Official Title: A Phase 4, Open-Label Study of the Pharmacokinetics and Safety of XARTEMIS® XR (7.5 mg Oxycodone Hydrochloride/325 mg Acetaminophen) in Postsurgical Adolescent Subjects (Ages 12 to 17) with Moderate to Severe Acute Pain

NCT Number: NCT02508935

Document Date: Protocol Version 3: 29-June-2016

CLINICAL STUDY PROTOCOL

A Phase 4, Open-Label Study of the Pharmacokinetics and Safety of XARTEMIS® XR (7.5 mg Oxycodone Hydrochloride/ 325 mg Acetaminophen) in Postsurgical Adolescent Subjects (Ages 12 to 17) with Moderate to Severe Acute Pain

Protocol Number: MNK15000300

Date of Original Protocol: 17 April 2014

Amendment 1 Dated: 21 October 2014

Amendment 2 Dated: 20 April 2015

DRAFT Amendment 3 Dated: 29 June 2016

Sponsor:
Mallinckrodt Inc
Clinical Research and Development
675 McDonnell Boulevard
Hazelwood, MO 63042
United States of America

PROTOCOL AMENDMENT 3 DATED JUNE 2016

SUMMARY OF CHANGES

Protocol Amendment 3 was developed primarily to revise the pharmacokinetic sampling and analysis, population definitions, and proposed number of subjects to be screened. The major protocol changes are summarized below:

1. Reduced the number of pharmacokinetic samples for the single-dose portion of the study. The 30 minute and 1, 3, and 11 hour sampling times were deleted and a 15 minute sample was added.
2. Revised the pharmacokinetic sampling intervals during the multiple dose portion of the study. For the multiple dose portion of the study, sampling was changed to 15 to 30 minutes, 45 to 90 minutes, 2 to 4 hours, and 6 to 8 hours after the fourth dose. In addition, one sample will be collected during the 12 to 18 hour time window after the fourth dose.
3. Study length was decreased to 54 hours to accommodate the shorter sampling time that will encompass only 4 doses of XARTEMIS XR.
4. Changed the number of doses of XARTEMIS XR required to complete the study from 5 doses to 2 or more doses.
5. Revised blood volumes to a total of 50 mL to be collected in the study, including 32 mL for pharmacokinetic samples.
6. Removed $AUC_{0\text{-}inf}$ from the pharmacokinetic parameters to be calculated.
7. Revised pharmacokinetic analyses so that noncompartmental analysis is performed only on plasma OC and APAP concentrations after the first dose.
8. Added Population PK modeling of single- and multiple-dose plasma OC and APAP concentration-time data.
9. Removed the Safety Completer and the PK Completer Populations from the analyses.
10. Redefined the PK Population to include subjects who provided at least 6 blood samples for measurement of acetaminophen and oxycodone.

11. Clarified the definition of the Modified Intent-to-Treat Population to include all subjects receiving at least 1 dose of XARTEMIS XR.
12. Removed Data Management from the list of additional study contacts and added [redacted] as the [redacted] in Section 2.2.
13. Revised the projected number of individuals to be screened from 60 to 72.
14. Clarified the use of the abbreviation for oxycodone (OC).

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PROTOCOL AMENDMENT 2 DATED 20 APRIL 2015

SUMMARY OF CHANGES

Protocol Amendment 2 was developed primarily to address concerns from potential study sites. The major protocol changes are summarized below:

1. The clinical technical lead and biostatistics contact information has been updated.
2. The list of acceptable surgical procedures was deleted from the inclusion criteria and replaced with the statement that the sponsor will pre-approve a list of acceptable surgical procedures prior to study start for each site. Surgical procedures other than those on the pre-approved list may be acceptable on a case by case basis if approved by the Medical Monitor and sponsor.
3. The inclusion criteria were further modified to require subjects to have a body mass index (BMI) > 5% and < 95% for their age, correct the definition of females of child-bearing potential, reduce the time after dosing that birth control is required, and eliminate the lists of required birth control methods.
4. The exclusion criteria were modified to allow subjects with a history of psychotherapy for anxiety, tension, agitation, psychiatric disorders, psychosis, or depression; to allow subjects with a history of attention deficit hyperactivity disorder requiring medication; and to allow subjects with a history of malignancy.

5. The time from subject anxiety, tension, agitation, psychiatric disorders, psychosis, or depression requiring hospitalization and/or medication was changed from within 3 years to within 6 months of screening.
6. Additional exclusion criteria were added to prohibit the enrollment of subjects with any other medical condition, abnormal vital sign (blood pressure, pulse rate, respiratory rate), body temperature, or physical examination or ECG finding which, in the investigator's medical opinion, would preclude safe participation in a clinical study; and to exclude subjects who have participated in any other clinical study within 30 days prior to the screening visit or who plan to participate in another clinical study while concurrently enrolled in this study.
7. The requirement for hepatitis screening has been removed.
8. The option of using unsweetened apple juice in place of water for study drug dosing was added.
9. The restriction of CYP2D6 and/or CYP3A4 inducers after XARTEMIS XR dosing has been removed.
10. The restriction on consumption of food or beverages containing xanthines in the 14 days prior to study start was removed.
11. The restriction of opioid medications for 60 minutes after XARTEMIS XR dosing has been removed.
12. The pharmacokinetic sample size has been reduced to 2 mL each.
13. The use of the provided ibuprofen as the rescue medication has been clarified to be optional.
14. The analysis populations have been updated and expanded and the wording of the statistical section has been updated to reflect these changes.
15. Graphs of BMI by age were added to the Attachments.
16. Additional minor changes to clarify language and to ensure consistency were made.

PROTOCOL AMENDMENT 1 DATED 21 OCTOBER 2014

SUMMARY OF CHANGES

Protocol Amendment 1 was developed primarily to address an FDA request to increase the minimum pain score required for continued treatment with XARTEMIS XR. The major protocol changes are summarized below:

1. The primary medical monitor name and contact information have been added.
2. The requirement for a serum or urine pregnancy test to be conducted for all female subjects at study exit or early termination has been added.
3. Subjects will be restricted from the use of any additional opioid therapy within 30 minutes prior to and 60 minutes after each dose of XARTEMIS XR.
4. The pain score subjects need to advance to the next dose of XARTEMIS XR was increased from ≥ 1 to ≥ 4.
5. The formula for calculating creatinine clearance was changed from the one referenced in the Modification of Diet in Renal Disease to a pediatric appropriate formula such as the Schwartz Equation and the appropriate reference was added.
6. Restrictions on food and water consumption around the time of dosing were removed.
7. References to the updated MNK-795 (XARTEMIS XR) Investigator's Brochure and Package Insert were added.
8. Additional minor changes to clarify language and to ensure consistency were also made.

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1 DISCLOSURE STATEMENT

Restricted Distribution of Documents

This document contains information that is confidential and proprietary to the sponsor. This information is being provided to the investigator solely for the purpose of evaluating and/or conducting a clinical study for the sponsor. The investigator may disclose the contents of this document only to study personnel under his/her supervision, institutional review boards (IRBs), or duly authorized representatives of regulatory agencies for this purpose under the condition that they maintain confidentiality. The contents of this document may not be used in any other clinical study, disclosed to any other person or entity, or published without the prior written permission of the sponsor. The foregoing shall not apply to disclosure required by any regulations; however, the investigator will give prompt notice to the sponsor of any such disclosure. All other nonpublic information provided by the sponsor, as well as any information that may be added to this document, also is confidential and proprietary to the sponsor and must be kept in confidence in the same manner as the contents of this document.

2 CONTACTS

2.1 Emergency Contacts

Role in Study	Name	Contact Information
Primary Contact:		
Medical Monitor	[redacted], MD [redacted] United States of America	Cell Phone: [redacted] E-mail (not for emergencies): [redacted]
Secondary Contact:		
Medical Monitor	[redacted], MD [redacted] to Mallinckrodt Inc 675 McDonnell Boulevard Hazelwood, MO 63042 United States of America	Cell phone: [redacted] E-mail (not for emergencies): [redacted]

Please see next page for additional telephone contact numbers in Section 2.2.

Please see Section 20.4 for detailed information regarding the Serious Adverse Event (SAE) Reporting Requirements for this study.

SAE reporting fax: 314-654-5759

SAE confirmation phone: 800-778-7898 (24-hour call center)

SAE confirmation email: GlobalPV@mallinckrodt.com

2.2 Additional Contacts

Sponsor: Mallinckrodt Inc
675 McDonnell Boulevard
Hazelwood, MO 63042
United States of America

Role in Study	Name	Contact Information
Clinical Trial Manager	[redacted]	[redacted]
Clinical Technical Lead	[redacted], PhD	
Pharmacokineticist	[redacted], PhD	
Biostatistics	[redacted], MS, MPH	

The Clinical Technical Lead is authorized to sign this protocol for the Sponsor.

3 SPONSOR SIGNATURE

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Sponsor Representative Signature	Date of Signature (DD Month YYYY)
Sponsor Representative Name (print)	

4 INVESTIGATOR SIGNATURE

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.

Investigator's Signature	Date of Signature (DD Month YYYY)
Investigator's Name and Title (print)	

5 ABBREVIATIONS

Abbreviation	Term
λ_z	elimination rate constant associated with the terminal (log-linear) portion of the 0 to 12 hour curve after the first dose of XARTEMIS XR
τ	dosing interval
%CV	percentage of coefficient of variation
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
ANDA	Abbreviated New Drug Application
APAP	Acetaminophen
API	active pharmaceutical ingredient
AST	aspartate transaminase
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}12h}$	area under the plasma concentration-time curve over the first 12 hour dosing interval
BMI	body mass index
BUN	blood urea nitrogen
C_{12h}	drug concentration at 12 hours after the first dose of XARTEMIS XR
CFR	Code of Federal Regulations
CI	confidence interval
CNS	central nervous system
C_{max}	observed peak drug concentration
CSR	clinical study report
CV	coefficient of variation
CYP	cytochrome
DFL	degree of fluctuation
DILI	drug induced liver injury
ECG	electrocardiogram
eCRF	electronic case report form
ER	extended release

Abbreviation	Term
GGT	γ-glutamyl transferase
GCP	Good Clinical Practice
GI	Gastrointestinal
GR	Gastroretentive
HbA1c	glycosylated hemoglobin
HDPE	high-density polyethylene
HEENT	head, eyes, ears, nose and throat
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
IR	Immediate release
IRB	Institutional Review Board
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LD	listed drug
MM	medical monitor
N	number of values
NAPQI	N-acetylimidoquinone
NDA	New Drug Application
NPRS	Numerical Pain Rating Scale
OC	oxycodone
PI	package Insert
PK	pharmacokinetic
PREA	Pediatric Research Equity Act
Q12h	every 12 hours
r^2	coefficient of determination
RBC	red blood cell
SAE	serious adverse event
$t_{1/2}$	apparent plasma terminal drug elimination half-life
$t_{1/2}^{x}$	apparent plasma terminal drug elimination half-life calculated as $1n(2)/\lambda_x$
$t_{1/2}^{z}$	apparent plasma terminal drug elimination half-life calculated as $1n(2)/\lambda_z$

Abbreviation	Term
TEAE	treatment-emergent adverse event
t_{lag}	time delay between drug administration at Hour 0 and the onset of absorption
T_{max}	observed time to reach maximum drug concentration
ULN	upper limit of normal
WBC	white blood cell

6 SYNOPSIS

This is a synopsis. The body of the protocol must be referenced for the complete study information.

Study Title: A Phase 4, Open-Label Study of the Pharmacokinetics and Safety of XARTEMIS® XR (7.5 mg Oxycodone Hydrochloride/325 mg Acetaminophen) in Postsurgical Adolescent Subjects (Ages 12 to 17) with Moderate to Severe Acute Pain

Protocol Number	MNK15000300	**Phase**	4	**Type**	Pediatric

Condition/Disease: Moderate to severe acute pain

Number of Subjects	48	**Duration of Subject Participation**	Approximately 4 weeks
Number of Study Centers	Multiple	**Duration of Study**	Approximately 1 year

Rationale: XARTEMIS® XR (MNK-795) is a controlled-release combination of oxycodone (OC) HCl/acetaminophen (APAP) indicated for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate. This study, planned for an adolescent (12 to 17 years of age) population, is the initial XARTEMIS XR clinical investigation being conducted in the pediatric population to satisfy the Pediatric Research Equity Act (PREA). Screening of approximately 72 individuals is planned in order to enroll up to 48 subjects and have at least 25 subjects who receive 2 or more doses of XARTEMIS XR.

Objectives:

Primary:

- To characterize the pharmacokinetic (PK) profile of XARTEMIS XR following single and multiple dose administration in adolescent subjects (12 to 17 years of age) experiencing moderate to severe acute pain.

Secondary:

- To determine the safety and tolerability of XARTEMIS XR in adolescent subjects (12 to 17 years of age).
- To determine the pain intensity differences from baseline over the first dosing period (eg, 1, 2, 4, 8 and 12 hours) following treatment of adolescent subjects (12 to 17 years of age) with XARTEMIS XR.

Design: This is a Phase 4, multicenter, open-label, single- and multiple-dose study of the PK and safety of XARTEMIS XR in postsurgical adolescent subjects aged 12 to 17 years with moderate to severe acute pain. In order to be able to adequately assess the safety of administering multiple doses of XARTEMIS XR in this population, subjects to be enrolled are those likely to require multiple days of treatment for pain (up to 48 hours) during a hospital stay. The subjects will check-in to the study site, undergo a surgical procedure and, if eligible, will receive orally administered XARTEMIS XR (Hour 0) with rich PK sampling through 12 hours after the first dose. If subjects are required to remain at the hospital and also require further treatment for pain, additional doses of XARTEMIS XR will be administered every 12 hours. Following the fourth dose of XARTEMIS XR, subjects will undergo sparse PK sampling through 18 hours postdose. If the subject requires a fifth dose, the last PK sample will be collected at 12 hours after the fourth dose but before receiving any additional pain medication. Subjects will exit the study when a hospital stay is no longer needed or sparse PK sampling following the fourth dose of XARTEMIS XR is complete. Pain intensity will be evaluated using the Numeric Pain Rating Scale (NPRS) at specified time points throughout the study. The subject's parent or legal guardian will be contacted via a follow-up telephone call 7 (± 2) days after the subject has received the last dose of XARTEMIS XR.

Inclusion Criteria:

1. Subject must be male or nonpregnant, nonlactating female, between 12 and 17 years of age (inclusive) at time of screening.

2. Subject must have a minimum weight of 100 pounds (45 kg) and have a body mass index (BMI) > 5% and < 95% for their age (see Attachment 1) at the time of screening.
3. Subject must report having moderate to severe acute pain (as determined from the NPRS where 0 = no pain, 10 = worst pain; subjects must have a level of 4 or more) after a pediatric surgical procedure (at baseline) that requires hospitalization. Sponsor will pre-approve a list of acceptable surgical procedures prior to study start for each site. Surgical procedures other than those on the pre-approved list may be acceptable on a case by case basis if approved by the Medical Monitor (MM) and sponsor.
4. Subject, if female of child-bearing potential (defined as postmenarche), must agree to abstain from unprotected sexual activity during study participation and for 2 weeks after study exit.
5. Subject, if male with reproductive potential, must agree to abstain from unprotected sexual activity during study participation and for 2 weeks after study exit.
6. Subject, if female of childbearing potential, must have negative pregnancy test (serum or urine) results at screening and check-in.
7. Subject's legally authorized representative (eg, parent, legal guardian) must voluntarily sign and date a parental permission/informed consent form (ICF) that is approved by an Institutional Review Board (IRB), and the subject must sign an IRB approved assent, before undergoing any protocol specific procedures or assessments.
8. Subject and the subject's parent or legal guardian must be able to read, understand and be willing to follow the study procedures and requirements and communicate meaningfully in English with the investigator and investigator's staff (if the subject cannot read or communicate meaningfully, then the subject's legally authorized representative [eg, parent, legal guardian] must meet this criterion).

