on the CRF.
- Perform alcohol breath test. Result will be recorded on the CRF
- Review changes in the subject's medical history including medication history since Screening.. If the medical history condition worsens, the event will be recorded in the CRF, in the AE section.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?" Any finding will be recorded in CRF
- Collect concomitant medications and record in the CRF.
- Provide standardized dinner at around 9 pm.

Subjects will begin fasting at least 10 hours prior to dosing on Day 1.

6.2.2 Visit 2: Day 1

Prior to randomization, the following procedures will be completed:

- Conduct brief physical examination by trained medical personnel at the investigator site. Any clinically relevant findings will be noted in the CRF, in the AE section.
- Collect supine blood pressure and pulse rate. The results for each measurement will be recorded in the CRF.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?" Any finding will be recorded in the CRF
- Randomization
- Administer the investigational product (see Study Treatments and Administration Sections).

After dosing, the following procedures will be completed:

- Collect images: A total of 30 image acquisitions will be recorded as follows: Anterior supine images will be recorded as 60 second frame acquisitions and recorded at 0-15 minutes (continuous imaging), 20, 25, 30, 35, 40, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 7, 8, 9 and 10 hrs. A window of ± 2 minutes will be allowed for each imaging period up to 1 hour (inclusive) and ± 3 minutes after 1 hour. The time when each imaging acquisition sequence starts will be recorded in source documents as well as the total number of images that have been acquired. Additional images may be acquired at the discretion of the investigator.
- Record changes in concomitant medication in the CRF.
- Assess symptoms by spontaneous reporting of AEs and by asking the subjects to respond to a non-leading question such as "How do you feel?" Any finding will be recorded in the CRF.
- Provide standardized lunch meal 4 hours post dose.
- After the last scintigraphic image is performed (~10 hours post dose), collect vital signs (BP and PR), blood and urine for laboratory tests and record on the CRF. Conduct brief physical examination by trained medical personnel at the investigator site. Any clinically relevant findings will be noted in the AE CRF page.
- Provide standardized dinner meal after laboratory tests are performed.
- Discharge the subject after all study procedures and fill in study completion page of CRF.

If a subject has any clinically significant, study-related abnormalities at the conclusion of a scheduled inpatient portion of the study, the GSK CH medical monitor (or designated representative) should be notified and depending on the abnormality, the subject may be asked to remain at the clinical site until such abnormalities are deemed not clinically significant, or it is safe for outpatient follow-up. If the subject is unable or unwilling to remain at the clinical

site and/or when outpatient follow-up is deemed appropriate, the GSK CH medical monitor (or designated representative) should be so notified, and the investigator should make every effort to arrange follow-up evaluations at appropriate intervals to document the course of the abnormalities.

6.3 Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or, behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

The following circumstances require discontinuation of study treatment and/or premature subject withdrawal:

- Protocol violation that may impact the outcome of the subject's safety
- Withdrawal of informed consent
- Vomiting shortly (within 60 minutes) after study drug administration
- Subject lost to follow-up
- Death

If a subject is discontinued or prematurely withdraws from the study, reasons for discontinuation or withdrawal and associated date must be documented in the relevant section(s) of the CRF.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. The Investigator or site staff should attempt to contact the subject twice. After two attempts, clinical site staff must send a registered letter. If no response is received from the subject, the subject will be considered lost to follow up. All attempts to contact the subject and information received during contact attempts must be documented in the CRF. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return for a final visit, if applicable, and follow-up with the subject regarding any unresolved AEs).

Lack of completion of all or any of the early termination procedures will not be viewed as protocol deviations so long as the subject's safety was preserved.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7 ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventative actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

7.1 Efficacy

Not applicable as there are no efficacy assessments.

7.2 Safety

The following safety assessments will be performed at times defined in the Study Procedures section of this protocol.

7.2.1 Laboratory Tests

Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory; or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical labs may be obtained at any time during the study to assess any perceived safety concerns.

Blood and urine Human Biological Samples (HBS) will be collected for safety laboratory tests. The volume of individual blood samples collected will be up to 8.5 mL and the volume of individual urine samples collected will be up to 50 mL. All samples will be assigned unique tracking identifiers.

Samples (blood and urine) will be processed, labelled and couriered to the analytical laboratory the same day as collection. If a sample is collected and processed on a day when it cannot be couriered to the analytical laboratory, the sample will be processed and stored at conditions stated in the analytical laboratory sample manual. Samples will be sent to and tested at Quest Diagnostics (1355 Mittel Blvd., Wood Dale, IL 60191, USA). Blood samples will be destroyed within 7 days of testing.

An aliquot of the urine sample will be taken for drug and cotinine testing at Scintipharma, Inc. (1721 Maywick View Lane, Lexington, KY 40504, USA). Such aliquots will be disposed of in the sanitary sewer system within 7 days of testing. Empty urine containers and used test devices will be placed in medical waste and destroyed within 3 months of testing.

All samples will be tracked from collection to destruction on a HBS Tracking Log.

