# MULTICENTER ACTUAL USE AND COMPLIANCE STUDY OF IBUPROFEN 600 MG IMMEDIATE RELEASE/EXTENDED RELEASE TABLETS AMONG TARGETED (AT-RISK) CONSUMERS IN A SIMULATED OVER-THE-COUNTER ENVIRONMENT

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| **Investigational Product Number:** | PF-00344559 |
| **Investigational Product Name:** | Ibuprofen 600 mg Immediate Release/Extended Release Tablets |
| **United States (US) Investigational New Drug (IND) Number:** | CCI [redacted] |
| **European Clinical Trials Database (EudraCT) Number:** | Not Applicable (N/A) |
| **Protocol Number:** | B4371011 |
| **Phase:** | 3 |

## Document History

| Document | Version Date | Summary of Changes and Rationale |
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| Original protocol | 18-April-2018 | Not applicable (N/A) |
| Amendment 1 Protocol/Final v2.0 | 12-September-2018 | Schedule of Activities: The schedule of activities table updated.<br><br>Section 1 and Protocol Summary: Purpose of June 20, 2018 FDA Type C meeting added.<br><br>Section 2 and Protocol Summary: Secondary endpoint regarding subjects who use product more than 10 consecutive days added.<br><br>Section 2.1, 9.2.1, and Protocol Summary: Expanded clarification and justification for the primary endpoint selection added.<br><br>Section 3: Study Schematic updated.<br><br>Section 3 and Protocol Summary: "At-risk" consumers added; Procedure to ask parent/guardian and adolescent subject at Enrollment Visit to help determine which of them will be responsible to administer the study medication and subsequently participate in remaining study added; Description that electronic-diary platform will capture concomitant medications added.<br><br>Section 3.1: Introduction regarding "Ask a Doctor Before Use" and elevated cardiovascular and gastrointestinal bleeding factors added.<br><br>Section 4.1: Clarification of certain |

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| | | inclusion criteria added.<br><br>Section 4.2: Addition of exclusion criteria regarding subject/household employment.<br><br>Section 6.5: Resupply Pharmacy Visit added.<br><br>Section 6.2: Mention of specific risk conditions in proposed recruitment advertising language removed.<br><br>Section 6.3: REALM-SF will be used as literacy screening tool for adults at Pre-Screening Telephone Call rather than REALM-Test, which will instead be moved to the Enrollment Visit.<br><br>Section 6.4:<br><br>Items 1& 2: Subject identity verification and confirmation of parent/guardian presence for adolescent subjects added; Item 4: Clarification regarding medical condition questions added.<br><br>Item 9: Adolescent subjects will sign to indicate assent added.<br><br>Item 11: Test results entered into ASCVD 10-Year Risk Calculator added.<br><br>Item 12: Allow subjects with "Ask a Doctor Before Use" conditions to continue to the pharmacy site (rather than excluding at Pre-Screening Telephone Call), make a selection decision and collect reasons why they desired to purchase prior to excluding them from the study.<br><br>Item 13: Attempts by subjects to purchase more than 5 packages of |

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| | | study medication during study will be described in the study report.<br><br>Item 15: Concomitant medication collection (within relevant time windows before and after study medication use) in the electronic diary with rationale added.<br><br>Item 16: Pre-paid mailer to return study product and/or electronic-diary added.<br><br>Section 6.6.1: Clarification regarding who will complete EOS interview added; Procedures discussed with subjects at conclusion of EOS telephone interview added.<br><br>Section 6.6.2: Nurse identification/verification of last administration date of study medication added.<br><br>Section 6.7: Clarification of reimbursement for study medication purchase added.<br><br>Section 7.1: Reading grade level scoring and descriptions regarding the REALM-SF, REALM, and REALM Teen tests added.<br><br>Section 7.4: Clarification of blood pressure assessment administration added.<br><br>Section 7.5: Clarification regarding the 10-year risk for atherosclerotic cardiovascular disease assessment added.<br><br>Section 8.4.4: updated.<br><br>Section 9.2.1: At-risk population subgroups for primary endpoints |