Exclusion Criteria:

1. Subject is from a vulnerable population (including mentally disabled children), other than a pediatric population, as defined by the Code of Federal Regulations Title 45, Part 46, Section 46.111(b), including but not limited to employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB.
2. Subject is expected to require a surgery that could influence the study outcome (eg, ventriculoperitoneal shunt repair in the setting of hydrocephalus).
3. Subject has an abnormal electrocardiogram (ECG) unless the investigator determines the ECG abnormalities are not clinically significant.
4. Subject has a screening pulse oximetry reading of < 95% while awake.
5. Subject has a history of laboratory test results obtained before screening that show the presence of human immunodeficiency virus (HIV), hepatitis B surface antigen, hepatitis C antibody, or active hepatitis A immunoglobulin M.
6. Subject has laboratory values that are greater than 2 times the upper limit of normal (with the exception of white blood cell [WBC] differential values). Enrollment of subjects with laboratory values that are between 1 and 2 times the upper limit of normal (ULN), below the lower limit of normal, or WBC differential > 2 x ULN, will be left to the investigator's discretion (no increased risk of participation in study based upon judgment of the investigator).
7. Subject has any history of renal disease that, in the opinion of the investigator, would contraindicate study participation; or subject has significantly impaired renal function, in the opinion of the investigator, as evidenced by an estimated glomerular filtration rate calculated using a pediatric appropriate formula such as the Schwartz Equation (Schwartz et al 2009).
8. Subject has a history or laboratory evidence of bleeding or clotting disorders or conditions.
9. Subject has a known or suspected history of alcoholism, marijuana or illicit drug abuse or misuse within 2 years before screening as evidenced from medical history or evidence of tolerance or physical

dependence before the first dose of XARTEMIS XR.

10. Subject has smoked or used nicotine-containing products within 6 months prior to screening as evidenced by medical history.
11. Subject has a history of psychiatric disorders, such as major depression disorder, anxiety disorders, or psychotic disorders requiring hospitalization and/or medication within 6 months prior to screening. A history of attention deficit hyperactivity disorder requiring medication is acceptable.
12. Subject has a diagnosis of epilepsy or other seizure disorder (a history of febrile seizures is acceptable).
13. Subject has had previous cardiothoracic surgery (subjects who have a history of patent ductus arteriosus ligations/surgery as infants are acceptable).
14. Subject has a history of conditions which might be specifically contraindicated or require caution while using OC, APAP, and/or ibuprofen (if used as a rescue medication) per the Investigator Brochure and/or the appropriate package insert.
15. Subject has a history of any drug allergy, hypersensitivity, or intolerance including OC, APAP, ibuprofen or excipients, or any opioid drug product which, in the opinion of the investigator, would place the subject at particular risk and compromise the safety of the subject in the study.
16. Subject has donated or had significant loss of whole blood (480 mL or more) within 30 days of screening (unless they have received a transfusion to correct the blood loss and have hematocrit and hemoglobin within the reference range at screening), or plans to donate blood or plasma during the course of the study.
17. Subject has a documented history of any pathologic, iatrogenic or surgical condition that, in the opinion of the investigator, would compromise the subject's ability to swallow, absorb, metabolize, or excrete XARTEMIS XR, including (but not limited to) intractable nausea and/or vomiting, severe gastrointestinal narrowing, perforation, obstruction, bleed, or gastric band surgery.
18. Subject has a history of a GI event (eg, perforation, obstruction, bleed) within 6 months prior to screening or any GI event greater than 6 months before screening that, in the opinion of the investigator, would make the subject unsuitable for study participation.
19. Subject has used any product containing OC or APAP within 48 hours prior to the first dose of XARTEMIS XR.
20. Subject has a history of conditions which might be specifically contraindicated or require caution to be used during the administration of APAP or OC including hypersensitivity to OC, or debilitated patients, those with severe impairment of hepatic, pulmonary, or renal function, myxedema or hypothyroidism, adrenocortical insufficiency (Addison's disease), central nervous system (CNS) depression or coma, toxic psychosis, urethral stricture, acute alcoholism, delirium tremens, severe kyphoscoliosis, or biliary tract dysfunction.
21. Subject has any other medical condition, abnormal vital sign (blood pressure, pulse rate, respiratory rate), body temperature, pulse oximetry; or any physical examination or ECG finding at screening which, in the investigator's medical opinion, would preclude safe participation in a clinical study.
22. Subject has received any investigational product or device within 30 days before screening, or is scheduled to receive an investigational device or another investigational drug (other than those in this study) during the course of this study.

Concomitant Medications:

Treatment with the following medications and therapies during the study are prohibited:

- Any investigational drug, device and/or experimental therapy (prohibited within 30 days before screening or throughout the study).
- Hormonal contraception and hormonal replacement therapies are prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.

- Any medication that, in the opinion of the investigator, may cause a clinically significant condition when used concomitantly with OC or APAP is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Any medication that is contraindicated (ie, precaution exists against concomitant use, and/or the potential exists for a clinically significant drug-drug interaction with XARTEMIS XR) is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Any medication that is known to moderately to strongly inhibit or induce CYP2D6 and/or CYP3A4 enzymes (see Attachment 2) is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the study. The use of CYP2D6 and/or CYP3A4 inhibitors or inducers is allowed peri-operatively as needed.
- Any medication containing OC or APAP is prohibited within 48 hours prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Subject pain should be managed to ensure that any supplemental opioid medication is not needed in the 30 minutes prior to each dose of XARTEMIS XR.
- Treatment with the optional rescue medication (ibuprofen) provided will be allowed during the study as needed (200 mg or 400 mg every 4 to 6 hours, maximum individual dose of 1,200 mg per 24 hours).

Investigational Medicinal Product and Rescue Medication Administration:
XARTEMIS XR (7.5 mg OC HCl/325 mg APAP tablets).
All subjects will be treated with 2 tablets of XARTEMIS XR every 12 hours (Q12h) for a maximum of 4 doses.
Optional rescue medication (ibuprofen) will be supplied for use during the study as needed (200 mg or 400 mg every 4 to 6 hours, maximum individual dose of 1,200 mg per 24 hours).
Additional analgesia or adjuvant therapies may be administered after the first dose of XARTEMIS XR according to the investigator's clinical practice. These therapies must not conflict with any of the inclusion or exclusion criteria or concomitant medications These additional therapies must be approved by the medical monitor and sponsor prior to study start, if possible.

Safety Evaluation:
Subject safety will be monitored from the time that the parent or legal guardian signs the ICF and the subject signs assent at screening (up to 14 days before dosing) through the completion of the follow-up telephone contact following the last dose of XARTEMIS XR, or early termination.
The following safety assessments will be evaluated: adverse events (AE), clinical laboratory tests, vital signs, body temperature, pulse oximetry, ECGs, physical examinations, and impaired judgment evaluation.

Pain Intensity Evaluation:
Pain assessments will be evaluated using subject reported pain intensity scores (NPRS). To be eligible, a subject's baseline NPRS score must be ≥ 4. NPRS scores will be obtained within 10 minutes prior to and at 1, 2, 4, and 8 hours after the first XARTEMIS XR dose. After the first dose of XARTEMIS XR, pain will be evaluated using the NPRS prior to the scheduled XARTEMIS XR doses at 12, 24, and 36 hours, if the pain score is ≥ 4, the subject will receive the next scheduled dose.

Pharmacokinetics:
Approximately 2 mL of blood will be collected in prechilled vacuum blood collection tubes, containing K_2EDTA as the anticoagulant, for determination of plasma concentrations of OC and APAP per the following schedule:

- Within10 minutes prior to the first dose of XARTEMIS XR and at 15 and 45 minutes (± 5 minutes); and 2, 4, 6, 8, 10, and 12 hours (± 10 minutes) after the first dose of XARTEMIS XR. The 12-hour blood draw must be completed prior to the administration of the second dose of XARTEMIS XR.
- Within 10 minutes prior to the third dose of XARTEMIS XR.
- Within 10 minutes prior to the fourth dose of XARTEMIS XR and at 15 to 30 minutes, 45 to 90

minutes, 2 to 4 hours, and 6 to 8 hours after the fourth dose of XARTEMIS XR. In addition, the last sample will be collected 12 to 18 hours after the fourth dose. If the subject requires further pain medication after the fourth dose of XARTEMIS XR, the last blood sample will be collected at 12 hours (± 10 minutes) after the fourth dose, but prior to the next dose of pain medication.

Volume: Subjects will have an estimated maximum total of approximately 50 mL of blood drawn during the course of the study, including 32 mL for PK sampling and 18 mL for laboratory safety assessments.

Pharmacokinetic Analysis:

Single Dose PK (Noncompartmental Analysis):

The following PK parameters will be determined for OC and APAP following the first dose (predose at 0 to 12 hours postdose):

- Area under the concentration-time curve over the first dosing interval ($AUC_{0\text{-}12h}$).
- Time delay between drug administration at Hour 0 and the onset of absorption (t_{lag}).
- Observed maximum drug concentration (C_{max}).
- Time of maximum observed plasma concentration (T_{max}).
- Apparent terminal elimination half-life ($t_{1/2}^{x}$).
- Apparent terminal elimination rate constant (λ_X).

Single/Multiple Dose PK (Population PK Modeling):

For those subjects administered single and/or multiple doses of XARTEMIS XR (≥ 2 doses), population PK analysis will be performed for OC and APAP.

Population PK analyses will be conducted via nonlinear mixed effect modeling using the nonlinear mixed-effects modeling software NONMEM®, Version 7 or higher ([redacted]). Adult PK data from XARTEMIS -XR Phase1 studies will be utilized for developing the initial models for both OC and APAP. A covariate analysis will be undertaken to determine the contribution of demographic and disease characteristics to variability in OC and APAP PK. Individual predicted OC and APAP PK parameters (clearance and volume of distribution) and exposure metrics (minimum plasma concentration at steady-state, the peak plasma concentration at steady state, the average concentration at steady-state, the area under the plasma time concentration curve at steady-state and other parameters) will be derived from the final model.

Statistical Methods:

The following populations will be identified and analyzed in this study:

- Safety Population – all subjects enrolled in the study that received any quantity of XARTEMIS XR. This population will be used as the primary safety population.
- PK Population - all subjects who received at least 1 dose of XARTEMIS XR and have provided at least 1 blood samples for the measurement of OC and APAP. This population will be used to for population PK analysis.
- Single-dose PK population – All subjects who received at least one dose of XARTEMIS XR and have provided at least 6 blood samples for measurement of OC and APAP after the first dose of XARTEMIS XR. This population will be used for single-dose PK analysis.
- Modified Intent-to-Treat (mITT) Population – All subjects who received at least 1 dose of XARTEMIS XR and have at least 1 postbaseline pain intensity measurement. This population will be used for analysis of pain intensity.

Descriptive statistics will be provided for PK parameters. The mean, SD, minimum, maximum, and median will be presented for continuous variables. Frequencies and percentages will be presented for categorical variables. Statistical methods will be included in the statistical analysis plan, which will be developed and finalized prior to study completion.

Pharmacokinetic Data Analysis:

PK parameter estimation will be performed using the actual elapsed times from dose administration to

sample collection. Individual plasma OC and APAP concentrations will be summarized at each nominal time point using descriptive statistics. Individual concentration plots and mean data graphs will be produced using both linear and semilogarithmic scales.

Safety Analysis:
Subject AEs and withdrawals due to AEs will be summarized. Change from baseline summaries will be presented for vital signs, temperature, pulse oximetry, and clinical laboratory results. Physical examination and ECG findings will be presented as appropriate.

Pain Intensity Analysis:
Subject-reported NPRS pain intensity scores, as well as pain intensity score change from baseline, will be presented descriptively with summary statistics by time point. No imputation of missing values or adjustment from the impact of rescue medication use will be used.

Sample Size:
The sample size of 48 enrolled subjects is planned to result in at least 25 subjects that will receive 2 or more doses of XARTEMIS XR) for safety evaluation. In order to enroll 48 subjects it is estimated that 72 individuals will need to be screened.

Ethical Considerations:
This study will be conducted in accordance with applicable laws and regulations including, but not limited to, the ICH Guideline for GCP and the ethical principles that have their origins in the Declaration of Helsinki. The IRB must review and approve the protocol and informed consent form before any subjects are enrolled. Before any protocol-required procedures are performed, the subject's parent or legal guardian must sign and date the IRB approved informed consent form and the subject must sign an IRB approved assent form.

7 SCHEDULE OF EVENTS

Table 7-1: Schedule of Study Events

Dose#					1									2		3		4													
Time	Screening[a]	Check-in[b]	Surgical Procedure	Baseline	0 h[c]	15m	45m	1h	2h	4h	6h	8h	10h	12h	Second Dose + 2 h	24h	Third Dose + 2 h	36h	Fourth Dose + 15 m	Fourth Dose + 30 m	Fourth Dose + 45m	Fourth Dose + 1h	Fourth Dose + 90m	Fourth Dose + 2 h	Fourth Dose + 4 h	Fourth Dose + 6 h	Fourth Dose + 8 h	Fourth Dose + 12 h	Fourth Dose + 18 h	Fourth Dose + 18 h/ET	Follow-up[d]
Assessment																															
ICF/Assent	X																														
Inc/Exc	X	X																													
Demography[e]	X																														
Medical/Surgical History[f]	X	X																													
Date of last Menstrual Period[g]	X	X																													
Physical Examination	X	X																												X	
ECG	X	X																												X	
Height	X																														
Weight	X	X																													
Vital Signs[h]	X	X		X				X	X	X				X	X	X	X	X				X		X	X					X	
Temperature[i]	X	X		X				X	X	X				X	X	X	X	X				X		X	X					X	
Pain Intensity Assessment[j]				X				X	X	X		X		X		X		X													
Continuous Pulse Oximetry[k]																X															
Record Pulse Oximetry[k]	X	X		X				X	X	X				X	X	X	X	X			X		X		X					X	
Laboratory Tests[l]	X	X																												X	
Pregnancy Test	X	X																												X	
PK Samples[m]				X		X	X		X	X	X	X	X	X		X		X	X			X			X		X		X			
XARTEMIS XR Dose[a]					X									X		X		X													
Optional Rescue Medication																		X													
Impaired Judgment																														X	
Con Meds and Adverse Events[e]																		X													

Con Meds = Concomitant Medications; ECG = electrocardiogram; ET = Early Termination; h = hours; ICF = informed consent form; Inc/Exc = Inclusion/Exclusion Criteria; m = minutes; NPRS = Numerical Pain Rating Scale; PK = Pharmacokinetics

[a]Within 14 days prior to the first XARTEMIS XR dose. Subjects who are taking prohibited medications at the time of screening must discontinue their use and complete a washout period before check-in.

[b]It is acceptable to complete the screening procedures on the same day as the check-in procedures. In this situation the medical history review, date of first day of last menstrual period, inclusion/exclusion criteria review, physical examination, weight, laboratory assessment, pregnancy test, and electrocardiogram (ECG) do not need to be repeated if both visits occur within 24 hours prior to dosing.

[c]Hour 0 (0h) is defined as the time of administration of the first dose of XARTEMIS XR on the study.

[d]To be completed via telephone contact at 7 (± 2) days after the last dose of XARTEMIS XR or early termination.

[e]Demography includes date of birth, gender, race and ethnicity.

[f]Detailed medical and surgical history will be taken at screening and check-in (if applicable) and will include the surgical procedure required for study entry.

[g]For post menarche female subjects.

[h]Vital signs (blood pressure, pulse, and respiration rate) will be measured at screening; check-in; within 15 minutes prior to the first and fourth doses of XARTEMIS XR; at 1, 2, and 4 hours (± 15 minutes) after the first and fourth doses of XARTEMIS XR; within 15 minutes prior to and at 2 hours (± 15 minutes) after the second and third doses of XARTEMIS XR; and at study exit or early termination.

[i]Body temperature will be measured at screening; check-in; within 15 minutes prior to the first and fourth doses of XARTEMIS XR; at 1, 2, and 4 hours (± 15 minutes) after the first and fourth doses of XARTEMIS XR; within 15 minutes prior to and at 2 hours (± 15 minutes) after the second and third doses of XARTEMIS XR; and at Study Exit or Early Termination. The same method of measurement will be used for all assessments for a single subject.

[j]Pain intensity will be evaluated by the subject using NPRS scores (Attachment 3). To be eligible, a subject's baseline NPRS score must be ≥ 4. NPRS scores will be obtained within 10 minutes prior to and at 1, 2, 4, and 8 hours (± 15 minutes) after the first XARTEMIS XR dose. After the first dose of XARTEMIS XR, pain will be evaluated using the NPRS within 30 minutes prior to the scheduled time of each subsequent XARTEMIS XR dose at 12, 24, and 36 hours. If the pain score is ≥ 4, subjects will receive the next scheduled dose as planned. If the pain score is < 4, the NPRS will be repeated every 30 minutes (± 5 minutes) from the scheduled time of dosing and subjects will receive their XARTEMIS XR dose when and if their pain score is ≥ 4. The pain scores can be repeated up to 1 hour after the scheduled dosing time. Subjects whose pain scores remain < 4 during this time will not qualify for further study drug administration, but will still have blood collected for PK analysis at 10 minutes prior to the originally scheduled dosing time. Subjects are eligible to stay in the study and continue to have all safety assessments until study exit, or may proceed to early termination assessments. Pain assessments should always be completed prior to any other procedures for a given period.