Table 7-1 Laboratory Tests

Hematology	Chemistry	Urinalysis	Virology	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC MPV Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN/urea and Creatinine Glucose (fasting) Calcium Magnesium Sodium Potassium Chloride Total CO2(Bicarbonate) AST, ALT Direct Bilirubin Total Bilirubin Alkaline phosphatase Uric acid Albumin Total protein GGT PT/INR	pH Glucose (qual) Protein (qual) Blood (qual) Ketones Nitrites Leukocyte esterase Urine Bilirubin Specific gravity Microscopy[a]	HIV-Ab HCV-Ab HBsAg and HBc-Ab (Total)	Urine drug screen[b] Breath alcohol Urine cotinine

Definitions: RBC= Red blood cell; MCV= Mean corpuscular volume; MCH= Mean corpusuclar hemoglobin; MCHC= Mean copusuclar hemoglobin concentration; MPV= Mean platelet volume; WBC= White blood cells; BUN=Blood urea nitrogen; HIV-Ab=Human Immunodeficiency Virus, HCV-Ab=Antibodies Hepatitis C Virus, HBsAg=Surface antigen of Hepatitis B; b

AST= transaminase; ALT= alanine transaminase; PT/INR= prothrombin time/ international normalized ratio; GGT= Gamma-glutamyl transpeptidase.

[a] Only if urine dipstick is positive for blood, protein, nitrites or leukocyte esterase.

[b] Minimum requirement for drug testing includes: cocaine, THC, opiates/opiods, benzodiazepines and amphetamines; to be done at visit 1 and visit 2 (day-1)

7.2.2 Physical Examinations

Physical examinations may be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation. A full physical examination will include head, ears, eyes, nose, mouth, skin, and lung examinations, lymph nodes, gastrointestinal, musculoskeletal, cardiovascular and neurological systems.
The brief physical examination will be focused on general appearance, the respiratory and cardiovascular systems, as well as towards subject reported symptoms.

Any untoward findings identified on physical exams will be captured as an adverse event, if those findings meet the definition of an AE.

7.2.3 Height and Weight

Height in centimeters (cm) and body weight in kilograms (kg) to the nearest 0.1 kilogram will be measured.

For measuring weight, a scale with appropriate range and resolution is used and must be placed on a stable, flat surface. Subjects must remove shoes, bulky layers of clothing, and jackets so that only light clothing remains. They must also remove the contents of their pockets and remain still during measurement of weight.

7.2.4 Blood Pressure and Pulse Rate

Additional collection times, or changes to collection times of blood pressure and pulse rate will be permitted, as necessary at the discretion of the investigator, to ensure appropriate collection of safety data.

Supine blood pressure will be measured with the subject's arm supported at the level of the heart and recorded to the nearest mm Hg after approximately 5 minutes of rest. The same arm (preferably the dominant arm) will be used throughout the study.

The same properly sized and calibrated blood pressure cuff will be used to measure blood pressure each time. The use of an automated device for measuring BP and pulse rate is acceptable, although, when done manually, pulse rate will be measured in the brachial/radial artery for at least 30 seconds.

7.2.5 Respiratory Rate

Respiratory rate will be measured after approximately 5 minutes rest in supine position by observing and counting the respirations of the subject for 30 seconds and multiplied by 2. When blood pressure is to be taken at the same time, respiration measurement will be done during the 5 minutes of rest and before blood pressure measurement.

7.2.6 Temperature

Temperature will be measured orally.

No eating, drinking or smoking is allowed for 15 minutes prior to the measurement.

7.2.7 Electrocardiogram

A standard 12 lead ECG will be performed at screening visit (Visit 1). Interpretation of the tracing must be made by a qualified physician or designee and documented on the ECG section of the CRF. Each ECG tracing should be labeled with the study number, subject initials, subject number, date, and kept in the source documents at the study site. Results and clinically significant abnormalities should be reported in the CRF. Clinically significant abnormalities should also be recorded on the AE CRF page at the baseline visit. Clinically significant findings must be discussed with the GSK CPL prior to enrolling the subject in the study.

Subjects should be in a quiet environment and not speak during the resting period or measurement. Generally, ECGs should not be collected within 3 hours after food or beverage consumption.