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| | | clarified.<br><br>Section 9.2.3: At-risk population subgroups for secondary endpoints clarified.<br><br>Section 9.3: Description of procedure to audio-record, transcribe and analyze verbatim responses from subjects to questions in the End-of-Study Interview added.<br><br>Section 9.3.1 and Protocol Summary: Description of identification of misuse clarified; Explanation of mitigating factors and the two types of mitigation (pre-specified and post-study) added; Mitigation plan clarified.<br><br>Section 9.3.1: Figure 2 depicting overview of error classification scheme removed; Clarification of knowledge-based mistakes added; Memory recall mistake removed.<br><br>CCI [redacted]<br><br>Section 11.1: Explanation of Data Management Plan added. |
| Amendment 2 | 06-March-2019 | Incorporated changes from PACL No. 1. Section 6.4: updated price of study drug to $5.00. Section 13.2: language added to clarify how coded subject information may be used.<br><br>Protocol Summary, Study Design: Clarified instances of use of oral OTC and prescription pain medications to "oral" (updated throughout protocol). Updated 30-Day Use Period to 30-Day Use Phase (updated throughout protocol). Modified timing of final telephone follow-up contact. Updated order of |

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| | | identifying whether parent/guardian or adolescent is responsible for study procedures after the enrollment interview to before medication purchase.<br><br>Protocol Summary, Numbers and Types of Subjects: Updated numbers.<br><br>Schedule of Activities: Updated window of Follow-Up Phone Contact. Added "oral" to footnote g.<br><br>Section 3: Figure 1 updated.<br><br>Section 3.1: ASCVD risk upper bound changed to <20% (updated throughout protocol) and updated rationale provided.<br><br>Section 4.2: Clarified exclusion criteria language (No. 7, 10, 11, 12).<br><br>Section 4.4.1: Updated language concerning usage of birth control.<br><br>Section 6.4: Reordered visit steps/procedures.<br><br>Section 6.6.1: Removed language about dosing summary report being sent to subjects if withdrawn from the study. Clarified options to complete the EOS Interview (1 & 3). Added that subjects will be reminded of the need to use birth control at the EOS call. Clarified that after a subject has started the EOS interview, no additional diary entries can be made.<br><br>Section 6.6.2: Updated call window for Follow-Up Phone Contact.<br><br>Section 6.8.1: Clarified study procedures for subjects who request |

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| | | to discontinue receipt of study treatment. Text moved from Section 6.8.2.<br><br>Section 6.8.2: Removed text about replacing subjects who withdraw from the study.<br><br>Section 7.5: Updated values entered into Risk Calculator. Updated ASCVD upper bound for inclusion in the CV Risk group and exclusion in the study.<br><br>Section 8.1.4: Updated time period for actively eliciting and collecting AEs and SAEs.<br><br>Section 8.4.4: Updated definition of medication error.<br><br>Section 9.1: Updated Individual Adult Group Sizes to address any risk groups failing to fill adequately.<br><br>Section 9.1: Updated numbers in Total Sample Size Requirements.<br><br>Abbreviations: Added PACL. |
| This amendment incorporates all revisions to date, including amendments made at the request of country health authorities and institutional review boards (IRBs/ethics committees (ECs). | | |

## TABLE OF CONTENTS

LIST OF TABLES ..... 11
LIST OF FIGURES ..... 11
PROTOCOL SUMMARY ..... 12
SCHEDULE OF ACTIVITIES ..... 21
1. INTRODUCTION ..... 24
1.1. Mechanism of Action/Indication ..... 25
1.2. Background and Rationale ..... 25
2. STUDY OBJECTIVES AND ENDPOINTS ..... 25
2.1. Rationale for Primary Endpoint Selection ..... 27
3. STUDY DESIGN ..... 28
3.1. Risk Group Classifications ..... 30
4. SUBJECT ELIGIBILITY CRITERIA ..... 32
4.1. Inclusion Criteria ..... 33
4.2. Exclusion Criteria ..... 33
4.3. Randomization Criteria ..... 35
4.4. Lifestyle Requirements ..... 35
4.4.1. Contraception ..... 35
4.5. Sponsor's Qualified Medical Personnel ..... 36
5. STUDY TREATMENTS ..... 37
5.1. Allocation to Treatment ..... 37
5.2. Breaking the Blind ..... 37
5.3. Subject Compliance ..... 37
5.4. Investigational Product Supplies ..... 37
5.4.1. Dosage Form(s) and Packaging ..... 37
5.4.2. Preparation and Dispensing ..... 37
5.5. Administration ..... 38
5.6. Investigational Product Storage ..... 38
5.7. Investigational Product Accountability ..... 39
5.7.1. Return or Destruction of Investigational Product Supplies ..... 39
5.8. Concomitant Treatment(s) ..... 39
6. STUDY PROCEDURES ..... 39