[k]Percentage of oxygen saturation will be determined by a single pulse oximetry reading at screening, check-in, and study exit or early termination. Continuous pulse oximetry will be initiated within approximately 15 minutes prior to the first XARTEMIS XR dose and continue until 12 hours after the fourth XARTEMIS XR dose or early termination. In addition, percent of oxygen saturation will be recorded within 15 minutes prior to and 1, 2, and 4 hours after the first and fourth doses of XARTEMIS XR; and within 15 minutes prior to and 2 hours (± 15 minutes) after the second andthird doses of XARTEMIS XR.

[l]Blood and urine samples for clinical laboratory testing will be collected at screening, check-in (if applicable), and study exit or early termination.

[m] Blood samples for PK analysis will be collected within 10 minutes prior to the first dose of XARTEMIS XR; at 15 and 45 minutes (± 5 minutes) and at 2, 4, 6, 8, 10, and 12 hours (± 10 minutes) after the first dose of XARTEMIS XR. The 12 hour postdose sample will be collected prior to administration of the second dose of XARTEMIS XR. Additional blood samples for PK analysis will be collected within 10 minutes prior to administration of the third and fourth doses of XARTEMIS XR; at 15 to 30 minutes, 45 to 90 minutes, 2 to 4 hours, and 6 to 8 hours after the fourth dose of XARTEMIS XR. In addition, if further pain medication is not required a final sample will be collected at 12 to 18 hours after the fourth dose. If the subject requires further pain medication, the final sample should be collected at 12 hours (± 10 minutes) after the fourth dose, but prior to the next dose of pain medication.

[n]XARTEMIS XR will be dosed every 12 hours. The first dose of XARTEMIS XR is defined as Hour 0. The second, third, or fourth doses may be delayed by up to 1 hour (+15 minutes) if the subject's NPRS score is < 4. If any dose is so delayed, subsequent doses will be given at the originally scheduled time unless delayed by an NPRS score of < 4. Subjects will switch to the standard of care pain medication if required for further treatment of pain after the fourth dose of XARTEMIS XR.
[o]All adverse events that occur from the time of the signing of the informed consent will be recorded in source documents. Adverse events will also be recorded in the electronic case report form (eCRF) for all subjects who receive any dose of XARTEMIS XR. All medications taken within the 30 days prior to screening and throughout the study will be recorded, including all peri-operative and operative treatments.

8 ETHICAL CONSIDERATIONS

This clinical study is designed to comply with ICH Guidance on General Considerations for Clinical Trials (62 FR 66113, 17 Dec 1997), Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authority for Pharmaceuticals (75 FR 3471, 21 Jan 2010), and Good Clinical Practice: Consolidated Guidance (62 FR 25692, 09 May 1997).

8.1 Institutional Review Board

It is the responsibility of the investigator to obtain the approval of the IRB before the start of the study. The IRB must be registered and active with the Office for Human Research Protections of the US Department of Health and Human Services. A copy of the approval letter along with a roster of IRB members and/or the US Department of Health and Human Services general assurance number will be retained as part of the study records. During the course of the study, the investigator will provide timely and accurate reports to the IRB on the progress of the study at appropriate intervals (not to exceed 1 year) and at the completion of the study. The investigator will notify the IRB of serious adverse events (SAEs) or other significant safety findings per IRB guidelines. The study protocol, informed consent form (ICF), advertisements (if any), and amendments (if any) will be approved by the IRB in conformance with CFR, Title 21, Part 56.

8.2 Ethical Conduct of the Study

The study will be conducted in full compliance with applicable US FDA regulations and ICH guidelines for GCP and in accordance with the ethical principles that have their origins in the Declaration of Helsinki.

8.3 Subject Information and Consent

The ICF must be approved by the sponsor and the IRB before any subjects provide consent.

At the screening visit, subjects will read the ICF and a Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable) after being given an explanation of the study. Before signing the ICF and the HIPAA authorization form (if applicable), subjects will have an opportunity to discuss the contents of these forms with study site staff.

Subjects must assent understanding of and voluntarily sign these forms in compliance with 21 CFR, Parts 50 and 312, before participating in any study-related procedures. Subjects will be made aware that they may withdraw from the study at any time. Subjects unable to give written informed consent must orally assent to the procedures, and written informed consent must be obtained from a legally authorized representative in accordance with state laws, as applicable.

The ICF must contain all applicable elements of informed consent and the mandatory statements as defined in the CFR and a HIPAA authorization form. Signed copies of the ICF and the HIPAA authorization form, if applicable, will be given to the subject.

The subject will be made aware of his/her right to see and copy his/her records related to the study for as long as the investigator has possession of this information. If the subject withdraws consent and/or HIPAA authorization, the investigator can no longer disclose health information, unless it is needed to preserve the scientific integrity of the study.

9 BACKGROUND INFORMATION AND RATIONALE

9.1 Overview

XARTEMIS® XR (MNK-795, formerly known as COV795) is a novel oral analgesic that was recently approved by the FDA for the management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate in adults (XARTEMIS XR Package Insert [PI] 2014). XARTEMIS XR is a controlled-release combination 7.5 mg oxycodone (OC) HCl/325 mg acetaminophen (APAP) therapy. Under the Pediatric Research Equity Act (PREA), the FDA has the authority to require pediatric studies on an approved drug product if there is substantial use expected in the pediatric population or the product would provide a meaningful therapeutic benefit and the absence of adequate labeling could pose significant risk. This study, planned for an adolescent (12 to 17 years of age) population, is the initial XARTEMIS XR clinical investigation being conducted in the pediatric population to satisfy the PREA.

XARTEMIS XR is the first FDA approved oral analgesic combination indicated for acute pain which incorporates an immediate-release (IR) and extended-release (ER) profile of both active pharmaceutical ingredients into a single product entity. Combining analgesic agents with different mechanisms of action offers a multimodal approach to therapy, with at least additive analgesic effects, lowers the overall dose of each active pharmaceutical ingredient (API), and minimizes side effects (AGS 2002, Barkin 2001, Beaver 1981, Beaver 1984, Beaver 1988, Gaskell et al 2009, Raffa 2001).

The American Pain Society states that the introduction of ER analgesics is an important innovation in the management of pain (American Pain Society 2008). Extended-release preparations provide more consistent plasma concentrations for better control of end of dose pain and reduced breakthrough medication usage, while additionally offering the convenience of less frequent dosing compared to IR preparations (McCarberg and Barkin 2001). Also, reduced frequency of dosing is known to increase patient compliance (Aronson and Hardman 1992, McCarberg and Barkin 2001).

Mallinckrodt designed a fixed-dose, opioid/nonopioid, and "biphasic" dual-release, IR/ER analgesic product (XARTEMIS XR) containing OC HCl and APAP for the management of

acute pain. The product utilizes Depomed's AcuForm™ gastroretentive (GR) drug delivery technology (XARTEMIS XR Package Insert [PI] 2014). Gastroretentive technology targets the release of the API in the upper gastrointestinal (GI) tract over an extended period, ie, 6 to 10 hours, to produce an extended duration of action (Glumetza® PI 2011, Gralise® PI 2012, Proquin XR® PI 2011). XARTEMIS XR is a multilayer IR/ER OC HCl/APAP GR, 12 hour oral analgesic tablet which seeks to enhance the pharmacokinetic (PK) performance, effectiveness, tolerability and safety of IR OC HCl/APAP (eg, Percocet® 7.5 mg OC/325 mg APAP, which is typically dosed every 4 to 6 hours) (Percocet PI 2013). The GR delivery system also conveys potential abuse-deterrent properties to the product (MNK-795 Investigator's Brochure [IB] 2014).

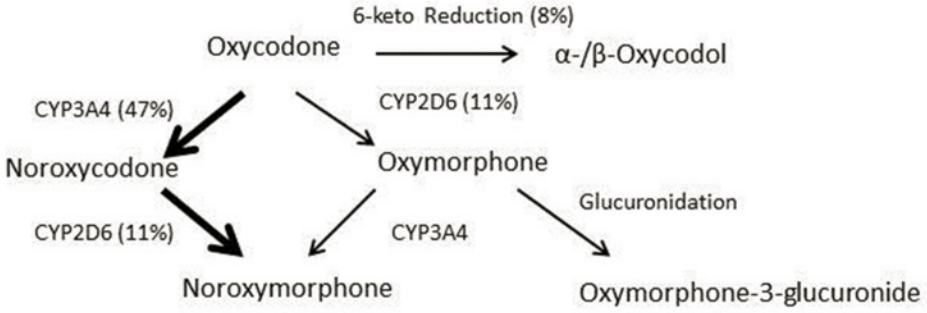
XARTEMIS XR provides analgesia when taken as 2 tablets (15 mg OC HCl/650 mg APAP per dose) every 12 hours (Q12h), resulting in a maximum daily dose of 30 mg of OC HCl and 1,300 mg of APAP in adults. The combination of OC and APAP takes advantage of the different mechanisms of action of the 2 drugs, ie, the nociceptive mechanism of action (of OC) and a centrally mediated analgesic mechanism (of APAP) (Desmeules et al 2003). The formulation is designed to reach therapeutic levels of both opioid and nonopioid drugs quickly (within 1 hour) through the IR layer component, with sustained analgesia over the dosing interval (12 hours) due to the ER layer component (MNK-795 IB 2014). Furthermore, the XARTEMIS XR formulation incorporates recent recommendations of the US FDA limiting the total APAP dose per tablet to 325 mg, increasing confidence in the safety of this formulation (Federal Register Notice 2011). XARTEMIS XR leverages the comfort that physicians already have with these well-understood and studied APIs, while also providing a product that is more conveniently dosed.

Oxycodone is a semisynthetic pure opioid agonist whose principal therapeutic action is analgesia. Other pharmacological effects of OC include anxiolysis, euphoria and feelings of relaxation. These effects are mediated by receptors (notably μ and κ) in the central nervous system for endogenous opioid-like compounds such as endorphins and enkephalins. Oxycodone produces respiratory depression through direct activity at respiratory centers in the brain stem and depresses the cough reflex by a direct effect on the medulla. Oxycodone also reduces GI motility, increases ureteral and bladder sphincter, and sphincter of Oddi tone, and

induces the release of histamine which causes pruritus, flushing, and sweating (MNK-795 IB 2014, Percocet® PI 2013).

Oral administration of conventional IR OC products produces an analgesic effect within an hour of dosing which persists for 3 to 6 hours (AHFS 2004). Mean absolute oral bioavailability of OC is approximately 85%. Oxycodone is 45% bound to human plasma proteins in vitro, with an apparent volume of distribution after intravenous administration of 211.9 ± 186.6 liters (MNK-795 IB 2014, Percocet PI 2013). Oxycodone is metabolized through cytochrome P450 oxidation and UDP-glucuronosyltransferase conjugation (glucuronidation). The metabolic pathway of OC (Coluzzi and Mattia 2005) is shown in Figure 9-1.

Figure 9-1: Oxycodone Hepatic Metabolism



The major metabolic pathway (bold arrows) of OC is by N-dealkylation to form noroxycodone by CYP3A4, while noroxycodone is further metabolized to noroxymorphone by CYP2D6. The minor metabolic pathway (narrow arrows) is by O-demethylation to form oxymorphone by CYP2D6, and 6-keto reduction of OC to α- and β-oxycodol. Oxymorphone is further metabolized to noroxymorphone by CYP3A4 or conjugated to form oxymorphone-3-glucoronide (Coluzzi and Mattia 2005).

Approximately 8% to 14% of the dose of OC is excreted in urine unchanged (over 24 hours). The metabolites of OC and their conjugates are also excreted principally in the urine. The

apparent elimination half-life following oral administration of a single IR dose of OC is 3.5 ± 1.43 hours (AHFS 2004, Percocet PI 2013).

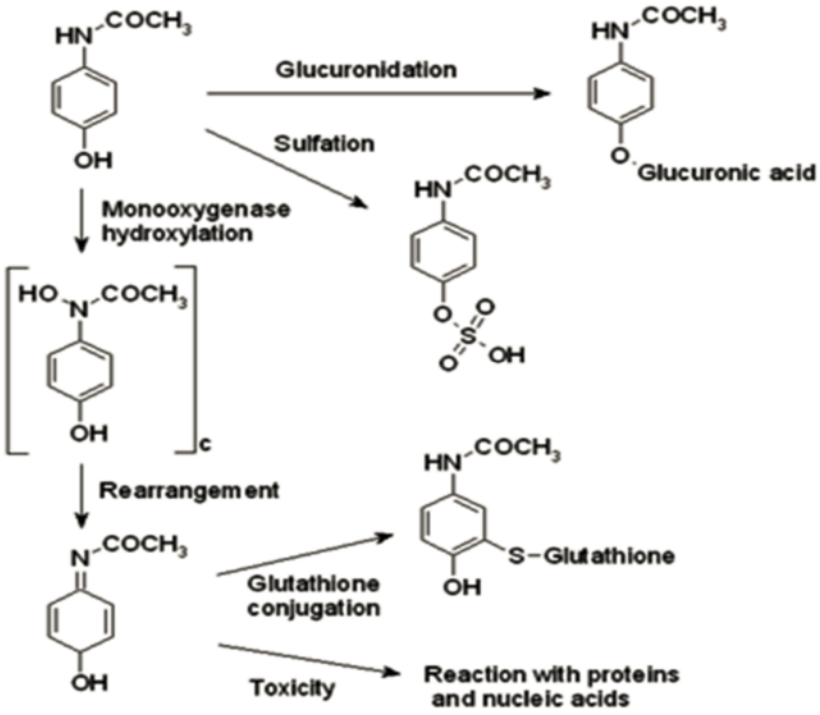
Acetaminophen is a nonopiate, nonsalicylate analgesic, and antipyretic agent. The site and mechanism of analgesic effect of APAP has not been determined. The antipyretic effect of APAP is accomplished through the inhibition of endogenous pyrogen action on the hypothalamic heat-regulating centers (Percocet PI 2013).

The absorption of APAP is rapid and almost complete from the GI tract after oral administration. Acetaminophen is uniformly distributed throughout most body fluids. Binding of APAP to plasma proteins is variable. The metabolic pathway for APAP (Prescott 2001) is shown in Figure 9-2. The primary metabolic pathway for APAP is hepatic conjugation. About 80% to 85% of the dose of APAP is conjugated, principally with glucuronic acid (glucuronidation), and to a lesser extent with sulfuric acid and cysteine. After hepatic conjugation, 90% to 100% of APAP is recovered in the urine within 24 hours (Percocet PI 2013).

Less than 5% of APAP is metabolized by the CYP P450 pathway (CYP3A4 and CYP2E1) to N-acetylimidoquinone (NAPQI). N-acetylimidoquinone is a toxic intermediate metabolite which is immediately inactivated by conjugation with glutathione, present in a finite and fixed amount. It is believed that NAPQI is responsible for liver injury and necrosis. At high doses, the capacity of metabolic pathways for APAP conjugation with glucuronic acid and sulfuric acid may be exceeded, resulting in increased metabolism of APAP by alternate pathways (Prescott 2001).

Acute and chronic excessively high doses of APAP may deplete the quantity-constrained glutathione stores, resulting in a reduction of NAPQI inactivation and thus increased risk of developing severe drug-induced liver injury (DILI) (FDA Guidance for Industry 2009, Watkins et al 2006). For this reason, the FDA has issued several recommendations surrounding safe use of APAP-containing products, including limiting the maximum amount of APAP per tablet to 325 mg (Federal Register Notice 2011).

Figure 9-2: Acetaminophen Hepatic Metabolism



The PK profile of OC and APAP combinations have been reported in numerous studies of IR products, and Mallinckrodt has conducted several Phase 1 PK studies of XARTEMIS XR and IR OC/APAP (MNK-795 IB 2014, Mallinckrodt Clinical Study Report (CSR) 2012a, Mallinckrodt CSR 2012b, Mallinckrodt CSR 2012c). These previous Phase 1 PK studies were conducted with XARTEMIS XR (at various OC/APAP mg amounts) using Percocet as the comparator in the adult population across the clinical development program. Since Percocet was not approved by the FDA under a New Drug Application (NDA), but rather an Abbreviated New Drug Application (ANDA), the Agency required Mallinckrodt to study XARTEMIS XR with the NDA approved listed drugs (LDs) Roxicodone® (15 mg) and Ultracet® (37.5 mg tramadol/325 mg APAP) as comparators.