7.3 Gamma Scintigraphy Measurements and Evaluations

7.3.1 Scintigraphic Acquisition

External gamma scintigraphy has been used extensively as a noninvasive technique for assessing the in vivo performance of drug delivery systems. In this study, gamma scintigraphy will be utilized to monitor gastric emptying and intestinal transit of a single radioactive marker by radiolabeling the drug formulation. The radioactive isotope technetium-99m DTPA (^{99m}Tc, t½ 6 hr, γ = 140 keV) is added to drug formulation before ingestion. All radiolabeled dosage forms will be assayed using a standardized dose calibrator to determine radioactive content. In vitro validation tests will be completed to verify that radiolabeling procedures of the caplet do not alter dosage form pharmaceutical characteristics. The radiolabeling procedure of the caplet will be described in a separate document that will be available before study start, i.e. before FSFV. Since the ^{99m}Tc-DTPA is not absorbed, gastrointestinal transit can be monitored using a gamma camera that captures images at frequent intervals after administration. Scintigraphic imaging will be performed with subjects in the supine position. Except during imaging or while conducting other clinical procedures, subjects will remain in the upright position (seated, standing or walking) until at least four hours post dose. Subjects will undergo a series of consecutive anterior scintigraphic images, each of sixty seconds in duration on Day 1 of each period at 0-15 minutes (continuous) and at 20, 25, 30, 35, 40, 45 min, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, 4.5, 4.75, 5, 5.5, 6, 7, 8, 9 and 10 hrs. A window of ± 2 minutes will be allowed for each imaging period up to 1 hour (inclusive) and ± 3 minutes after 1 hour.

The drug formulation will be radiolabeled with not more than 108 µCi (4 MBq) of ^{99m}Tc-DTPA. Prior to ingesting the radiolabeled formulation, two removable external markers (2-3 microcuries of technetium-99m) will be placed on each subject to facilitate consistent positioning underneath the gamma camera. The first marker will be placed on the right side of the subject's chest (approximately at the fifth intercostal rib) and a second marker will be placed on the hip bone (approximately the left anterior superior ileac spine). The scintigraphy analysis software ScinWin (GammaForge, Louisville, KY) uses these markers to automatically align and register the images to the same relative position. Variations in subject positioning or actual

subject movement are thereby corrected facilitating accurate image analysis. Scintigraphic imaging will begin immediately following ingestion of the radiolabeled drug formulation using a large field of view gamma camera (Siemens BasiCam) equipped with a low energy all-purpose parallel hole collimator. The multi-channel analyzer will be set to 10-15% window and tuned to the 140 keV photopeak of ^{99m}Tc.

Scintigraphic data will be recorded and stored electronically using ScinCam image acquisition software (GammaForge, Louisville, KY).

7.3.2 Gamma Scintigraphy Data Analysis

Scintigraphic images will be analyzed in a time-lapse format. Regions of interest (ROI) will be drawn to include the stomach, proximal small intestine, distal small intestine and colon (SCINWIN, GammaForge, Louisville, KY). Each image will be corrected for radioactive decay and background radiation. The primary analysis will evaluate the gastric emptying time and first gastric emptying (or time to reach duodenum) and complete gastric emptying time. Parameters such as the following will be determined as necessary: time for half of the tracer to leave the stomach (T50% gastric emptying, $GET_{50\%}$), small intestine transit time ($SITT50_{\%}$), and time for half of the tracer to arrive at the colon (T50% colon arrival, $ATC_{50\%}$).

7.3.3 Radioactivity Exposure

Each subject will receive a single dose of Treatment A or Treatment B containing the radioactive marker Tc-99m-DTPA. The maximum amount of radioactivity to be administered to each subject per dose (Treatment A or B) is 108 µCi (4.00 MBq) of ^{99m}Tc-DTPA on a single occasion. Treatment A will consist of a single dose of up to 108 µCi (4.00 MBq) of ^{99m}Tc-DTPA and Treatment B will consist of two caplets containing up to 54 µCi (2.00 MBq) of ^{99m}Tc-DTPA each for a total of up to 108 µCi (4.00 MBq) of ^{99m}Tc-DTPA.

The radiation dose from the administration of a 108 µCi total dose of ^{99m}Tc DTPA into the GI tract has been calculated (See Appendix 13.1). A total effective dose of up to 0.100 mSv (0.0100 rems) will be administered. The additional risk of developing a fatal malignancy as a result of this exposure has been estimated as approximately 1 in 200,000 for an adult in normal health. (ICRP 2007).

The National Council on Radiation Protection and Measurements (NCRP) indicates that the effective dose from natural background radiation which everyone receives per year (excluding radon) is about 1 mSv (0.1 rems). The average annual effective dose from radon alone is estimated as 2 mSv (0.2 rems) per year. The NCRP indicates that larger exposures to more limited groups of persons are not especially hazardous, provided they do not occur often to the same groups. The NCRP has recommended that the maximum permissible annual effective dose be 5 mSv (0.5 rems) for individuals with infrequent exposure to radioactivity (NCRP 1993). For workers who are occupationally exposed to radioactivity, the NCRP recommends that the effective dose in any 1 year should not exceed 50 mSv (5 rems), which is approximately 500 times greater than the effective dose that each subject will receive in the present study.

The primary target organ (upper colon wall) will receive a maximum dose of 0.458 mSv (0.0458 rems) for the *entire study*, which is approximately 100 times lower than the recommended maximum amount of radiation exposure to a target organ achieved after a *single dose* (50 mSv or 5 rems) of a radiopharmaceutical, and lower than the annual recommended amount of radiation exposure to a target organ (150 mSv or 15 rems), as specified in 21 CFR 361.1.

To avoid recruitment of radiation workers or serial study volunteers, subjects who have been exposed to ionizing radiation exceeding an effective dose of 10 mSv (1 rem) above background over the previous 3 year period as a result of occupational exposure or previous participation in research studies, not including clinically justified (therapeutic or diagnostic) exposures, will be excluded.