6.1. Study Sites ..... 39
6.2. Recruitment Methods ..... 39
6.3. Telephone Pre-Screening ..... 40
6.4. Pharmacy Enrollment Visit ..... 41
6.5. Resupply Pharmacy Visit ..... 45
6.6. 30-Day Use Phase ..... 45
6.6.1. End-of-Study Telephone Interview ..... 45
6.6.2. Follow-Up Phone Contact (Up to Day 75) ..... 48
6.7. Reimbursement for Study Medication Purchase ..... 48
6.8. Subject Withdrawal or Early Termination ..... 48
6.8.1. Withdrawal of Consent: ..... 48
6.8.2. Lost to Follow-Up: ..... 49
7. ASSESSMENTS ..... 49
7.1. Health Literacy Assessment ..... 49
7.2. Pregnancy Testing ..... 50
7.3. Finger-Stick Cholesterol Test ..... 51
7.4. Blood Pressure Test ..... 51
7.5. 10-Year Risk for Atherosclerotic Cardiovascular Disease (ASCVD) Assessment ..... 52
7.6. Rater Qualifications ..... 52
8. ADVERSE EVENT REPORTING ..... 52
8.1. Requirements ..... 52
8.1.1. Additional Details on Recording Adverse Events on the CRF ..... 54
8.1.2. Eliciting Adverse Event Information ..... 54
8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal section) ..... 54
8.1.4. Time Period for Collecting AE/SAE Information ..... 54
8.1.4.1. Reporting SAEs to Pfizer Safety ..... 54
8.1.4.2. Recording Non-Serious AEs and SAEs on the CRF ..... 55
8.1.5. Causality Assessment ..... 55
8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities ..... 55
8.2. Definitions ..... 55
8.2.1. Adverse Events ..... 55

8.2.2. Abnormal Test Findings ....56
8.2.3. Serious Adverse Events ....57
8.2.4. Hospitalization ....57
8.3. Severity Assessment ....58
8.4. Special Situations ....59
8.4.1. Protocol-Specified Serious Adverse Events ....59
8.4.2. Potential Cases of Drug-Induced Liver Injury ....59
8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure ....61
8.4.3.1. Exposure During Pregnancy ....61
8.4.3.2. Exposure During Breastfeeding ....62
8.4.3.3. Occupational Exposure ....62
8.4.4. Medication Errors ....62
9. DATA ANALYSIS/STATISTICAL METHODS ....63
9.1. Sample Size Determination ....64
9.2. Dosing Compliance Analysis ....65
9.2.1. Analysis of the Primary Endpoint ....65
9.2.2. Performance Threshold Selection and Rationale ....66
9.2.3. Analysis of Secondary CCI [redacted] Dosing Compliance Endpoints ....66
CCI [redacted]
[redacted]
CCI [redacted]
9.4. Safety Analysis ....70
CCI [redacted]
9.6. Interim Analysis ....71
9.7. Data Monitoring Committee ....71
10. QUALITY CONTROL AND QUALITY ASSURANCE ....71
11. DATA HANDLING AND RECORD KEEPING ....72
11.1. Case Report Forms/Electronic Data Record ....72
11.2. Record Retention ....72
12. ETHICS ....73
12.1. Institutional Review Board/Ethics Committee ....73

12.2. Ethical Conduct of the Study ....73
12.3. Subject Information and Consent ....73
12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP ....74
13. DEFINITION OF END OF TRIAL ....75
13.1. End of Trial in All Participating Countries ....75
14. SPONSOR DISCONTINUATION CRITERIA ....75
15. PUBLICATION OF STUDY RESULTS ....75
15.1. Communication of Results by Pfizer ....75
15.2. Publications by Investigators ....76
16. REFERENCES ....78
ABBREVIATIONS ....79

## LIST OF TABLES

Table 1. REALM-SF Test Grade-Equivalent Reading Levels ....50
Table 2. REALM Test Grade-Equivalent Reading Levels ....50
Table 3. REALM-Teen Test Grade-Equivalent Reading Levels ....50
CCI [redacted]

## LIST OF FIGURES

Figure 1. Study Schematic ....30
CCI [redacted]