Studies have investigated the PK, bioavailability and safety of single and multiple doses of XARTEMIS XR compared with the LDs Roxicodone (15 mg) and Ultracet (37.5 mg

tramadol/325 mg APAP), and Percocet (7.5 mg OC HCl/325 mg APAP), as well as the effect of food on the PK of XARTEMIS XR. XARTEMIS XR doses ranged from 7.5 mg OC HCl/325 mg APAP to 30 mg OC HCl/1,300 mg APAP. Total dose normalized exposure to OC and APAP (2 tablets XARTEMIS XR [7.5 mg OC HCl/325 mg APAP]) following a single dose (area under the concentration-time curve [AUC]) or during the dosing interval at steady state ($AUC_{0\text{-}12h}^{ss}$) were equivalent to Roxicodone or Ultracet and Percocet (Mallinckrodt CSR 2012d, Mallinckrodt CSR 2012e). In a multiple dose study, the degree of fluctuation (DFL) comparing observed maximum drug concentration (C_{max}^{ss}) to observed minimum drug concentration (C_{min}^{ss}) with respect to average concentration (C_{avg}^{ss}) for OC, was equivalent to Roxicodone and 23% less for XARTEMIS XR than for Percocet (Mallinckrodt CSR 2012d). The DFL for APAP was equivalent to Ultracet and Percocet. Both OC and APAP from XARTEMIS XR accumulated to the same extent as for Roxicodone, Ultracet and Percocet. Maximum plasma concentrations of OC and APAP were generally observed at about 3 hours and 0.75 hours postdose, respectively. Following single and multiple doses of 2 tablets of XARTEMIS XR (7.5 mg OC/325 mg APAP), average maximum drug concentration (C_{max}) values of about 16 ng/mL and 25 ng/mL for OC and 5,000 ng/mL and 5,300 ng/mL for APAP were consistently observed. Intersubject variation was minimal (percentage coefficient of variation [%CV] 20% to 30%) for XARTEMIS XR and similar to that observed for the LDs and Percocet. Dose normalized C_{max} for OC following single and multiple doses of 2 tablets of XARTEMIS XR (7.5 mg OC/325 mg APAP) were equivalent to the LD, Roxicodone, and C_{max} for APAP was equivalent to the LD, Ultracet, as well as Percocet. As expected from an ER tablet, OC C_{max} following a single dose of XARTEMIS XR was generally about 10% lower than Roxicodone and 20% lower than Percocet. Plasma OC concentrations from XARTEMIS XR plateaued over the 12 hour dosing interval and APAP levels were below 1,000 ng/mL by 10 to 12 hours postdose, as desired. The apparent elimination half-life ($t_{1/2}$) for OC (4 to 6 hours) and the half-life for APAP (5 to 7 hours) were similar between XARTEMIS XR and IR products (Roxicodone or Ultracet and Percocet); indicating complete absorption of OC and APAP from the ER tablet, XARTEMIS XR, by 12 hours after dosing.

Food has not been previously reported to have a significant effect on the AUC of OC, though peak plasma concentrations are typically increased by approximately 25% after IR and ER OC product administration with a high-fat meal compared to the fasting state (AHFS 2004). Multiple studies have investigated the impact of diet upon the safety and PK of XARTEMIS

XR (MNK-795 IB 2014). A high- or low-fat breakfast did not affect the total exposure (AUC) observed with OC and APAP from XARTEMIS XR (Mallinckrodt CSR 2012c). Peak exposure observed with OC from XARTEMIS XR administered to subjects fed a high-fat meal was not significantly different from C_{max} when XARTEMIS XR was administered under fasting conditions, but a 25% increase in mean peak exposure was observed when subjects were dosed with XARTEMIS XR after a low-fat meal. A 24% and 23% decrease in mean peak exposure was observed with APAP in subjects under fed conditions (high- and low-fat meals, respectively) compared to fasted, respectively. These differences are not clinically significant and XARTEMIS XR can be administered with or without food.

In studies with Roxicodone and Ultracet as the LDs the dose-normalized area under the concentration-time curve from time zero to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve over the dosing interval $AUC_{0\text{-}12h}^{ss}$, and C_{max}^{ss}, C_{min}^{ss}, and C_{avg}^{ss} of OC for XARTEMIS XR were equivalent to those for Roxicodone and the dose-normalized $AUC_{0\text{-}inf}$, $AUC_{0\text{-}12h}^{ss}$, C_{avg}^{ss}, and C_{max}^{ss} of APAP for XARTEMIS XR were equivalent to those for Ultracet.

9.2 Product Description

The XARTEMIS XR formulation (7.5 mg OC HCl/325 mg APAP) contains 25% OC HCl (1.875 mg)/50% APAP (162.5 mg) in the IR layer component (designed to provide rapid analgesic onset), and 75% OC HCl (5.625 mg)/50% APAP (162.5 mg) in the ER layer component, which serves to provide an extended duration of analgesia when administered orally Q12h.

The inactive ingredients are microcrystalline cellulose, pregelatinized corn starch, citric acid anhydrous powder, (ethylenedinitrilo) tetraacetic acid disodium salt, hydroxypropyl cellulose, croscarmellose sodium, colloidal silicon dioxide, polyethylene oxide, and magnesium stearate. The 7.5 mg OC HCl/325 mg APAP tablet is finished with an Opadry II Blue (85F99167) outer coating (MNK-795 IB 2014).

Polyethylene oxide is a functional excipient that serves as the predominant GR technology component. Polyethylene oxide expands when exposed to fluid; XARTEMIS XR is designed to be retained in the stomach, thereby targeting the release of both drugs to the upper GI tract

where APAP absorption is optimal (Kimura et al 1994, MNK-795 IB 2014). Dissolution studies have demonstrated that XARTEMIS XR is slowly solubilized by water, alcohol, and gastric fluids, suggesting that dose dumping is unlikely regardless of transit time through the GI system or if taken with alcohol (MNK-795 IB 2014).

9.3 Dosage and Administration

The adult dosing regimen is 2 tablets (total of 15 mg OC HCl/650 mg APAP) Q12h, which is deemed age-appropriate for this adolescent population (El-Tahtawy et al 2006, Ji et al 2012, Kokki et al 2006, Zuppa et al 2011).

9.3.1 Dose and Regimen Justification

In the 12 Phase 1 clinical studies performed with XARTEMIS XR, employing doses ranging from 7.5 mg OC HCl/325 mg APAP to 30 mg OC HCl/1,300 mg APAP, no serious adverse effects or clinically significant abnormal changes in laboratory parameters or vital sign measurements have been observed (MNK-795 IB 2014, MNK-795 (XARTEMIS) XR PI 2014). In safety data from two Phase 3 (one placebo-controlled, one open-label) trials where multiple doses of XARTEMIS XR were administered for up to 42 days, the most common adverse reactions (reported by ≥ 10% in any XARTEMIS XR dose group) were nausea, dizziness and vomiting (XARTEMIS XR PI 2014). In clinical studies (performed by the innovators) using Roxicodone, Ultracet, and Percocet, common adverse events (AEs) experienced by subjects include lightheadedness, dizziness, drowsiness or sedation, nausea, and vomiting. XARTEMIS XR, Roxicodone, Ultracet, and Percocet may be administered with or without food (XARTEMIS XR PI 2014, Percocet PI 2013, Roxicodone PI 2009, Ultracet PI 2011).

Safety concerns associated with APAP have recently been raised in the scientific and regulatory community. Overdose from prescription combination products containing APAP account for nearly half of all cases of APAP-related liver failure in the United States, many of which result in liver transplant or death. Most of the cases of severe DILI occur in patients who took more than the maximum recommended prescribed dose of an APAP-containing product in a 24-hour period (4,000 mg), took multiple APAP-containing products at the same time, or drank alcohol while taking APAP products (Federal Register Notice 2011). For this

multiple-dose study, the risk of severe DILI is minimal because the low daily total dose utilized (1,300 mg) is far below the maximum recommended daily APAP dose.

The GR technology platform has been utilized for several marketed products (Glumetza®, Gralise®, and Proquin® XR). Available safety information indicates that the incidence of AEs with GR products is similar to the non-GR comparator groups. These findings suggest that the GR technology used in XARTEMIS XR is unlikely to result in any additional risk to subjects, though the safety and effectiveness of Glumetza, Gralise, and Proquin has not been established in pediatric patients (Glumetza PI 2011, Gralise PI 2012, Proquin XR PI 2011).

The current multiple-dose study is designed to accurately characterize and reflect the PK of OC and APAP from XARTEMIS XR in adolescent pediatric patients 12 to 17 years of age in moderate to severe acute pain after trauma or a postoperative procedure. To further aid subject safety, a minimum weight for subject eligibility was selected for all subjects and frequent vital signs, pulse oximetry measurements, and changes in mental status will be closely monitored for signs of opioid side effects. These steps have been designed to provide a balance between providing a safe and statistically robust study that also allows for the most sensitive characterization of the key PK parameters of the formulation.

To date, the XARTEMIS XR safety and tolerability profile has been comparable to Percocet (Percocet PI 2013). Based upon the maturation of the metabolic pathways for OC and APAP in this age population, their ability to swallow the tablet and comparable dosing requirements to that of adult patients, Mallinckrodt believes the XARTEMIS XR IR/ER bilayer formulation is age-appropriate for 12 to 17 year-old subjects.

Ultimately, the clinical use and therapeutic application of XARTEMIS XR in a multilayer IR/ER, OC/APAP GR formulation, dosed Q12h, is expected to offer greater patient convenience, potentially improve sleep, and may lessen the frequency and severity of end-of-dose pain (American Pain Society 2008, Hale et al 2007, Markenson et al 2005, Nicholson et al 2006, Pan et al 2007).

9.4 Adverse Events

In the 14 clinical trials with XARTEMIS XR completed to date, which have employed doses between 7.5 mg OC HCl/325 mg APAP and 30 mg OC HCl/1,300 mg APAP, the product

appears to be safe and well-tolerated. The most common AEs included nausea, dizziness and vomiting.

9.5 Rationale

XARTEMIS XR is designed to provide rapid pain relief (onset < 1 hour) with sustained analgesia for up to 12 hours. The efficacy and safety of an immediate-release oral combination of OC and APAP is well established in adults, with over 4 decades of use in the United States, Asia, Australia, Europe, and Canada. In the US, Percocet (an IR OC/APAP combination) was first approved by FDA in 1976 for the treatment of moderate to moderately severe pain; Percocet is not indicated for use in children.

This is a Phase 4, multicenter, open-label study to evaluate the PK performance and safety of the XARTEMIS XR oral formulation in 12 to 17 year old adolescent subjects with acute pain. This study is being conducted in order to satisfy the sponsor's commitment to the PREA. The XARTEMIS XR bilayer tablet is considered age appropriate for 12 to 17 year olds, based on maturation of the metabolic pathways for OC and APAP in this age group, their ability to swallow the tablet, and dosing requirements comparable to the adult population. Future studies in subjects < 12 years of age are being planned; for these studies, an age-appropriate formulation will be used.

10 OBJECTIVES

10.1 Primary

- The primary objective is to characterize the PK profile of XARTEMIS XR following single and multiple dose administrations in adolescent subjects (12 to 17 years of age) experiencing moderate to severe acute pain.

10.2 Secondary

- To determine the safety and tolerability of XARTEMIS XR in adolescent subjects (12 to 17 years of age).

- To determine the pain intensity differences from baseline over the first dosing period (eg, 1, 2, 4, 8, and 12 hours) following treatment of adolescent subjects (12 to 17 years of age) with XARTEMIS XR.

11 STUDY DESIGN

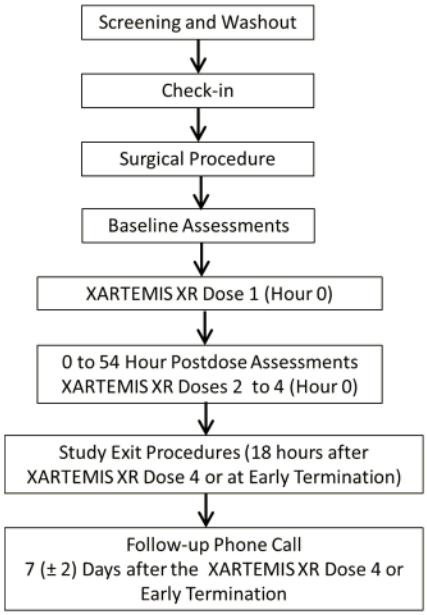
11.1 Description

This is a Phase 4, multicenter, open-label, single- and multiple-dose study of the PK and safety of XARTEMIS XR in adolescent subjects aged 12 to 17 years with moderate to severe acute pain.

This study is being conducted to assess PK and safety in adolescent subjects. It will be possible to compare PK parameters and safety results with those determined in adults in previous studies with XARTEMIS XR.

The overall study design is illustrated in Figure 11-1.

Figure 11-1: Study Design



11.2 Approximate Duration of Subject Participation

Subjects will participate in the study for a total of approximately 4 weeks, including a 2 week screening and washout period, a study period of up to 54 hours, and a follow-up telephone contact scheduled for approximately 1 week (7 ± 2 days) after the last dose of XARTEMIS XR.

11.3 Approximate Duration of Study

The duration of the study from Site Initiation to the Close-out visit will be dependent on the ability of the site(s) to identify and enroll eligible subjects and is expected to be approximately 1 year. The end of the study is completion of the final follow-up telephone contact for the final subject. Adverse events will be followed and reported to the sponsor through the follow-up phone contact.

11.4 Approximate Number of Subjects

Approximately 72 individuals will be screened at multiple sites in the United States to ensure 48 subjects will be enrolled. If more than 1 site is used, approximately 10 to 18 subjects will

be enrolled at each site. This may vary based on enrollment capabilities of each site. All attempts will be made to enroll equal numbers of subjects within the age range and between genders such that one-third of subjects will be 12 to13 years of age, one-third will be 14 to15 years of age, and one-third will be 16 to17 years of age, with each age range equally distributed by gender.

12 SELECTION OF SUBJECTS

12.1 Inclusion Criteria

Subject must meet all of the following criteria at screening and check-in to be eligible for the study:

1. Subject must be male or nonpregnant, nonlactating females between 12 and 17 years of age (inclusive) at time of screening.
2. Subject must have a minimum weight of 100 pounds (45 kg) and have a body mass index (BMI) > 5% and < 95% for their age (see Attachment 1) at the time of screening.
3. Subject must report having moderate or severe acute pain (as determined from the Numerical Pain Rating scale [NPRS] where 0 = no pain, 10 = worst pain; subjects must have a level of 4 or more) after a pediatric surgical procedure (at baseline) that requires hospitalization. Sponsor will pre-approve a list of acceptable surgical procedures prior to study start for each site. Surgical procedures other than those on the pre-approved list may be acceptable on a case by case basis if approved by the Medical Monitor (MM) and sponsor.
4. Subject, if female of child-bearing potential (defined as postmenarche), must agree to abstain from unprotected sexual activity during study participation and for 2 weeks after study exit.
5. Subject, if male with reproductive potential, must agree to abstain from unprotected sexual activity during study participation and for 2 weeks after study exit.
6. Subject, if female of childbearing potential, must have negative pregnancy test (serum or urine) results at screening and check-in.

7. Subject's legally authorized representative (eg, parent, legal guardian) must voluntarily sign and date a parental permission/ICF that is approved by an IRB, and the subject must sign an IRB approved assent, before undergoing any protocol specific procedures or assessments.
8. Subject and the subject's parent or legal guardian must be able to read, understand, and be willing to follow the study procedures and requirements and communicate meaningfully in English with the investigator and investigator's staff (if the subject cannot read or communicate meaningfully, then the subject's legally authorized representative [eg, parent, legal guardian] must meet this criterion).