7.4 Blood Volume

The total blood sampling volume for each subject in this study is approximately 54 .5 mL. The table below reflects approximate sample volumes needed for each measured endpoint. The actual collection times of blood sampling may change, but the total blood volume collected will not increase. Additional blood samples may be taken for safety assessments at the discretion of the investigator or GSK CH.

Table 7-2 Blood Volume

Sample Type	Sample Volume (mL)		Total Volume (mL)
	Screening	Study Period	
Safety Labs	33.5	21	54.5

This total volume does not include discarded blood from pre-draws used to remove fluid from flushed catheters, if applicable.

8 ADVERSE EVENT AND OTHER EVENTS OF SPECIAL INTEREST REPORTING

8.1 Definitions of Adverse Events and Serious Adverse Events

8.1.1 Adverse Event

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of an investigational or washout product or medical device, whether or not considered related to the investigational or washout product or medical device.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT meeting the AE definition:

- Any clinically significant abnormal laboratory findings (if applicable) or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.
- Medical or surgical procedure (e.g., endoscopy, appendectomy) is not the AE. The condition that leads to the procedure is an AE (e.g., appendicitis).
- Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.1.2 Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is any untoward medical occurrence at any dose that:

- **Results in death**
- **Is life-threatening**
  - The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe;

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred, or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- **Results in persistent or significant disability/incapacity**
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption
- **Results in congenital anomaly/birth defect**
- **Other situations**
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

8.2 Reporting Period

8.2.1 Adverse Event

AEs (serious and nonserious) will be collected from the signing the informed consent and until 5 days following last administration of the investigational product. For studies that have a run-in period or washout period, adverse events will be collected from the time the run-in or washout period begins.

Medical occurrences that start after obtaining informed consent will be recorded on the AE section of the case report form (CRF)

8.2.2 Serious Adverse Event

SAEs assessed as **related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or related to a GSK concomitant medication will be recorded from the time a subject provides informed consent, which is obtained prior to the subject's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product and until 5 days following last administration of the investigational product.

SAEs assessed as **not related** to study participation (e.g., investigational product, protocol mandated procedures, invasive tests, or change in existing therapy) or not related to a GSK concomitant medication will be recorded from the signing of informed consent and until 5 days following last administration of the investigational product.

8.3 Reporting Procedures

The investigator and any designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE and remain responsible for following up on AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study.

The investigator is to report all directly observed AEs and all AEs reported by the study subject. In addition, each study subject will be questioned about AEs.

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.

The investigator or site staff will then record all relevant information regarding an AE/SAE in the CRF.

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.

There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission to GSK.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms. Clinical AEs will be described by diagnosis and not by symptoms when possible (e.g., upper respiratory tract infection, seasonal allergy, etc. instead of runny nose).

Medical conditions reported prior to the time period for reporting AEs/SAEs should be recorded as part of the subject's medical history.

AEs elicited by the investigator in a standard manner at the study visits should also be recorded in the AE section of the CRF. Care will be taken not to introduce bias when detecting AE and/or SAE. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrence.

8.3.1 Adverse Event

All AEs will be reported on the AE page(s) of the CRF by the investigator or site staff. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AE should be reported using concise medical terminology on the CRF as well as on the form for collection of SAE information.

8.3.2 Serious Adverse Event

A paper copy of the SAE form provided in the investigator study master file should be completed as fully as possible.

It is essential to enter the following information:

- Protocol and subject identifiers
- Subject's demography
- Description of events, with diagnosis if available
- Investigator opinion of relationship to study product
- Criterion for seriousness.

The following are desirable and are of particular relevance for investigator and GSK CH assessment of the SAE report:

- Date of onset of AE
- Date AE stopped, if relevant
- Study product start date
- Study product end date if relevant
- Action taken on study product
- Outcome if known

The SAE form, completed as fully as possible, must be e-mailed to the GSK CH Clinical Operations Safety Reporting email box with the study number and subject number in the subject line of the email **immediately and under no circumstance should this exceed 24 hours** after study site personnel learn of the event. The investigator will submit any updated SAE data to the sponsor, **immediately and under no circumstance should this exceed** 24 hours of it being available. The GSK CH Study Manager should also be notified of the situation by telephone or email.

Email Serious Adverse Events to:

PPD

The GSK CH Study Manager or designee will be responsible for forwarding the SAE form to the Case Management Group, Global Clinical Safety and Pharmacovigilance mailbox (PPD).

The initial report will be followed up with more information as relevant, or as requested by the GSK CH study manager.

8.3.3 Sponsor's Reporting Requirements to Regulatory Authorities and Ethics Committees

GSK has a legal responsibility to notify, as appropriate, the local regulatory authority and other regulatory authorities about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to GSK is essential so that legal obligations and ethical responsibilities towards the safety of subjects are met.

GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/EC and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE or other specific safety information e.g., summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.4 Evaluating Adverse Events and Serious Adverse Events

8.4.1 Severity Assessment

The investigator or designee will make an assessment of severity for each AE and SAE reported during the study and will assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities.

Note: An AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.4.2 Causality Assessment

The causality assessment is one of the criteria used when determining regulatory reporting requirements. For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. Generally, the facts (evidence) or arguments to suggest a causal relationship should be provided.

The investigator will use clinical judgment to determine the relationship and will also consult the Investigator Brochure (IB), Safety Statement and/or Product Information, for marketed products, in the determination of his/her assessment. Alternative causes, such as underlying disease(s), concomitant therapy, other risk factors, and the temporal relationship of the event to the study product will be considered and investigated.

There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. **However, it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.** The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.

8.5 Withdrawal Due to an Adverse Event and Serious Adverse Events

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.6 Pregnancy

8.6.1 Time period for collecting pregnancy information

Pregnancy information on female partners of a male subject will attempt to be collected on all pregnancies reported 3 months following administration of any investigational product to the male subject. Information on pregnancy identified during the screening phase and prior to investigational product administration does not need to be collected.

8.6.2 Action to be taken if pregnancy occurs

The investigator will attempt to collect pregnancy information on any female partner of a male subject, who becomes pregnant while participating in the study after administration of the investigational product and for up to 3 months after the last dose of the investigational product. The investigator will record pregnancy information on the appropriate form provided by GSK CH and submit it to GSK within 2 weeks of learning of the female partner of the male subject becoming pregnant. The female partner of a male subject will be followed to determine the outcome of the pregnancy. Information on the status of the mother and infant / neonate (including concomitant medications taken by the mother during the pregnancy) will be forwarded to GSK. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported.
While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination for medical reasons will be recorded as an AE or SAE as defined in Section 8.1.

A spontaneous abortion is always considered to be an SAE and will be reported as such. An SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject completed the study and considered by the investigator as possibly related to the investigational product, must be promptly forwarded to GSK. While the investigator is not obliged to actively seek this information in former study participants, he or she may learn of an SAE through reporting.

8.7 Follow-up of Adverse Events and Serious Adverse Events

After the initial report, the investigator is required to proactively follow up with each subject and provide further information on the subject's condition.

All AEs/SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up.

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed CRF.

The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

Investigators are not obliged to actively seek AEs or SAEs in former subjects. However, if the investigator learns of any SAE, including the death, at any time after a subject has been discharged from the study, and considers the event reasonably related to the investigational product or study participation, the investigator will promptly notify GSK by emailing the information to the GSK CH Clinical Operations Safety Reporting email box (PPD). The GSK CH Study Manager or designee will be responsible for

forwarding the information to the Case Management Group, Global Clinical Safety and Pharmacovigilance group mailbox at GSK (PPD).

The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

9 DATA MANAGEMENT

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

For this study, subject data will be entered into an electronic CRF, using a validated data system.

9.1 Source Documents/ Data

The source documents (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratory and at the medico-technical departments involved in the clinical study) which contain the source of data recorded in the CRF should be specified in Section 6. The CRF can be used as a source document at the discretion of data management.

Each subject will be assigned and identified by a unique Number. Any reference made to an individual subject within the study must be done using the unique Screening Number.

9.2 Case Report Form

A CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

For each subject who has given informed consent/assent and has been screened, CRF must be completed and signed by the Principal Investigator (or authorized designee) to certify that the data are complete and correct.

Management of clinical data will be performed in accordance with applicable Vendor and GSK CH standards, and data cleaning procedures to ensure the integrity of the data e.g. removing errors and inconsistencies in the data.

In order to protect the privacy of subjects, no Personally Identifiable Information (PII) (including the subject's name or initials or full birth date) is to be recorded in the CRF or as part of the query text.

All CRF pages should be completed during a subject assessment when the CRF has been designated as the source. Data that is sourced elsewhere should be entered into the CRF in an agreed upon timeframe between the Investigator and Sponsor.

GSK CH will obtain and retain all CRFs and associated study data at the completion of the study.

9.3 Data Handling

Documentation of all data management activities should allow step-by-step retrospective assessment of data quality and study performance.
Any changes or corrections to data will be performed in the Electronic Data Capture (EDC) System, and it will include rationale for changes. The EDC system has an audit trail, which will provide a complete record of the changes and corrections endorsed by the Investigator.

AEs will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and concomitant medications terms (if applicable) using an internal validated medication dictionary, GSK Drug.

9.3.1 Queries

Programmed edit checks will be generated automatically, as the data is being entered into the system. Data Management will also run reports and listings on the CRF data, in addition to the queries already programmed and generated by the system, to raise manual queries as needed for site clarification or correction. The Clinical Dictionary Development and Management Group will raise queries as needed on safety data to code the terms (AEs and Drugs) appropriately.

The study monitor at the study site will review the CRFs in accordance with the monitoring plan, and any queries will be generated in the EDC System to the Investigator or designee, enabling the errors to be addressed in parallel with Data Management review. The study monitor can also run reports and listings on the CRFs, to raise manual queries as needed for site clarification or correction.