## PROTOCOL SUMMARY

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| **BACKGROUND AND RATIONALE** | Pfizer has developed an ibuprofen 600 mg immediate release/extended release (IR/ER) tablet formulation (Advil® 12 Hour) that approximates the early release characteristics of an ibuprofen 200 mg tablet with ER properties that are intended to maintain plasma concentrations adequate for analgesic efficacy over a 12-hour dosing interval. Pfizer submitted a CCI [redacted] CCI to the United States (US) Food and Drug Administration (FDA) on 23 April 2014 for an ibuprofen 600 mg IR/ER tablet for over-the-counter (OTC) use, with the proposed trade name of Advil 12 Hour. Pfizer received a Complete Response Letter (CRL) on 23 February 2015 in which the Agency requested Pfizer to design a consumer program to: 1) evaluate subjects with low literacy to understand when and how they use the product; 2) identify individuals with medical conditions that may put them at greater risk for adverse effects when using nonsteroidal anti-inflammatory drugs (NSAIDs) and determine whether the labeling allows them to make appropriate decisions with regard to use of this product versus an IR product; 3) evaluate subjects with severe pain to determine if these individuals will deselect from using the product rather than taking more than the recommended dose when their pain is not relieved; and 4) understand additional measures that would discourage the behaviors of consumers who may override the label.<br><br>Following these discussions with FDA, Pfizer conducted extensive qualitative consumer research to understand the baseline motivators and behaviors behind consumer use and misuse within the analgesic category, as well as follow-up interviews among a segment of the misusers in an earlier Advil 12 Hour Actual Use Study (AUS) (B4371008). On 09 March 2017, Pfizer met with the FDA to discuss the label development program and additional consumer research that would be needed leading up to a resubmission. In the meeting and official minutes, the FDA encouraged Pfizer to conduct a new AUS to characterize the misuse of Advil 12 Hour among those at increased risk, and to deeply understand the reasons for misuse. The Agency also provided feedback regarding which at-risk subpopulations should be studied, including elderly consumers (>65 years of age), consumers with an increased risk of gastrointestinal (GI) bleeding or cardiovascular (CV) adverse events, consumers who experience severe pain, and low literacy subjects. Adolescents (12-17 years of age) should also be included for pediatric safety assessments, and the study should enroll a large proportion of frequent OTC analgesic users to increase the incidence of misuse. On 20 June 2018, FDA granted a Type C |

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| | meeting to discuss the design of Pfizer's proposed AUS. Specifically, Pfizer and FDA met once again to discuss and clarify issues surrounding the primary endpoint, subjects with "Ask a Doctor Before Use" conditions, methods to pre-select for low reading ability, collecting concomitant NSAID use information during the Use Phase, and other important topics relevant to this study and the program. This protocol describes the AUS design and at-risk populations that will be employed to address the FDA's specific requests and advice for this critical component of the consumer research program. |
| **OBJECTIVES AND ENDPOINTS** | The primary objective of this AUS is to evaluate compliance with the labeled dosing directions for Advil 12 Hour and to understand why misuse occurred and if it was a conscious decision by the subject. A secondary objective is to evaluate the safety of Advil 12 Hour in unsupervised actual use and how it relates to misuse.<br><br>Accordingly, the following primary and secondary endpoints will be evaluated.<br><br>**Primary Endpoint:**<br><br>• Proportion of subjects who exceed the maximum daily dose (1200 mg) on two or more calendar days during the use period.<br><br>**Secondary Endpoints:**<br><br>• Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period.<br><br>• Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period due to reasons categorized as unintentional misuse only (ie, subjects who did not understand the dosing instructions on the package).<br><br>• The proportion of subjects who exceed the maximum amount per dose (600 mg) on 1 or more occasions.<br><br>• The proportion of subjects who exceed the maximum amount per dose (600 mg) on two or more occasions.<br><br>• The proportion of subjects who exceed the maximum daily dose on 10 or more calendar days.<br><br>• The proportion of subjects who exceed the maximum daily dose |

on 7 or more calendar days.

- The proportion of subjects who take more than two doses (ie, more than two dosing occasions) on a calendar day.
- The proportion of subjects who re-dose in <12 hours, <10 hours and <8 hours on 1 or more occasions.
- The proportion of subjects who use the product on more than 10 consecutive days.