12.2 Exclusion Criteria

A subject is ineligible for the study if they meet any of the following criteria at screening and check-in:

1. Subject is from a vulnerable population (including mentally disabled children), other than a pediatric population, as defined by the Code of Federal Regulations Title 45, Part 46, Section 46.111(b), including but not limited to employees (temporary, part-time, full time, etc) or a family member of the research staff conducting the study, or of the sponsor, or of the clinical research organization, or of the IRB.
2. Subject is expected to require a surgery that could influence the study outcome (eg, ventriculoperitoneal shunt repair in the setting of hydrocephalus).
3. Subject has an abnormal electrocardiogram (ECG) unless the investigator determines the ECG abnormalities are not clinically significant.
4. Subject has a screening pulse oximetry reading of < 95% while awake.
5. Subject has a history of laboratory test results obtained before screening that show the presence of human immunodeficiency virus (HIV), hepatitis B surface antigen, hepatitis C antibody, or active hepatitis A immunoglobulin M.
6. Subject has laboratory values that are greater than 2 times the upper limit of normal (with the exception of white blood cell [WBC] differential values). Enrollment of subjects with laboratory values that are between 1 and 2 times the upper limit of normal (ULN), or below the lower limit of normal, or WBC differential > 2 x ULN , will be left to the

investigator's discretion (no increased risk of participation in study based upon judgment of the investigator).

7. Subject has any history of renal disease that, in the opinion of the investigator, would contraindicate study participation; or subject has significantly impaired renal function, in the opinion of the investigator, as evidenced by an estimated glomerular filtration rate calculated using a pediatric appropriate formula such as the Schwartz Equation (Schwartz et al 2009).
8. Subject has a history or laboratory evidence of bleeding or clotting disorders or conditions.
9. Subject has a known or suspected history of alcoholism, marijuana or illicit drug abuse or misuse within 2 years before screening as evidenced from medical history or evidence of tolerance or physical dependence before the first dose of XARTEMIS XR.
10. Subject has smoked or used nicotine-containing products within 6 months prior to screening as evidenced by medical history.
11. Subject has a history of psychiatric disorders, such as major depression disorder, anxiety disorders, or psychotic disorders requiring hospitalization and/or medication within 6 months prior to screening. A history of attention deficit hyperactivity disorder requiring medication is acceptable.
12. Subject has a diagnosis of epilepsy or other seizure disorder (a history of febrile seizures is acceptable).
13. Subject has had previous cardiothoracic surgery (subjects who have a history of patent ductus arteriosus ligations/surgery as infants are acceptable).
14. Subject has a history of conditions which might be specifically contraindicated or require caution while using OC, APAP, and/or ibuprofen (if used as a rescue medication) per the IB and/or the appropriate package insert.
15. Subject has a history of any drug allergy, hypersensitivity, or intolerance including OC, APAP, ibuprofen or excipients, or any opioid drug product which, in the opinion of the investigator, would place the subject at particular risk and compromise the safety of the subject in the study.

16. Subject has donated or had significant loss of whole blood (480 mL or more) within 30 days of screening (unless they have received a transfusion to correct the blood loss and have hematocrit and hemoglobin within the reference range at screening), or plans to donate blood or plasma during the course of the study.
17. Subject has a documented history of any pathologic, iatrogenic or surgical condition that, in the opinion of the investigator, would compromise the subject's ability to swallow, absorb, metabolize, or excrete XARTEMIS XR, including (but not limited to) intractable nausea and/or vomiting, severe GI narrowing, perforation, obstruction, bleed, or gastric band surgery.
18. Subject has a history of a GI event (eg, perforation, obstruction, bleed) within 6 months prior to screening or any GI event greater than 6 months before screening that, in the opinion of the investigator, would make the subject unsuitable for study participation.
19. Subject has used any product containing OC or APAP within 48 hours prior to the first dose of XARTEMIS XR.
20. Subject has a history of conditions which might be specifically contraindicated or require caution to be used during the administration of APAP or OC including hypersensitivity to OC, or debilitated patients, those with severe impairment of hepatic, pulmonary, or renal function, myxedema or hypothyroidism, adrenocortical insufficiency (Addison's disease), central nervous system (CNS) depression or coma, toxic psychosis, urethral stricture, acute alcoholism, delirium tremens, severe kyphoscoliosis, or biliary tract dysfunction.
21. Subject has any other medical condition, abnormal vital sign (blood pressure, pulse rate, respiratory rate), body temperature, pulse oximetry; or any physical examination or ECG finding at screening which, in the investigator's medical opinion, would preclude safe participation in a clinical study.
22. Subject has received any investigational product or device within 30 days before screening, or is scheduled to receive an investigational device or another investigational drug (other than those in this study) during the course of this study.

13 PRIOR AND CONCOMITANT TREATMENT

The start and stop date and time, dosage, frequency, route of administration, and indication for relevant prior medications (30 days prior to screening) and concomitant medications and therapies (including peri-operative and operative medications/therapies) will be recorded in the source documents and in the electronic case report form (eCRF).

13.1 Prohibited During Study

Prior and Concomitant Medications

Treatment with the following medications and therapies during the study are prohibited:

- Any investigational drug, device and/or experimental therapy (prohibited within 30 days before screening or throughout the study).
- Hormonal contraception and hormonal replacement therapies are prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Any medication that, in the opinion of the investigator, may cause a clinically significant condition when used concomitantly with OC or APAP is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Any medication that is contraindicated (ie, precaution exists against concomitant use, and/or the potential exists for a clinically significant drug-drug interaction with XARTEMIS XR) is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the remainder of the study.
- Any medication that is known to moderately to strongly inhibit or induce CYP2D6 and/or CYP3A4 enzymes (see Attachment 2) is prohibited within 14 days prior to the first dose of XARTEMIS XR and throughout the study. The use of CYP2D6 and/or CYP3A4 inhibitors or inducers is allowed peri-operatively as needed.
- Any medication containing OC or APAP is prohibited within 48 hours prior to the first dose of XARTEMIS XR and throughout the remainder of the study.

- Subject pain should be managed to ensure that any supplemental opioid medication is not needed in the 30 minutes prior to each dose of XARTEMIS XR.

If any nonstudy drug is taken during the study (including peri-operative and operative medications), all pertinent information will be recorded in the eCRF and source documents.

Washout Period: If a subject is taking a prohibited medication prior to enrolling in the study they must discontinue the medication for at least 14 days prior to the first dose of XARTEMIS XR or at least 5 times the half-life of the prohibited medication, whichever is longer.

Foods

Subjects will be instructed to abstain from food containing poppy seeds (eg, muffins, bagels, and cakes) and alcohol for 48 hours prior to the first dose of XARTEMIS XR and through the last blood draw. Subjects will be instructed to abstain from grapefruit or grapefruit juice-containing drinks (including Fresca® and Squirt®) and drinks containing herbal supplements for 14 days prior to in the first dose of XARTEMIS XR through the conclusion of the study.

Food or beverages containing xanthines (eg, coffee, tea, caffeine-containing sodas, colas, chocolate or other caffeinated products) will not be allowed from the completion of the surgical procedure to the conclusion of the study.

Exercise

Subjects will be instructed to refrain from strenuous exercise throughout the duration of the study. Strenuous exercise is defined as any time a subject cannot carry on a conversation without interruption due to heavy breathing or exertion.

13.2 Permitted During Study

Post-surgery opioid rescue pain medication based on study site's standard practice is allowed but should be pre-approved by the MM and the sponsor. Optional rescue medication (ibuprofen) will be supplied for use during the study as needed (200 mg or 400 mg every 4 to 6 hours; maximum individual dose of 1,200 mg per 24 hours). Additional medications will be permitted during the study for the treatment of AEs and pain except as noted in Section 13.1.

Additional analgesia or adjuvant therapies may be administered after taking XARTEMIS XR according to the investigator's clinical practice. These therapies must not conflict with any of the inclusion or exclusion criteria or concomitant medications (These additional therapies must be approved by the MM and sponsor prior to study start, if possible.

13.3 Treatment Compliance

Compliance is monitored by study personnel at the site by mouth and hand checks.

14 PROCEDURES

The schedule of study events is summarized in the Schedule of Events (Table 7-1).

14.1 Dosing

Subjects will receive 2 tablets of XARTEMIS XR every 12 hours up to a maximum of 4 doses. After the first dose of XARTEMIS XR, treatment may be terminated (ie, XARTEMIS XR permanently discontinued) if it is no longer needed for the treatment of pain (ie, if the subject has a NPRS of < 4 from 30 minutes prior through 1 hour after a scheduled XARTEMIS XR dose), or subject is no longer needed for hospital stay, or at any time at the discretion of the subject's parent/guardian. Subjects will switch to the standard of care pain medication if required for further treatment of pain after the fourth dose of XARTEMIS XR.

If the subject is in bed, the subject's head of bed will be elevated as much as possible (at least 45 degrees).

14.2 Confinement

Subjects will enter the study site on the day of check-in and will remain at the hospital as long as a hospital stay is needed per medical reasons. Administrations of XARTEMIS XR will only be given during subject's hospital stay. Once a dose of XARTEMIS XR is administered, subjects should remain at the hospital to provide the PK samples specifically required for the particular dose.

14.3 Screening Procedures

Screening assessments must be performed within 14 days of check-in. The following procedures will be performed at screening:

1. Subject assent (if applicable) and written parental or legal guardian informed consent.
2. Inclusion/exclusion criteria.
3. Demographics.
4. Medical and surgical history.
5. First day of last menstrual period (for postmenarche female subjects only).
6. Concomitant medications, including all medications taken within 30 days before screening.
7. Physical examination.
8. Height and weight.
9. 12-lead ECG.
10. Vital signs (blood pressure, pulse rate, respiratory rate).
11. Body temperature.
12. Pulse oximetry.
13. Clinical laboratory tests.
14. Urine or serum pregnancy test (female subjects only).
15. Adverse events (captured during screening).

14.4 Check-in Procedures

It is acceptable, if it can be arranged, to complete all screening procedures on the same day as check-in. In this situation, the medical and surgical history review, first day of last menstrual period, inclusion/exclusion criteria review, the physical examination, ECG, weight measurement, pregnancy test, and clinical laboratory tests do not need to be repeated during check-in procedures.

At check-in subjects will complete these assessments:

1. Inclusion/exclusion criteria review.
2. Medical and surgical history review.
3. First day of last menstrual period.
4. Physical examination.
5. Weight.
6. 12-lead ECG.
7. Vital signs.
8. Body temperature.
9. Pulse oximetry.
10. Clinical laboratory tests.
11. Urine or serum pregnancy test (female subjects only).
12. Adverse events and concomitant medications.

14.5 Baseline

After completing the surgical procedure and prior to receiving the first dose of XARTEMIS XR, subjects will have these assessments:

1. NPRS (predose assessment must be ≥ 4 for subject to qualify for the study).
2. Continuous pulse oximetry (start) and predose pulse oximetry reading.
3. Vital signs.
4. Body temperature.
5. PK Sampling.
6. Adverse events and concomitant medications review (including all peri-operative and operative medications and events).

14.6 Hours 0 to 36 Procedures

After completing the baseline procedures, subjects will receive their first dose of XARTEMIS XR (Hour 0); subjects will then undergo the following postdose procedures:

1. XARTEMIS XR dosing at Hour 0, Hour 12 (second dose if needed), and Hour 24 (third dose if needed).
2. NPRS.
3. Vital signs.
4. Body temperature.
5. Continuous pulse oximetry and pulse oximetry readings.
6. PK sampling at 15 minutes and 45 minutes (± 5 minutes); and 2, 4, 6, 8, 10, and 12 hours (± 10 minutes) after the first dose of XARTEMIS XR. The 12-hour blood draw must be completed prior to the administration of the second dose of XARTEMIS XR.
7. Baseline PK sampling prior to the third dose of XARTEMIS XR, if applicable.
8. Rescue medication dosing (if needed).
9. Adverse event and concomitant medication review.

Subjects will exit the study if they provide the PK samples following the first dose, and the second or third dose of XARTEMIS XR is not needed, or the hospital stay is not needed. Subjects who require up to and including the fourth dose of XARTEMIS XR will continue with the following procedures.

14.7 Hours 36 to 54 Procedures

For subjects who continue to require XARTEMIS XR for the treatment of pain, the fourth dose of XARTEMIS XR will be administered 36 hours after the first dose. The following procedures will be completed after the fourth dose of XARTEMIS XR.

1. Continuous pulse oximetry until 12 hours after fourth XARTEMIS XR dose and pulse oximetry readings.
2. Vital signs.

3. Body temperature.
4. PK sampling. Within 10 minutes prior to the fourth dose of XARTEMIS XR and at 15 to 30 minutes, 45 to 90 minutes, 2 to 4 hours, and 6 to 8 hours after the fourth dose of XARTEMIS XR. In addition, one sample will be collected during the 12 to18 hour time window after the fourth dose, if further pain medication is not required. If pain medication is still required following the fourth dose of XARTEMIS XR, a sample will be collected at 12hours (± 10 minutes) after the fourth dose, but prior to the next dose of pain medication.
5. Rescue medication dosing (if needed).
6. Adverse events and concomitant medications review.

Subjects will exit the study once the PK samples following the fourth dose of XARTEMIS XR are provided.

14.8 Study Exit or Early Termination Procedures

All subjects will have a complete safety assessment performed at exit (study exit procedures) or at early termination (if applicable). The assessment will include the following procedures:

1. Physical examination.
2. Vital signs.
3. Body temperature.
4. Pulse oximetry.
5. Clinical laboratory tests.
6. Urine or serum pregnancy test (female subjects only).
7. Adverse events and concomitant medication review.
8. Impaired judgment evaluation.
9. Subjects will switch to the standard of care pain medication if further treatment of pain is required after the fourth dose of XARTEMIS XR.
10. Schedule follow-up telephone contact.

14.9 Follow-up (Telephone Contact)

Approximately 7 (± 2) days after receiving the last dose of XARTEMIS XR (or early termination, if applicable) the subject's parent or legal guardian will be contacted by telephone. Information regarding AEs and SAEs experienced and concomitant medications taken since the last dose of XARETEMIS XR or early termination will be recorded.

15 INVESTIGATIONAL MEDICINAL PRODUCT AND NON-INVESTIGATIONAL PRODUCT ADMINISTRATION

15.1 Investigational Medicinal Product (XARTEMIS XR)

Eligible subjects meeting all study entry criteria will be enrolled into the study and will receive the investigational medicinal product XARTEMIS XR as a 2 tablet initial dose, followed with 2 tablets every Q12h for 4 doses as needed for the treatment of pain. Subjects will switch to the standard of care pain medication if required for further treatment of pain after the fourth dose of XARTEMIS XR.

XARTEMIS XR contains a Schedule II controlled substance. XARTEMIS XR will be packaged in a high density polyethylene (HDPE) bottle containing 100 tablets. The bottle will be labeled per regulations with the product name, product lot number, protocol number, recommended storage conditions and the Federal Caution Statement "Caution: New Drug – Limited by Federal (or United States) Law to Investigational Use." The Mallinckrodt Inc. company name and address will be included.

15.2 Non-investigational Product (Ibuprofen)

Optional rescue medication (ibuprofen 200 mg tablets) will be supplied in bulk for use during the study as needed (200 mg or 400 mg every 4 to 6 hours, maximum individual dose of 1,200 mg per 24 hours).

15.3 Methods of Assigning Subjects to Treatment Groups

All subjects will be assigned the same treatment. Each subject will be assigned a unique identifier. The investigator must maintain a subject master log linking the subject identifier to the subject's name. The investigator must follow all applicable privacy laws in order to protect

a subject's privacy and confidentiality. Information that could identify a subject will be masked on material received by the sponsor.

15.4 Dosing Procedures

Subjects will receive 2 tablets of XARTEMIS XR Q12h orally during the treatment phase. Each dose of XARTEMIS XR will be administered with 8 ounces (240 mL) of water. Unsweetened apple juice may be substituted for the water if there is an indication that the subject will not be able to swallow the study drug with water. However, the volume of liquid must be the same (8 ounces) and the substitution must be documented. If the subject is in bed the subject's head of bed will be elevated as much as possible (at least 45 degrees).

Optional rescue medication (ibuprofen 200 mg tablets) may be used as needed during the study. Doses should be 200 mg or 400 mg every 4 to 6 hours (maximum individual dose of 1,200 mg per 24 hours). Each dose of rescue medication should be administered with 8 ounces (240 mL) of water or apple juice.

A hand and mouth check will be conducted by the study site after each dose to ensure all study drug has been consumed.

15.5 Storage and Disposition of Clinical Supplies

XARTEMIS XR and ibuprofen will be maintained in a secure area at the study site. XARTEMIS XR and ibuprofen are to be stored at controlled room temperature at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

15.6 Retention Samples

Per 21 CFR 320.63 and 320.38, retention samples of XARTEMIS XR will be held by the study site or a third party designee. Appropriate retention samples must be stored under conditions consistent with the product labeling for a period of at least 5 years following the date on which the application is approved (or if the application is not approved, for at least 5 years following the date of completion of the study).