9.4 External Data

External Data are subject data obtained externally to the CRF. These data are generated from laboratory instruments, computers or other sources and then transcribed into a file and format agreed upon by GSK CH to identify the subject and time point referenced in the CRF and/or protocol.

An agreed upon quality control process is performed against the transcribed data to the source to ensure the accuracy of the transcription. The transcribed data is transmitted in an agreed upon format to GSK CH.

Reconciliation will be performed between the transcribed data and the clinical database to ensure subject and time point referenced in the Clinical Database match before Clinical Database Freeze (locking of the database) can occur.

10 STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1 Sample Size Determination

Since this study does not have any statistical power, formal sample size calculation has not been performed. It is planned to screen approximately 42 subjects to allow a total of 28 subject to be randomized to have at least 24 subjects evaluable (12 subject per arm). This is a sufficient number to provide descriptive statistics.

10.2 Statistical Methods and Analytical Plan

Additional details of the proposed statistical analysis will be documented in the statistical analysis plan (SAP), which will be written following finalization of the protocol and prior to study analysis (as appropriate).

10.2.1 Demographic and Baseline Characteristics

Baseline data (i.e. the last available value prior to the start of the treatment phase), relevant screening data and demographic characteristics will be summarized for the safety population.

10.2.2 Scintigraphy Analysis

The scintigraphy variables are:

- time to onset of gastric emptying for treatment arm A and B.
- time to completion of gastric emptying for treatment arm A and B.
- GE25%, GE50%, GE90% values for each treatment A and B,
- the amount remaining in the stomach at 15, 30, 45, 60, 75, 90, 105, 120, 180, 240 min for each Treatment arm A and B
- sectional areas under the gastric emptying curve and total AUC; and gastric emptying $t_{1/2}$ values.
- small intestinal transit times for each treatment arm A and B.

The scintigraphy variables of scintigraphic analysis will be summarized by treatment arm using descriptive statistics (mean, minimum, median, maximum and standard deviation, CVs and 95% CI for the Means). There are no formal hypotheses being tested in this study.

10.2.2.1 Criteria for assessing Scintigraphy

Use the scintigraphic images to measure the gastric emptying time to onset and completion as for treatment arms A and B.

10.2.3 Safety Analysis

Safety variables will be summarized for the safety population.

Adverse Event:

Treatment Emergent AEs, i.e. AEs that are emergent or that worsen after the administration of treatment arm A or B, will be summarized by presenting, for each treatment, the number and percentage of subjects having any AE, any AE in each MedDRA System Organ Class (SOC) and having each individual AE. The subset of AEs suspected of a relationship to study drug will be presented similarly. All treatment-emergent AEs will also be tabulated by severity. Any other information collected (e.g. action taken, duration, outcome) will be listed. Each AE will be attributed to the treatment taken most recently before the onset of the AE.

Physical examination

Physical Examination data will be listed with abnormal values flagged.

Laboratory tests:

Laboratory data will be listed with abnormal values flagged.

10.2.3.1 Criteria for assessing safety

Laboratory tests and monitoring of AEs as well as brief physical examination outcomes will be used to assess the safety and tolerability of the study products

10.2.4 Definition of Analysis Populations

Scintigraphy analysis population will be conducted on all subjects who received the radiolabeled treatments arm A or B and who did not vomit shortly (within 60 minutes) after study drug administration, who have sufficient data to determine time to onset and completion of gastric emptying and who had no major protocol deviations.

The Safety population will include all subjects who receive a radiolabeled hot drink independently if they are included or not in the scintigraphy analysis.

10.2.5 Exclusion of Data from Analysis

Exclusion of any data from the analyses will be determined during a Data Review Meeting prior to database lock. Any reasons for exclusion from an analysis population will be listed, if applicable.

10.2.6 Handling of Dropouts and Missing Data

Subjects who drop out will not be replaced, i.e. their randomization number will not be re-used.

10.2.7 Interim Analysis

No interim analysis is planned for this study

11 STUDY GOVERNANCE CONSIDERATIONS

11.1 Quality Control

In accordance with applicable regulations including GCP, and GSK procedures, GSK or designee (i.e. third party vendor) monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.

When reviewing data collection procedures, the discussion will include identification, agreement and documentation of data items for which the CRF will serve as the source document.

GSK or designee will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The extent and nature of monitoring will be described in a written monitoring plan on file at GSK CH. The investigator (or designee) agrees to allow the monitor direct access to all relevant documents and agrees to co-operate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.2 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.

In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

The investigator(s) will notify GSK CH or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with GSK CH or its agents to prepare the study site for the inspection and will allow GSK CH or its agent, whenever feasible, to be present during the inspection. The investigator will promptly apply copies of the inspection finding to GSK CH or its agent. Before response submission to the

regulatory authority, the investigator will provide GSK CH or its agents with an opportunity to review and comment on responses to any such findings.

The sponsor will be available to help investigators prepare for an inspection.