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[redacted]

**Rationale for Primary Endpoint Selection:**

The primary endpoint was selected based on input from the FDA, considerations of the study population, and the incremental CV and GI bleeding risk of misusing the study medication. The FDA indicated that a primary endpoint of interest was the proportion of subjects who exceed the maximum daily dose (1200 mg) (ie, misuse) even once. Pfizer has proposed the primary endpoint as the proportion of subjects who exceed the maximum daily dose on two or more calendar days, based on the justification of data from large, long-term clinical trials' (ie, TARGET,[3] CLASS,[4] and PRECISION[5]) CV and GI safety outcomes in subjects receiving prescription doses of ibuprofen. Based on these publications of controlled clinical trials on long-term use of prescription ibuprofen, it is conservatively estimated that each day of misuse would incur an incremental 0.0011% (1.1/100,000) risk of an -Antiplatelet Trialists' Collaboration (APTC) non-hemorrhagic CV event, and an incremental 0.0014% (1.4/100,000) risk of upper GI bleeding compared to the estimated risk for 1200 mg ibuprofen per day. Therefore, two days of misuse for the proposed primary endpoint would not incur a clinically meaningful increase in the risk of a serious CV or GI outcome (2.2/100,000 and 2.8/100,000, respectively) compared to one day of misuse in an OTC population. Even if subjects were to misuse on 7 days, the incremental risks of a serious CV or GI outcome would be 0.0077% (7.7/100,000) and 0.0098% (9.8/100,000), respectively, which qualify as "very rare" adverse events (less than 0.01% or 1/10,000) according to the World Health Organization (WHO) (International Conference on Harmonisation (ICH) Council for International Organizations of Medical Sciences (CIOMS) guidance). For these reasons, Pfizer considers the proposed primary endpoint of the proportion of subjects who exceed the maximum daily dose on two or more calendar days among these at-risk study populations to be a highly sensitive endpoint to assess OTC suitability, and represents a minimal incremental clinical risk for those consumers who exceed this threshold frequency of misuse.

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| **STUDY DESIGN** | This will be an open-label, multicenter, 30-day, unsupervised AUS among targeted (at-risk) adult and adolescent consumers designed to mimic an OTC-like environment. More specifically, "at-risk" consumers, as discussed with the FDA, will comprise elderly consumers (>65 years of age), consumers with an increased risk of gastrointestinal (GI) bleeding or cardiovascular (CV) adverse events, consumers who experience severe pain, low literacy subjects, and adolescents (younger than the age of majority in their state, hereafter referred to as "12-17 years of age," although some sites may also designate 18-year-olds as younger than the age of majority, according to state requirements). Sites will be pharmacies in diverse geographic locations around the US. Prospective adult subjects will be recruited via general population and targeted risk condition advertising--- (although subjects will not be informed as to specific health conditions for which they are being recruited), while adolescents will be recruited using targeted, outbound pre-recruiting telephone calls. Subjects (or the parents/guardians of prospective adolescent subjects) responding to the advertisements or recruitment calls will be initially screened by telephone, and eligibility will subsequently be verified in-person at the pharmacy site.<br><br>Adult subjects and the parents/guardians of adolescent subjects who qualify will answer questions related to the subject's attitudes toward, and usage of, oral OTC and prescription pain medications, and will have the opportunity to purchase and use the study medication based only on their reading of the Drug Facts Label (DFL) and other information on the package. Data regarding subjects' use of the study medication will be captured in an electronic diary. The electronic diary will also capture information on concomitant medications to elucidate concurrent use of NSAIDs (see Section 6.4). Subjects (and either the parents/guardians of adolescent subjects or adolescent subjects) may return to the pharmacy site at any point during the 30-Day Use Phase to purchase additional study medication (up to 5 packages maximum at any point during the study). Finally, between Days 31 and 40, subjects (or the parents/guardians of adolescent subjects) will provide detailed explanatory information about the subject's reasons for misuse, as well as information about adverse events (AEs), in an end-of-study (EOS) telephone interview; the EOS telephone interview will be audio-recorded in order to capture subjects' verbatim responses. The EOS telephone interview will be followed by a self-administered Attitudes and Beliefs electronic questionnaire, and a final telephone follow-up contact (at least 28 (and up to 35) calendar days after the subject's 30-Day Use Phase or, for subjects who use the investigational product after Day 30, at |