15.7 Drug Accountability

In accordance with FDA requirements, the investigator will, at all times, be able to account for all XARTEMIS XR furnished to the study site. A drug accountability record will be maintained for this purpose. The study site must maintain accurate records indicating dates and quantity of XARTEMIS XR received, to whom it was dispensed (subject-by-subject accounting) and accounts of any XARTEMIS XR accidentally or deliberately destroyed. All unused XARTEMIS XR not involved in immediate subject dosing will be maintained under locked storage at the study site in order to comply with FDA guidelines for conducting clinical trial studies in support of new drug applications. Appropriate XARTEMIS XR retention samples must be maintained by the study site or a third party designee under appropriate storage conditions.

All used and unused clinical supply containers will be maintained at the study site until drug accountability is performed by the sponsor. With the exception of retention samples, unused XARTEMIS XR will be returned to the sponsor for final disposition, upon the completion of drug accountability at the study site unless local destruction is agreed to in writing.

15.8 Compliance Monitoring

Compliance is monitored by study personnel at the study site. Subject identification will be verified and subjects will receive each dose of XARTEMIS XR under direct observation. Study compliance will be verified by monitoring.

16 SAFETY

Subjects will be closely monitored for signs of opioid adverse reactions, which include but are not limited to nausea, vomiting, and respiratory depression.

16.1 Adverse Events

In the case of a serious opioid-related AE, naloxone may be administered intravenously to the subject at the investigator's discretion.

Refer to Section 20 for details on the handling of AEs and SAEs.

16.2 Clinical Laboratory Tests

The required clinical laboratory tests are listed in Attachment 1.

Samples for clinical laboratory testing may be collected under fasted or non-fasted conditions for all visits. The date and time of all sample collection must be documented on the laboratory report. Clinical laboratory specimens may be processed at the study site's laboratory or shipped to the core laboratory, as applicable.

Hematology, serum chemistry, and urinalysis samples will be collected at screening, check-in, and at study exit or early termination.

In addition:

- All female subjects will have a serum or urine pregnancy test at the screening, at check-in, and at study exit or early termination. Results must be available prior to dosing with XARTEMIS XR. Subjects with positive results will be ineligible for study entry. If applicable, the subject's agreement to use contraception will be recorded in source documentation.

Out-of-Range Screening Laboratory Values

Screening or check-in laboratory values that are > 2 times the ULN of the reference ranges specified by the clinical laboratory will exclude the subject from the study (with the exception of WBC Differential values). Enrollment of subjects with laboratory values that are between 1 and 2 times the ULN, below the lower limit of normal, or WBC differential > 2 x the ULN will be left to the investigator's discretion. Screening samples for laboratory testing may be redrawn 1 time to confirm out-of-range values.

Out-of-Range Exit Laboratory Values

Study exit/early termination laboratory determinations that fall outside the specified reference ranges will be assessed by the investigator for clinical significance. If the out of range value is deemed to be a clinically significant change from check-in by the investigator, an AE will be recorded. The investigator will continue to monitor the subject until the laboratory value

returns to normal, the investigator determines that follow-up is no longer medically necessary, or the subject is referred to a nonstudy physician. If the investigator determines the abnormal value is not a clinical concern, the investigator's evaluation will be documented and no further action is required.

Unscheduled Clinical Laboratory Tests

Unscheduled clinical laboratory tests may be performed as deemed clinically necessary by the investigator. The unscheduled laboratory tests date and time of collection will be recorded.

16.3 Medical and Surgical History

Medical and surgical history will be obtained at screening. Medical history will include a review of the following systems: general, dermatological, head, eyes, ears, nose, and throat (HEENT), respiratory, cardiovascular, GI, genitourinary, gynecological, endocrine, musculoskeletal, hematological, neuropsychological and immune (allergies). Historical and current medical conditions will be recorded in the source documents and eCRF.

At check-in each subject's medical history will be reviewed and updated to include any changes since screening. The surgical procedure that is the subject of this study will be included in the subject's medical history.

16.4 Date of First Day of Last Menstrual Period

The date of the first day of the last menstrual period for post-menarche female subjects will be recorded at screening and check-in.

16.5 Demography

The date of birth, gender, race, and ethnicity of each subject will be recorded at screening.

16.6 Height, Weight and BMI

Each subject's height and weight will be measured at screening, and weight will be measured at check-in. BMI will be calculated using the following formula:

$$\text{weight (kg)}/[\text{height (m)}]^2 \quad \text{OR} \quad \text{weight (kg)}/[\text{height (cm)}]^2 \times 10{,}000$$

16.7 Physical Examination

A brief physical examination, including: HEENT, general appearance, skin, neck, throat, chest, heart, abdomen, extremities, and neurological will be done at screening, check-in, and study exit or early termination. The date and time and findings of screening, check-in and exit physical examinations will be recorded.

Any change from values obtained at the screening that is considered clinically significant by the investigator will be recorded as an AE.

16.8 Vital Signs

Vital signs will be obtained after the subject has been seated or reclined for a minimum of 5 minutes (minimum) and will include systolic and diastolic blood pressures (mm Hg), pulse rate (beats/min), and respiratory rate (breaths/min). Both the date and time for all vital sign measurements will be documented.

Vital signs will be measured at the screening; check-in; within 15 minutes prior to the first and fourth doses of XARTEMIS XR; at 1, 2, and 4 hours (± 15 minutes) after the first and fourth doses of XARTEMIS XR; within 15 minutes prior to and 2 hours (± 15 minutes) after the second and third doses of XARTEMIS XR; and at study exit or early termination.

Screening Vital Signs

Vital signs should be within an acceptable range as determined by the investigator for the subject's age. A subject with clinically significant vital sign abnormalities as determined by the investigator at screening or check-in does not qualify for the study. However, abnormal screening/baseline vital signs may be repeated once. For ambulating subjects, repeat the vital signs after the subject has remained seated for approximately 5 minutes with feet on the floor and arm supported at heart level, if possible.

On-Study Vital Signs

If an on-study vital sign value is deemed to be a clinically significant change from baseline by the investigator or requires a change in the subject's clinical management during the study, an AE will be recorded. The investigator will continue to monitor the subject until the

measurement returns to normal, or the investigator determines that follow-up is no longer medically necessary, or the subject is referred to a nonstudy physician. If the investigator determines the change is not clinically significant, the investigator's evaluation will be documented and no further action is required.

Unscheduled Vital Sign Assessments

Additional unscheduled vital sign measurements may be performed as deemed clinically necessary by the investigator. The date, time, and results of any unscheduled vital signs will be recorded.

16.9 Body Temperature

Body temperature will be measured at screening; check-in; within 15 minutes prior to the first and fourth XARTEMIS XR doses; at 1, 2, and 4 hours (±15 minutes) after the first and fourth XARTEMIS XR); within 15 minutes prior to and 2 hours (±15 minutes) after the second and third doses of XARTEMIS XR; and at study exit or early termination. The same method of measurement will be used for all assessments for a single subject.

Screening Temperature

Body temperature should be within an acceptable range as determined by the investigator for the subject's age. A subject with clinically significant abnormal body temperature as determined by the investigator at screening, check-in or baseline will be excluded from participation in the study. An out-of-range temperature may be repeated once approximately 5 minutes following the initial assessment.

On-study Temperature

If an on-study temperature value is deemed to be a clinically significant change from baseline by the investigator or requires a change in the subject's clinical management during the study, an AE will be recorded. The investigator will continue to monitor the subject until the measurement returns to normal, or the investigator determines that follow-up is no longer medically necessary, or the subject is referred to a nonstudy physician. If the investigator

determines the change is not clinically significant, the investigator's evaluation will be documented and no further action is required.

Unscheduled Temperature Assessments

Additional unscheduled temperature measurements may be performed as deemed clinically necessary by the investigator. The date, time, and results of any unscheduled temperature measurements will be recorded.

16.10 Pulse Oximetry

Percentage of oxygen saturation will be determined by a single pulse oximetry reading at screening, check-in, and study exit or early termination. Continuous pulse oximetry will be initiated within 15 minutes prior to the first dose of XARTEMIS XR and continue until 12 hours after the fourth dose of XARTEMIS XR (or early termination, if appropriate). Oxygen saturation (%) will be recorded within 15 minutes prior to dosing and 1, 2, and 4 hours after the first and fourth doses of XARTEMIS XR; and within 15 minutes prior to and 2 hours (± 15 minutes) after the second and third doses of XARTEMIS XR.

Out-of-range Screening Pulse Oximetry

A subject with a screening, check-in or baseline pulse oximetry below 95% saturation will be excluded from participation in the study. An out-of-range screening pulse oximetry may be repeated once approximately 5 minutes following the initial assessment.

Out-of-range On-study Pulse Oximetry

A subject with on-study oxygen saturation < 92% must have pulse oximetry repeated once approximately 5 minutes after the initial assessment. Supplemental oxygen will be administered to any subject whose pulse oximetry upon repeat evaluation remains less than 92% and should be titrated to maintain the subject's baseline pulse oximetry. This level of hypoxia will be considered an AE. The investigator will continue to monitor the subject until the pulse oximetry returns to normal, the investigator determines that follow-up is no longer medically necessary, or the subject is referred to a nonstudy physician. Trained site personnel

will be available to respond to subject emergencies during the period of confinement, in addition to having a crash cart and emergency equipment in close proximity.

16.11 Electrocardiogram

A 12-lead ECG will be obtained for all subjects at screening, check-in, and study exit or early termination. The date and time of the ECG must be documented on the ECG tracing. An appropriately trained and experienced physician must interpret this ECG. Date, time, and clinical parameters from all ECG's will be entered on the eCRF.

Abnormal Screening or Check-in ECG

A subject with an abnormal screening or check-in ECG which is considered clinically significant by the investigator will be excluded from study entry. A repeat ECG may be done to confirm findings. Subjects with ECG abnormalities not considered clinically significant may be enrolled if mutually agreeable to the investigator and MM.

Abnormal Study Exit or Early Termination ECG

A subject with changes in the ECG since the screening and/or check-in assessments will have a repeat ECG approximately 15 minutes following the initial assessment. If the subject's ECG has not returned to baseline or resolved following the repeat measurement, site personnel will immediately notify the investigator of the abnormal measurement. An AE will be opened if the investigator determines the change is clinically significant or requires a change in the subject's clinical management. The investigator will continue to monitor the subject until the measurement returns to normal, or the investigator determines that follow-up is no longer medically necessary, or the subject is referred to a nonstudy physician. If the investigator determines the change is not clinically significant, the investigator's evaluation will be documented and no further action is required.

Unscheduled ECG Assessments

Additional ECGs may be performed any time throughout the study if deemed necessary to document or follow-up an adverse reaction.

16.12 Pain Evaluation

Pain will be evaluated by the subject using NPRS (Attachment 3) scores. Pain assessments should always be completed prior to all other procedures at any given time point.

Baseline Pain Scores

Subjects with a baseline NPRS score of < 4 will be excluded from participation in the study.

On-study Pain Scores

Pain will be evaluated by the subject using NPRS scores within 10 minutes prior to and 1, 2, 4, and 8 hours (± 15 minutes) after the first XARTEMIS XR dose.

After the first dose of XARTEMIS XR, pain will be evaluated using the NPRS within 30 minutes prior to the scheduled time of each subsequent XARTEMIS XR dose at 12, 24, and 36 hours. If the pain score is ≥ 4, subjects will receive the next dose as scheduled. If the pain score is < 4, the NPRS will be repeated every 30 minutes (± 5 minutes) and subjects will receive their XARTEMIS XR dose when and if their pain score is ≥ 4. The pain scores can be repeated up to 1 hour after the scheduled dosing time. Subjects whose pain scores remain < 4 during this time will not qualify for further study drug administration, but will have blood collected for PK analysis only at 10 minutes prior to the originally scheduled dosing time. No additional blood will be collected for PK and subjects are eligible to stay in the study and continue to have all safety assessments until study exit or may proceed to early termination assessments.

If dosing is delayed as outlined above, all subsequent doses will be administered as per the original schedule (ie, 12, 24, and 36 hours after the first XARTEMIS XR dose).

16.13 Impaired Judgment Evaluation

To ensure subject safety, subjects will be evaluated for the presence of lightheadedness, dizziness, sedation, confusion, visual disturbances, weakness or uncoordinated muscle movements prior to leaving the study site after the last blood draw and completion of study exit procedures. The impaired judgment evaluation also will be administered to subjects at Early Termination.

The presence of any of the above symptoms should be recorded as an AE and will necessitate continued confinement of the subject until such symptoms have ceased. The date and time of the impaired judgment evaluation will be documented. Subjects will be discharged when deemed appropriate by the investigator.

17 PHARMACOKINETICS

17.1 Blood Collection and Processing

Whole blood (2 mL) will be collected in prechilled vacuum blood collection tubes, containing K_2EDTA as the anticoagulant. Blood will be collected for determination of plasma concentrations of OC and APAP.

17.1.1 Single Dose PK Sampling

Blood samples will be collected within 10 minutes prior to the first dose of XARTEMIS XR; at 15 and 45 minutes (± 5 minutes); and at 2, 4, 6, 8, 10, and 12 hours (± 10 minutes) after the first dose of XARTEMIS XR. The 12-hour blood sample must be collected at the scheduled time prior to the second XARTEMIS XR dose even though the actual time of dosing is dependent on subject's pain score (see Section 16.12). The time and date of collection for each sample will be recorded.

17.1.2 Multiple Dose PK Sampling

Venous blood samples for PK analysis will be collected within 10 minutes prior to the scheduled time of administration of the third and fourth dose of XARTEMIS XR, even though the actual time of dosing is dependent on subject's pain score (see Section 16.12).

Additional blood samples for PK analysis will be collected at 15 to 30 minutes, 45 to 90 minutes, 2 to 4 hours, and 6 to 8 hours after (± 10 minutes) after, the fourth dose of XARTEMIS XR. In addition, one sample will be collected during the 12 to 18 hour time window after the fourth dose, if further pain treatment is not required. If further treatment for pain is required, the final blood sample will be collected at 12 hours (± 10 minutes) after the fourth dose, but prior to the any further pain treatment.

It is recommended that an indwelling intravenous catheter (eg, Hepwell/Hep-lock) be placed to reduce subject discomfort associated with multiple blood samplings.

17.1.3 Total Volume of Blood Collected

Subjects will have an estimated maximum total of approximately 50 mL of blood drawn during the course of the study (32 mL for PK sampling and 18 mL for laboratory safety assessments). This estimated maximum total blood volume to be drawn from subjects is well within the limits specified by multiple organizations and IRBs, including the National Institutes of Health Clinical Center, which recommends that total blood to be drawn for research purposes be less than 7 mL/kg per 6 weeks (and < 450 mL) and less than 3 mL/kg per single blood withdrawal.

17.1.4 Sample Processing and Shipping

Specific instructions for sample processing and shipping will be provided in a separate document.

17.2 Pharmacokinetic Analysis

17.2.1 Bioanalytical Methodology

The samples for measurement of OC and APAP will be analyzed by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. The lower limit of quantification is 0.100 ng/mL for OC and 100 ng/mL for APAP. The quantitative LC-MS/MS method uses APAP-d_4 and OC-d_6 as the internal standards. The method has been validated for linearity, precision, accuracy, ruggedness, recovery, and specificity. In addition, stability studies have been carried out under short- and long-term conditions. The method has been adequately validated for the analysis of plasma samples from this study.

17.2.2 Pharmacokinetic Parameters

Pharmacokinetic parameters will be evaluated for PK analysis population. The PK parameters to be estimated will include the following:

Single Dose PK (Noncompartmental Analysis):

The following single-dose PK parameters will be determined for OC and APAP after the first dose of XARTEMIS XR (predose at 0 hour to12 hours postdose) using noncompartmental analysis:

- Area under the concentration-time curve over the first dosing interval ($AUC_{0\text{-}12h}$).
- Time delay between drug administration at Hour 0 and the onset of absorption (t_{lag}).
- Observed maximum drug concentration (C_{max}).
- Time of maximum observed plasma concentration (T_{max}).
- Apparent terminal elimination half-life ($t_{1/2}{}^{x}$).
- Apparent terminal elimination rate constant (λ_X).

No value for λ_x and $t_{1/2}{}^{x}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile or if the coefficient of determination (r^2) < 0.90. The λ_x will not be estimated if there are less than 3 time points in the terminal log-linear phase (not including T_{max}).