11.3 Regulatory and Ethical Considerations

11.3.1 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, investigator brochure/safety statement (including any updates) and other relevant documents, e.g., recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to GSK CH prior to the initiation of the study, and also when subsequent amendments to the protocol are made.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and GSK CH in writing immediately after the implementation.

11.3.2 Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), guidelines for GCP (ICH 1996 and revision 2), and the Declaration of Helsinki (World Medical Association 2013).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

11.3.3 Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by laws.

When study data are compiled for transfer to GSK CH and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by GSK CH in order to de-identify study subjects. The use of initials should be avoided.

The study site will maintain a confidential list of subjects who participated in the study, linking each subject's numerical code to his or her actual identity. In case of data transfer, GSK CH will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed and approved by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed informed consent document.

11.3.4 Subject Recruitment

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures. Use of ethics committee approved, generic, prescreening questionnaire to assess basic subject characteristics to determine general eligibility for this study is allowed. This generic questionnaire may be used by sites as a phone script and/or to review internal databases to identify subjects.

GSK CH will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

11.3.5 Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

Within a GSK CH a serious breach is defined as a breach likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in GSK CH- sponsored human subject research studies.

In the event of any prohibition or restriction imposed (i.e., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, GSK CH should be informed immediately.

In addition, the investigator will inform GSK CH immediately of any urgent safety measures taken by the investigator to protect the study subjects against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

11.4 Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins in accordance with applicable GSK processes.

11.5 Provision of Study Results to Investigators

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

11.6 Records Retention

Following closure of the study, the investigator must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

The records (study/ site master file) must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.

Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.

The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The investigator must assure that the subject's anonymity will be maintained. On CRFs or other documents submitted to GSK CH, subjects should not be identified by their names or initials, but by an identification code. The investigator should keep a separate log of subjects' codes, names and addresses. Documents not for submission to GSK CH, e.g. subjects' written consent forms, should be maintained by the investigator in strict confidence.

Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary unless local regulations or institutional policies require a longer retention period. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.

No study document should be destroyed without a prior written agreement between GSK CH and the investigator. The investigator must notify GSK of any changes in the archival

arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

11.7 Conditions for Terminating the Study

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of GSK CH.

If a study is prematurely terminated, GSK CH will promptly notify the investigator. After notification, the investigator must promptly contact all participating subjects and should assure appropriate therapy/ follow-up for the subjects. As directed by GSK CH, all study materials must be collected and all CRFs completed to the greatest extent possible. Where required by the applicable regulatory requirements, GSK CH should inform the regulatory authority(ies) and the investigator should promptly inform the IRB/EC and provide the IRB/EC a detailed written explanation of the termination or suspension.

If the IRB/EC terminates or suspends its approval/favorable opinion of a trial, the investigator should promptly notify the GSK CH and provide GSK CH with a detailed written explanation of the termination or suspension. Upon completion or premature discontinuation of the study, the GSK CH monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK CH Standard Operating Procedures

11.8 Definition of Study End/ End of Study

Study End (SE) date is defined as the date of the last subject visit of the last subject to complete the study (LSLV).

12 REFERENCES

[Gwaltney Jr JM, Phillips CD, Miller RD et al, (1994)] Computed tomographic study of the common cold. N Engl J Med.330(1):25–30.

[Hodges LA & Hughes A & Targett D & Durcan M (2014)] Does a Hot Drink Provide Faster Absorption of Paracetamol Than a Tablet? A Pharmacoscintigraphic Study in Healthy Male Volunteers. Pharm Res (2014) 31:2078–2085.

[Hengstmann JH, Goronzy J (1982)] Pharmacokinetics of H-3 Phenylephrine in Man. European Journal of Clinical Pharmacology; 21 (4):335-341.

[Prescott L. Paracetamol (acetaminophen): a critical bibliographic review]. London: Taylor & Francis; 1996.

CCI

[Prescott LF, Yoovathaworn K, Makarananda K et al, (1993)]. Impaired absorption of paracetamol in vegetarians. *Br J Clin Pharmacol* 1993; 36:237-240.

[Wald A, Thiel DHV, Hoechstetter et al, (1981)]. Gastrointestinal transit: the effect of

the menstrual cycle. Gastroenterology 1981; 80:1497-1500.

[National Council on Radiation Protection and Measurements (NCRP) (1993)]. Limitations of Exposure to Ionizing Radiation. NCRP Report No 116, Bethesda, MD; 1993]. NCRP Publications ISBN#0-929600-30-4.

[ICRP 103 (2007)] vol. 37, 2-4, 2007

[INTEGRATED ADDENDUM TO ICH E6(R1): GUIDELINE FOR GOOD CLINICAL PRACTICE E6(R2)]

13 APPENDIX

13.1 RADIATION DOSIMETRY

Maximum estimated radiation dose to various organs from the oral administration of the following:

CCI

13.2 RADIOLABELING PROCEDURE

The preparation of the radiolabeled doses will be documented in a detailed dose preparation record that is prepared by the study site and offered to the sponsor for review. Example step wise procedures are summarized in the following.