- The plasma concentrations of OC and APAP will be analyzed for each subject using noncompartmental analysis methods. The C_{max} and T_{max} will be determined directly from the observed concentration data. The λ_x will be estimated by a log-linear regression of the terminal monoexponential portion of the observed plasma concentrations after the first. The half-life will be calculated as $0.693/\lambda_x$. Using the single-dose data, the area under the concentration-time curve from 0 to 12 hours after the first dose ($AUC_{0\text{-}12h}$) will be calculated.

Single/Multiple Dose PK (Population PK Analysis):

Population PK analyses will be conducted via nonlinear mixed effect modeling using the nonlinear mixed-effects modeling software NONMEM®, Version 7 or higher ([redacted]). Adult PK data from XARTEMIS-XR Phase1 studies will be utilized for developing the initial models for both OC and APAP. A covariate analysis will be undertaken to determine the contribution of demographic and disease characteristics to variability in OC and APAP PK. Individual predicted OC and APAP PK parameters (clearance

and volume of distribution) and exposure metrics(minimum plasma concentration at steady-state, the peak plasma concentration at steady state, the average concentration at steady-state, the area under the plasma time concentration curve at steady-state and other parameters) will be derived from the final model.

18 LABORATORY DETERMINATIONS

Refer to the Schedule of Study Events (**Error! Reference source not found.**) for time points for collection of laboratory test samples. Attachment 4 lists clinical laboratory tests required for this study.

19 STATISTICAL METHODS AND PLANNED ANALYSIS

19.1 General Considerations

Data from the site(s) will be listed, analyzed, and included in the clinical study report.

Descriptive statistics for continuous variables will include number of values (N), mean, SD, median, minimum, and maximum, unless otherwise noted. Frequency and percentages will be calculated for categorical variables. All statistical significance testing will be two-tailed using $\alpha = 0.05$, unless otherwise specified. Data summary and analyses will be performed with SAS® 9.2 or higher.

19.2 Analysis Populations

The following populations will be identified and analyzed in this study:

- Safety Population – all subjects enrolled in the study that received any quantity of XARTEMIS XR. This population will be used as the primary safety population.

- PK Population - all subjects who received at least 1 dose of XARTEMIS XR and have provided at least 1 blood samples for the measurement of OC and APAP. This population will be used to for population PK analysis.

- Single-dose PK population – All subjects who received at least one dose of XARTEMIS XR and have provided at least 6 blood samples for measurement of OC and APAP after

the first dose of XARTEMIS XR. This population will be used for single-dose PK analysis.

- Modified Intent-to-Treat (mITT) Population – All subjects who received at least 1 dose of XARTEMIS XR and have at least 1 postbaseline pain intensity measurement. This population will be used for analysis of pain intensity.

19.3 Subject Characteristics

19.3.1 Demographics

Subjects in the Safety Population will be included in a listing of subject demographic characteristics (including frequencies and percentages of subjects in three age groups: 12 to 13, 14 to 15, and 16 to 17 years of age). Summary statistics will be presented for the Safety Population.

19.3.2 Medical and Surgical History

The medical and surgical history data will not be summarized but will be presented in a data listing for subjects in the Safety Population.

19.3.3 Concomitant Treatments

Concomitant treatments will not be summarized but will be presented in a data listing for subjects in the Safety Population.

19.3.4 Subject Disposition and Exposure to XARTEMIS XR

The number of subjects who complete the study and who do not complete the study, both overall and according to reasons for discontinuation from the study, will be summarized for the Safety Population. Subject disposition will be presented in a data listing. The number of subjects who received any treatment as well as the number of doses received will also be summarized. The number of subjects from each analysis population will be summarized and presented.

19.4 Pharmacokinetic and Statistical Analysis

Single dose PK parameters will be summarized using the Single-dose PK Population. Population PK parameters will be summarized using the PK Population. In addition, individual plasma OC and APAP concentrations will be summarized at each time point

Descriptive statistics reported will include the arithmetic mean, SD, CV, geometric mean, minimum, maximum, and median. The geometric mean will not be reported for T_{max} and t_{lag}.

Individual concentration plots and mean data graphs will be produced using both linear and semilogarithmic scales.

19.5 Safety Analysis

Safety listings will report data from subjects in the Safety Population. Safety summary tables will be presented for both the Safety Population.

19.5.1 Adverse Events

Adverse events will be coded using MedDRA. All AEs will be presented in a data listing. Only treatment emergent adverse events (TEAEs) will be included in all summaries.

TEAEs will be defined as an event that emerges during treatment having been absent pretreatment, or worsens relative to the pretreatment state (ie, occurring after the first administration of XARTEMIS XR).

Treatment emergent adverse events, treatment related TEAEs, severity of TEAEs, and TEAEs leading to early discontinuation will be summarized by system organ class and preferred term for all dosed subjects. All TEAEs leading to early discontinuation will be presented in data listings.

For this study, the hospitalization for the qualifying study procedure is not considered an AE.

19.5.2 Clinical Laboratory Tests

Summary statistics for clinical laboratory tests will be calculated at each assessment time point as well as for their changes from baseline for hematology and serum chemistry test

results. Clinically significant changes from baseline assessed as AEs will be presented in a data listing.

19.5.3 Physical Examination Findings

Clinically significant changes from baseline assessed as AEs will be presented in a data listing.

19.5.4 Electrocardiogram Findings

ECG measures at each assessment time point and changes from baseline (predose) for the measures of heart rate, PR interval, QRS interval, QT interval corrected for heart rate using Bazett's formula, and RR interval at each time point will be summarized. Clinically significant changes from baseline assessed as AEs will be presented in a data listing.

19.5.5 Vital Signs, Temperature and Pulse Oximetry

Actual values and changes from baseline for vital signs (diastolic blood pressure, systolic blood pressure, respiratory rate, pulse rate), body temperature, and pulse oximetry will be summarized for each time point.

19.5.6 Impaired Judgment Evaluation

The impaired judgment evaluations will not be presented in a data listing.

19.6 Pain Intensity Analysis

Pain intensity scores (NPRS), as well as pain intensity score change from baseline, will be summarized by time point using the mITT population. No imputation of missing values or adjustment from the impact of rescue medication use will be used.

19.7 Interim Analysis

No interim analysis of the data is planned.

19.8 Statistical Power and Sample Size Considerations

Clearance and volume of distribution were computed for OC and APAP in two XARTEMIS XR adult PK studies (Studies COV15000171 and COV15000256). The point estimate of the standard deviation for the volume of distribution for APAP was the highest among the standard deviations of these two log-transformed PK parameters (0.41). Therefore, a conservative estimate for the standard deviation of 0.50 is used.

In order to target a 95% CI within 60% and 140% of the geometric mean estimates of the clearance and volume of distribution for XARTEMIS XR with 80% power, a total of 14 subjects must complete dosing (2 or more doses), PK blood collections and provide PK data (Wang et al 2012).The sample size of 48 enrolled subjects is planned to result in at least 25 subjects receiving 2 or more doses of XARTEMIS XR. It is estimated that in order to enroll 48 subjects, approximately 72 individuals will need to be screened.

19.9 Deviations From Statistical Analysis Plan

Any deviations from the planned statistical analysis will be described and justified in the final clinical study report as appropriate.

20 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

20.1 Safety

For safety information on XARTEMIS XR, refer to the most recent versions of the IB and PI (MNK-795 IB 2014, XARTEMIS XR PI 2014). For the ibuprofen rescue medication (if used), the PI (Ibuprofen PI 2014) will be used as the reference for safety information.

20.2 Definitions

20.2.1 Adverse Event

An AE is any untoward or undesirable medical occurrence in a subject who is administered an investigational medicinal product, which does not necessarily have to have a causal relationship with this treatment. Examples of AEs include but are not limited to:

- Clinically significant laboratory findings

- Clinically significant changes in physical examination findings
- An AE occurring due to investigational medicinal product overdose whether accidental or intentional
- An AE occurring from investigational medicinal product abuse
- An AE associated with investigational medicinal product withdrawal

20.2.2 Unexpected Adverse Event

An unexpected AE is defined as an AE, the nature and severity of which is not consistent with the applicable product information in the most recent version of the Investigator's Brochure and the appended package insert.

20.2.3 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose results in any of the following outcomes:

- Death.
- A life-threatening AE.
- Inpatient hospitalization or prolongation of existing hospitalization.
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- Results in a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency department or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

20.2.4 Death

Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE Form. All causes of death must be reported as SAEs. The investigator should make every effort to obtain and send death certificates and autopsy reports to Mallinckrodt.

20.2.5 Life-threatening Event

A life-threatening event refers to immediate risk of death as the event occurred per the reporter. A life-threatening event does not include an event that, had it occurred in a more severe form, might have caused death but, as it actually occurred, did not create an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

20.2.6 Hospitalization

Hospitalization is defined as an official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes a criterion for an AE to be serious; however, it is not in itself considered an SAE. In absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported by the investigator as an SAE. Such situations include, but are not limited to, the following:

- A hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
- A hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (eg, stent removal after surgery). This should be recorded in the study file.
- A hospitalization for a preexisting condition that has not worsened.

Note that the following hospitalizations are not considered SAEs in Mallinckrodt clinical studies:

- A visit to the emergency department or other hospital department of less than 24 hours that does not result in admission (unless considered "important medical event" or life-threatening event).

20.3 Adverse Event and Serious Adverse Event Classifications

20.3.1 Investigational Medicinal Product Relatedness

The following classifications should be used when evaluating the relationship of AEs or SAEs to study treatment (Table 20-1).

Table 20-1: Adverse Event Relationships

Relationship	Definition
Not Related	No relationship between the experience and the administration of study treatment; related to other etiologies such as concomitant medications or subject's clinical state.
Unlikely Related	The current state of knowledge indicates that a relationship is unlikely.
Possibly Related	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject.
Related	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment and can be confirmed with a positive re-challenge test or supporting laboratory data.

20.3.2 Severity Assessment

For purposes of consistency, if required the investigator may use the intensity grades presented in Table 20-2.

Table 20-2: Adverse Event Severity Grades

Grade	Definition
Mild	Does not interfere with subject's usual function and activities
Moderate	Interferes to some extent with subject's usual function and activities
Severe	Interferes significantly with subject's usual function and activities

If an AE increases in severity (eg, from moderate to severe); decreases in severity (eg, changes from moderate to mild); or there is a change in seriousness, a new AE will be opened and the original AE will be closed. If an AE is still ongoing at the time of a subject's completion of the follow-up telephone call, the event will be marked as ongoing in the eCRF and the resolution/stop date and time will be left blank.

To ensure there is no confusion or misunderstanding of the difference between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided:

The term "severe" is used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical importance (such as a severe headache). This is not the same as "serious," which is based on the subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

20.4 Adverse Event and Serious Adverse Event Collection, Recording and Reporting

AEs and SAEs will be collected from signing of the ICF through completion of the follow-up telephone call, which will take place 7 (± 2) days after the last dose of XARTEMIS XR or early termination. The investigator is required to collect the AE or SAE regardless of the severity of the event or its relationship to study treatment. The investigator must follow up on all AEs and SAEs until the event has resolved or stabilized, or at such time the investigator refers the subject to a nonstudy physician (see Section 20.4.2.2). The investigator will document the further follow-up information in the subject's source document.

During the period specified above, the investigator will:

- Collect all AEs and SAEs on the source documents.
- Record all AEs and SAEs in the source documents from the signing of the ICF through the completion of the follow-up telephone call. Record all AEs and SAEs in the eCRF from the time subject receives at least the first dose of XARTEMIS XR through the completion of the follow-up telephone call for all subjects who are enrolled in the study.
- Report all SAEs on the SAE Report Form to Mallinckrodt Pharmacovigilance.
- Report all pregnancies on the Pregnancy Surveillance Form to Mallinckrodt Pharmacovigilance.
- Submits the Safety Alert from Mallinckrodt Pharmacovigilance to the IRB.

The reporting requirements for AEs are summarized in Table 20-3.

Table 20-3: Reporting Requirements for Adverse Events

Seriousness	Reporting Time	Type of Report
All Serious	Within 24 hours of first knowledge of event	Initial report on the SAE Form, appropriate eCRF, and source document
	Within 24 hours of receipt of follow-up information	Follow Up report on the SAE Form, appropriate eCRF, and source document
Nonserious	Per case report form submission procedure	Appropriate eCRF and source document

20.4.1 Adverse Events

Adverse events can be reported spontaneously or elicited during open-ended questioning (ie, "How have you been feeling since your last visit?"), examination, or evaluation of a subject. Signs and symptoms must be recorded using standard medical terminology. For subjects incapable of giving consent, the legally acceptable representative may provide information regarding the subject's status.

All fields on the AE eCRF page should be completed for each event with a full description of the event and date and time of onset/start and resolution/stop. A medical diagnosis if known, should be recorded in lieu of each individual sign and symptom associated with the diagnosis and experienced by the subject. If no medical diagnosis is known, the term used by the subject to describe the event or signs noted by the site personnel should be recorded.

20.4.2 Serious Adverse Events

20.4.2.1 Initial Reporting

Serious adverse events (based on FDA/ICH definition of an SAE) require immediate reporting to Mallinckrodt or designated representative.

- For all fatal or life-threatening events, the investigator, or designee, must report information to the MM.
- For all SAEs, the investigator, or designee, must complete the SAE Report Form with the minimum information required by FDA and ICH and fax it to Mallinckrodt at 314-654-5759 within 24 hours of first knowledge of the event even if the experience does not appear to be related to the investigational medicinal product.
- The investigator, or designee, will receive acknowledgement of receipt of the SAE Report Form from Mallinckrodt.
- Should the investigator or designee have any difficulty in sending the SAE Report, they may contact Mallinckrodt Drug Safety at 800-778-7898 (24 hour call center) or email: GlobalPV@mallinckrodt.com.
- If there is any doubt about whether the information constitutes an SAE, the information is to be treated as an SAE.

20.4.2.2 Follow Up Reporting

- The investigator or designee must complete an SAE Report Form for all follow-up information received and fax it to the sponsor 314-654-5759 within 24 hours of receipt (eg, detailed written descriptions that include copies of relevant subject records, autopsy reports and other supporting documents). The investigator(s) or designee will receive acknowledgement of receipt for each SAE Report Form from Mallinckrodt.

- The investigator or designee is required to provide all related information/supporting documentation of an SAE until the SAE is resolved or stabilized. If the subject has been referred to a nonstudy physician for follow-up treatment, the Mallinckrodt Pharmacovigilance physician may request additional information as applicable.
- The investigator(s) or designee is required to submit the Safety Alert Form to the responsible IRB/Independent Ethics Committee.
- The sponsor will submit safety reports to the FDA.

20.5 Pregnancy Reporting

Certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated. This includes the following:

- Pregnancy exposure to an investigational medicinal product, except for exposure to prenatal vitamins. Subjects should not become pregnant during the study. If the subject becomes pregnant, study treatment must be discontinued immediately. The investigator must report the pregnancy by submitting the appropriate form to Mallinckrodt, or designated representative, within 24 hours of confirmation of a pregnancy (ie, positive serum pregnancy test result). The outcome of pregnancy (eg, spontaneous abortion, live birth, still birth, congenital anomalies, birth defects) must be reported by submitting the appropriate form to Mallinckrodt or designated representative within 24 hours of the pregnancy outcome being submitted to the study site. If the pregnancy results in a live birth, a post-delivery follow-up will be performed at least 28 days after the baby is born and must be reported to Mallinckrodt within 24 hours of the study site becoming aware of the follow-up information. Both maternal and paternal investigational medicinal product exposures are collected. Pregnancy exposure information is collected even if the investigational medicinal product is not contraindicated for use in pregnancy.

21 SUBJECT DISCONTINUATION OR WITHDRAWAL

21.1 Subject Withdrawal

Subjects who discontinue, or are withdrawn from the study for any reason, will be required to have the exit safety assessments to assess their continued well-being. They will receive all

scheduled safety assessments including an impaired judgment evaluation prior to release from the study site unless the subject withdraws consent.

A subject may be discontinued from the study for the following medical or administrative reasons. The reason for discontinuation will be recorded.

Withdrawal by Subject:

Subjects will be free to discontinue from the study at any time. Subjects who have received at least one dose of XARTEMIS XR but do not complete the study will not be replaced.

Pain Score < 4:

Subjects who have NPRS scores of < 4 from 30 minutes prior to through 1 hour after any scheduled XARTEMIS XR dose will not qualify for further study drug administration, but will have blood collected for PK analysis only at 10 minutes prior to the originally scheduled dosing time. No additional blood will be collected for PK. Subjects are eligible to stay in the study and continue to have all safety assessments until study exit or may proceed to early termination assessments.