Treatment A: Theraflu Solution (will be prepared on visit 2 day 1, maximum 3 hours before administration)

- Pour the drug powder contents from an individual sachet into a single glass bottle (with cap). Confirm transfer of material by weight.
- Heat distilled drinking water to approximately 90-95°C and add 225 mL of the heated water to the bottle containing the drug powder (confirm the addition of the 225 mL of water by weight). Screw the cap onto the bottle and mix to dissolve the contents of the sachet.
- Allow the dissolved Theraflu solution to cool to approximately 40-50°C.
- After cooling, a small volume (1 to 10 microliters) of ^{99m}Tc-DTPA is added to the individual bottles containing the drug solution to achieve a maximum of 108 µCi (4 MBq) per individual dose at the time of dosing.
- The container is capped, labeled for individual subject use and stored at a temperature between 35-45°C until administration.

Treatment B: Theraflu ExpressMax Daytime Severe Cold and Cough Caplet (will be prepared up to 18 hours before administration)

- Individual caplets are radiolabeled by adding Tc-99m DTPA into approximately the center portion of the caplet.
- The caplet is oblong, approximately 17.8 mm long, 7.4 mm wide, and 6.0 mm thick. The caplet weight is approximately 630 mg. One side the caplet is inscribed with "1143D*"* and the opposite side is blank and has no inscription.
- The original caplet weight is determined. On the blank side inscribed, a hole, approximately 1 mm diameter is drilled to a depth of approximately one-half of the caplet's thickness (~2-2.5 mm deep). After drilling, the caplet is re-weighed.
- Tc-99m DTPA (dissolved in saline) is carefully pipetted into the hole as a low volume liquid (approximately 0.5 – 2 microliters) such that the maximum radioactive level does not exceed 54 µCi (2 MBq) per individual caplet at the time of dosing. The applied liquid is allowed to air dry at room temperature.
- The hole is filled with the equivalent powder blend from a crushed caplet. The caplet weight is again recorded.

- The surface area of the filled region of the caplet may be sealed with an appropriate material if determined to be necessary.
- Radiolabeled caplets are packaged as unit doses (2 caplets per container), labeled for individual subject use and stored at room temperature until administration.

The preparation of the radiolabeled doses will be documented in a detailed dose preparation record that is prepared by the study site and offered to the sponsor for review.

13.3 ABBREVIATION

The following is a list of abbreviations that may be used in the protocol.

Table 13-1 Abbreviation

Abbreviation	Term
AE	adverse event
ALT	alanine transaminase
ALP	alkaline phosphatase
AST	aspartate transaminase
AUC	area under the curve
BMI	body mass index
BP	blood pressure
BPM	beats per minute
BUN	blood urea nitrogen
cGMP	Current good manufacturing practice
CRF	case report form
CV	Coefficient of variation
DCT	data collection tool
^{99m}Tc-DTPA	Technetium-99m-diethylene-triamine-pentaacetate
EC	ethics committee
ECG	electrocardiogram
EDC	Electronic data capture
EDTA	edetic acid (ethylenediaminetetraacetic acid)
FDA	Food and Drug Administration (United States)
FSFV	First subject first visit
FSH	follicle-stimulating hormone
GCC	Global Clinical Supplies
GCP	Good Clinical Practice
GE	Gastric emptying
GGT	gamma-glutamyl transpeptidase
GSK CH	GlaxoSmithKline Consumer Health
GSK CPL	GlaxoSmithKline Clinical Pharmacologist

Abbreviation	Term
hCG	human chorionic gonadotropin
HDL-C	high density lipoprotein cholesterol
HIV	human immunodeficiency virus
HIV-Ab	Human Immunodeficiency Virus antibody
HCV-Ab	Antibodies Hepatitis C Virus
HBcAg	Core antigen of Hepatitis B
HBsAg	Surface antigen of Hepatitis B
IB	investigator's brochure
ICH	International Conference on Harmonisation
IHV	InVentiv Health Care
ID	identification
INR	international normalized ratio
IRB	institutional review board
IRC	internal review committee
IUD	intrauterine device
IUS	Intrauterine system
K_2EDTA	dipotassium ethylene diamine tetraacetic acid
LDL-C	low density lipoprotein-cholesterol
LFT	liver function test
LSLV	last subject last visit
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MedDRA	medical Dictionary for Regulatory Activities
mSv	millisievert
N/A	not applicable
NCRP	national council on radiation protection
PI	principal investigator
PR	pulse rate
PT	prothrombin time
QC	quality control
QTc	corrected QT
RBC	red blood cell
rem	roentgen equivalent man
RNA	ribonucleic acid
RR	Respiratory rate
SAE	serious adverse event
SCr	serum creatinine
SGOT	serum glutamic oxaloacetic transaminase

Abbreviation	Term
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
SOP	standard operating procedure
SS	safety statement
$T_{1/2}$	terminal half-life
THC	tetrahydrocannabinol
ULN	upper limit of normal
US	United States
USPI	United States package insert
WBC	white blood cell