Adverse event:

If a dosed subject suffers an AE that, in the judgment of the investigator, sponsor or MM, presents an unacceptable consequence or risk to the subject, the subject will be discontinued from further participation in the study.

Emesis:

If a subject experienced emesis before dosing, the subject will be discontinued. If the subject experiences emesis within 12 hours after the first dose the subject may be considered intolerant to the drug. No further PK blood samples will be collected, no further dosing attempts will be made and the subject will be discontinued from the study. If the subject experiences emesis more than 12 hours after the first dose the subject will be allowed to discontinue from the study or continue in the study if his or her legal guardian so chooses with consent of the investigator. Any emesis experienced at any point during the study will be considered an AE.

Death:

In the event that a subject dies during the study, death will be the reason for discontinuation.

Lost to Follow-up:

If at any point during the study a subject cannot be contacted, the subject will be considered lost to follow-up.

Protocol Violation:

If at any point during the study a subject is determined to have been erroneously enrolled into the study, the subject will be discontinued from the study.

Met Withdrawal Criteria:

If a subject develops any of the exclusion criteria (Section 12.2) or fails to meet an inclusion criterion (Section 12.1) during the study that is not considered to be an AE or is noncompliant, the subject will be discontinued from further participation in the study.

Other:

If the above reasons are not applicable, please use the "Other" option and provide the appropriate reason for subject withdrawal.

If a subject's parent or legal guardian refuses to allow the subject to remain in the study site for safety assessments after being discontinued or withdrawn from the study, the subject's parent or legal guardian will be asked to sign a release acknowledging the subject left the clinical facility against medical advice.

For subjects who discontinue or are withdrawn from the study for any reason, the investigator will notify the sponsor. Subjects are eligible to stay in the study and continue to have all safety assessments until study exit or may proceed to early termination assessments.

22 STUDY SUSPENSION, TERMINATION, AND COMPLETION

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor and the IRB and provide them with a detailed written explanation. Upon study completion, the investigator will provide the sponsor, IRB, and regulatory agency with final reports and summaries as required by regulations. For Investigational New Drug Application studies, or when the data will be used in support of an Investigational New Drug Application, the investigator must submit a written report to the sponsor and the IRB within 3 months after the completion or termination of the study. Study termination and follow-up will be performed in compliance with Mallinckrodt standard procedures.

23 PROTOCOL AMENDMENTS

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB and sponsor approval except when necessary to eliminate apparent immediate hazards to the subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB within 5 working days, and submitted to the appropriate regulatory agency in the required time frame.

24 QUALITY CONTROL AND ASSURANCE

The sponsor performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel and the investigator review the protocol, the IB, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these study site visits, information recorded in the eCRFs will be verified against source documents.

24.1 Study and Study Site Discontinuation Criteria

The sponsor, investigator, MM or FDA officials may discover conditions during the study that indicate that the study or study site should be terminated. This action may be taken after appropriate consultation between the sponsor and investigator. Conditions that may warrant termination of the study/study site include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- The decision on the part of the sponsor to suspend or discontinue testing, evaluation or development of the investigational medicinal product.
- Failure of the investigator to enroll subjects into the study at an acceptable rate.
- Failure of the investigator to comply with pertinent FDA regulations.
- Submission of knowingly false information from the study site to the sponsor, study monitor, or FDA.
- Insufficient adherence to protocol requirements

Study/study site termination and follow-up will be performed in compliance with Mallinckrodt SOPs.

25 DIRECT ACCESS, DATA HANDLING, AND RECORD-KEEPING

25.1 Investigator

The investigator will permit study-related monitoring, audits, IRB review, and regulatory inspections by providing direct access to original source data and documents.

All subject information will be recorded on source documents. The eCRFs must be fully completed and include all required data for all subjects enrolled. All eCRF data must be submitted to the sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

Any significant changes in study personnel will require an updated Statement of Investigator (ie, FDA form 1572), which will be filed with the sponsor

The investigator must notify their IRB of protocol violations in accordance with local regulatory and IRB requirements.

25.2 Sponsor

The eCRF data are stored in a database and processed electronically. The sponsor's MM reviews the data for safety information. The data are reviewed for completeness, and logical consistency. Automated validation programs will identify missing data, out-of-range data, and other data inconsistencies. Clinical laboratory data may be processed electronically. Requests for data clarification are forwarded to the study site for resolution.

26 SUBJECT INJURY

In general, subject to specific provisions in the clinical trial agreement, if a subject is injured as a direct result of an investigational medicinal product, the sponsor will pay for reasonable and necessary medical treatment for the injury, to the extent that such expenses are not covered by the subject's medical insurance, a government program, or other responsible third party. If laws or regulations of the locality in which the study is taking place require additional payment of expenses, the sponsor shall comply with such laws or regulations. Where applicable, the sponsor has taken specific national insurance.

27 RECORDS RETENTION

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential. Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational medicinal product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained. Prior to destruction of any study essential documents, the investigator must first obtain written approval from the sponsor.

28 BIOLOGICAL SAMPLES

Blood samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the subject's identity. After the study ends, the clinical laboratory samples will be destroyed. Bioanalytical samples (ie, plasma) for measurement of drug/metabolite content will be retained for 5 years at a biological storage facility. The subject may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from that sample will still be used for this research.

29 PUBLICATION POLICY

29.1 Sponsor's Publication Policy

The sponsor's policy is to publish or otherwise communicate the results of its hypothesis-testing clinical studies, regardless of outcome, for marketed products, compound(s) or product(s) being investigated that are later approved for marketing. Hypothesis-testing clinical studies are those studies intended to provide meaningful results by examining prestated questions using predefined statistically valid plans for data analysis, thereby providing firm evidence of safety and/or efficacy to support product claims.

Exploratory studies, in contrast, serve to set direction for possible future studies. They have significant statistical limitations, provide only preliminary information about a disease, condition, or product, and are not designed to provide final conclusions on product claims. The sponsor does not commit to publish or otherwise communicate the results of every exploratory study, because this information is of an exploratory nature and often highly proprietary. However, if information from an exploratory study is of significant medical importance, the sponsor will publish or otherwise communicate the results.

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

29.2 Investigator's Ability to Publish

Terms and provisions of publication rights are governed by the Publication Section in the clinical trial agreement.

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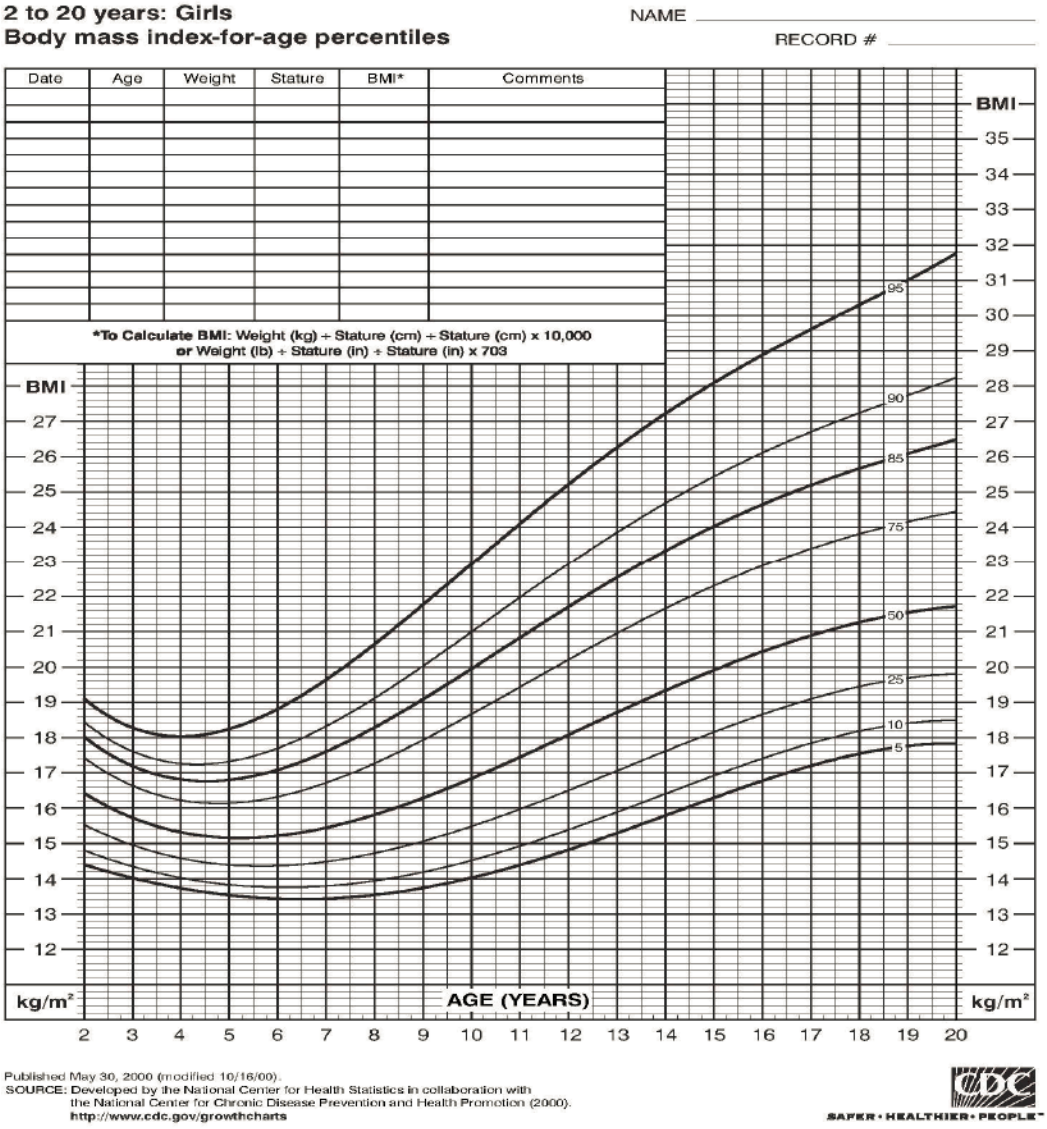
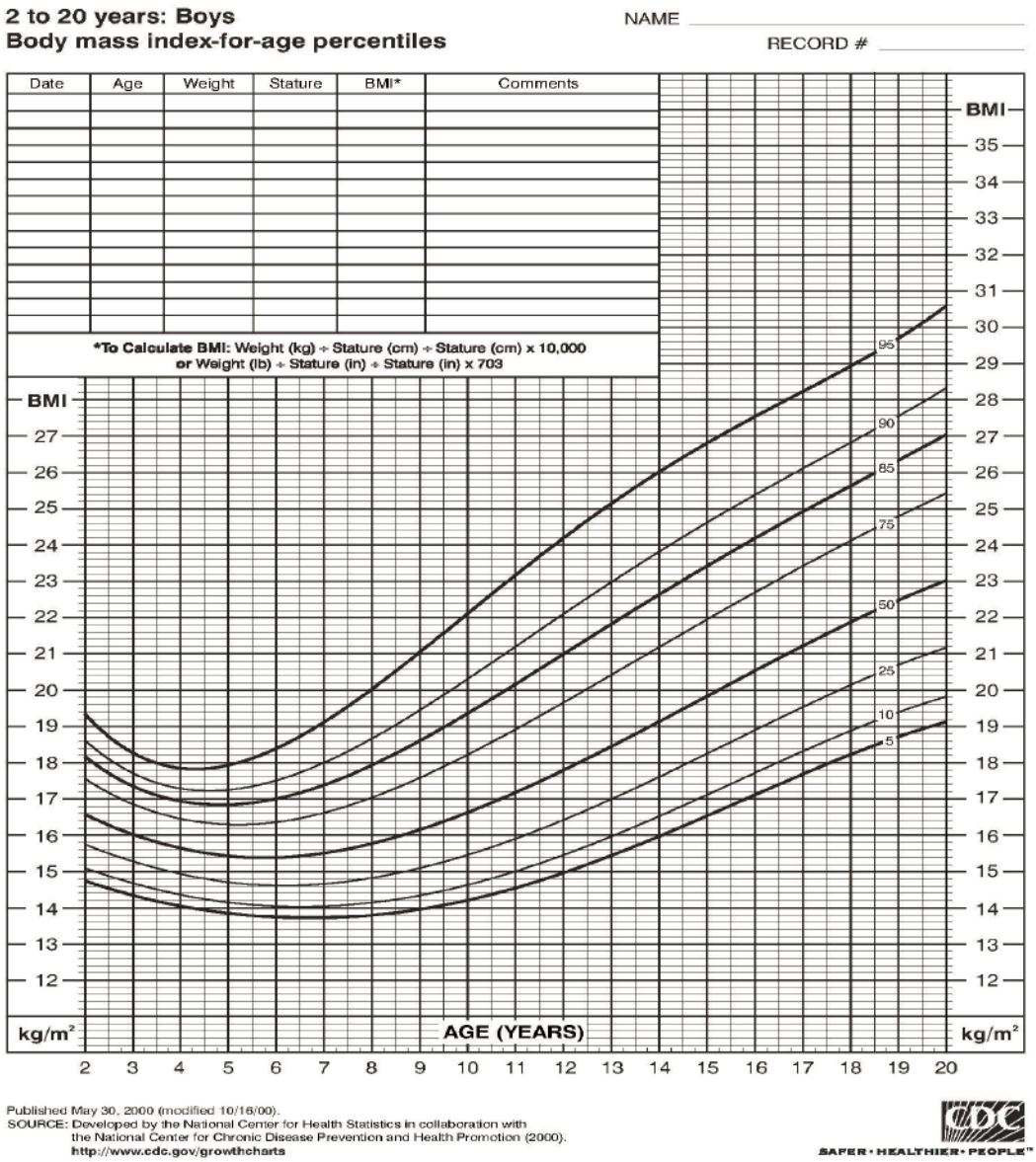
31 ATTACHMENTS

31.1 Attachment 1: Body Mass Index





Source: www.cdc.gov/growthcharts

31.2 Attachment 2: Clinically Relevant Drugs Causing Interactions through CYP2D6 and CYP3A4

This table contains a list of drugs causing clinically relevant drug interactions in humans by inhibiting CYP2D6, CYP 3A4, or inducing CYP3A4. This list is not all inclusive and should only be used as a guide.

	CYP2D6 Inhibitors	CYP2D6 Inducers	CYP3A4 Inhibitors	CYP3A4 Inducers
Strong inhibitors[1]	Bupropion Cinacalet Fluoxetine Paroxetine Quinidine	Dexamethasone Rifampin	Clarithromycin Indinavir Itraconazole Ketoconazole Nefazodone Nelfinavir Ritonavir Saquinavir Suboxone Telithromycin	Barbiturates Carbamazepine Efavirenz Glucocorticoids Modafinil Nevirapine Oxcarbazepine Phenobarbital Phenytoin Pioglitazone Rifabutin Rifampin St. John's wort Troglitazone
Moderate inhibitors[2]	Duloxetine Sertraline Terbinafine		Aprepitant Diltiazem Erythromycin Fluconazole Grapefruit juice Verapamil	

Source: Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. Indiana University School of Medicine (2007). Page last modified 12 Jul 2013 "http://medicine.iupui.edu/clinpharm/ddis/clinical-table/" Accessed 04 April 2014.

[1] Strong inhibitors are those that result in a > 5-fold increase in the plasma AUC values or more than 80% decrease in clearance.

[2] Moderate inhibitors are those that result in a > 2-fold increase in the plasma AUC values or 50% to 80% decrease in clearance.

31.3 Attachment 3: Numerical Pain Rating Scale

Subjects will be asked to rate their **current** pain intensity level using the following (0-10) NPRS.

0 1 2 3 4 5 6 7 8 9 10

No Pain	Worst Pain

31.4 Attachment 4: Clinical Laboratory Tests

CLINICAL LABORATORY ASSAYS	
Serum chemistry	
Alanine aminotransferase (ALT)	Cholesterol
Albumin	Chloride
Alkaline phosphatase (ALP)	Creatinine
Aspartate aminotransferase (AST)	γ-Glutamyl transferase (GGT)
Bilirubin (direct)	Glucose
Bilirubin (total)	Phosphorus
Blood urea nitrogen (BUN)	Potassium
Calcium	Sodium
Carbon dioxide	
Hematology Assays	
Glycosylated hemoglobin (HbA1c)	
Hematocrit	
Hemoglobin	
Platelet count	
Red blood cell (RBC) count	
White blood cell (WBC) count, including differential	
Urinalysis	
Blood	Red blood cells
Casts	White blood cells
Color	pH
Glucose	Clarity
Leukocyte esterase	Specific gravity
Protein	