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| | least 28 (and up to 35) calendar days after last recorded dose of investigational product) to capture any potential adverse events and to confirm appropriate contraception usage, after which participation will end.<br><br>Note that for adolescent subjects 12-17 years of age, the initial telephone screening and pharmacy enrollment visit assessments (with the exception of the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test[7] and instances where the investigator may exercise judgment to determine if the parent/guardian and/or adolescent subject should both be present for and respond to questions in the birth control verification discussion or other sensitive content areas) will be directed to and managed by the parent/guardian, who will answer for and on behalf of the adolescent subject, and must be present to enroll the adolescent into the study and purchase study medication. However, to allow for real-world, naturalistic medication use behaviors between parents/guardians and adolescent subjects, the parent/guardian and adolescent subject will be asked before the study medication purchase by the parent at the pharmacy enrollment visit to identify which of them usually administers the oral OTC pain reliever medications the adolescent takes, and that person will have the primary responsibility to administer the study medication and subsequently participate in remaining study assessments including completion of the electronic diary, the end-of-study (EOS) telephone interview and the self-administered Attitudes and Beliefs questionnaire. In cases where the parent/guardian and the adolescent report they "both" usually administer oral OTC pain reliever medications the adolescent takes, the parent/guardian and adolescent will be asked to decide which of them will have primary responsibility for entering data and participating in all future assessments. |
| **STUDY TREATMENTS** | This is an open label study. Subjects or the parents/guardians of prospective adolescent subjects will purchase study medication, which will consist of Advil 12 Hour 600 mg IR/ER tablets (40 tablets per bottle), with a labeled dosing regimen of one 600 mg IR/ER tablet every 12 hours, not to exceed 2 tablets in 24 hours (total daily dose = 1200 mg ibuprofen). However, subjects will be free to take the medication (or not take it) according to their own (or in the case of the adolescent subject, the parent's/guardian's) understanding and decisions based on the Drug Facts Label and other packaging instructions throughout the 30-Day Use Phase. |
| **NUMBERS AND TYPES OF** | The total number of subjects expected to enroll into the study is 820 (including approximately 720 adults and 100 adolescents). |

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| **SUBJECTS** | Accordingly, the number of subjects expected to be screened by telephone is 14,409, of whom approximately 7,029 would meet all initial screening criteria and schedule an enrollment visit appointment. Among these, it is expected that 3,046 would visit a participating pharmacy research site, and 820 would meet all eligibility criteria, purchase study medication and enter the Use Phase. Finally, among enrolled subjects it is expected approximately 700 would be available for the dosing compliance endpoint analysis (compliance-evaluable subjects are those that take at least one dose of study medication and record it in the electronic diary), including approximately 620 adults and 80 adolescents.<br><br>**Risk Group Classifications:**<br><br>The adult portion of the study sample will consist entirely of subjects from the following special at-risk populations of interest, including:<br><br>1. Cardiovascular (CV) Risk.<br><br>2. Gastrointestinal (GI) Bleeding Risk.<br><br>3. History of Severe Pain.<br><br>4. >65 Years of Age.<br><br>Note that because of substantial overlap in these frequently co-morbid conditions, subjects from the at-risk groups are not recruited in any specific, fixed proportions. Approximately 30% of each adult at-risk group (groups 1-4 above) will be classified as low- literacy based on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test in order to evaluate dosing compliance and other important behaviors among subjects at increased risk due to low health literacy. Among adult subjects, heavy oral OTC pain reliever users (ie, those who report taking an average of 30 or more doses per month on average in the 3 months preceding enrollment) will be enrolled in approximately a 2:1 ratio with moderate users (5-29 doses in the previous 3 months).<br><br>**Additional Cohort of Interest:**<br><br>Adolescent subjects will be included for pediatric compliance and safety assessments. |

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| | 5. Adolescent Subjects (12-17 years of age). |
| **STATISTICAL METHODS** | The Primary Endpoint (proportion of subjects who exceed the maximum daily dose, 1200 mg, on two or more days during the use period) will be calculated as:<br><br>Adult compliance-evaluable subjects exceeding 1200 mg/day on ≥2 days, divided by the total number of adult compliance-evaluable subjects.<br><br>The complement of this number (1 – obtained proportion) will be calculated. This is the correct performance rate.<br><br>The Primary Endpoint will be considered successfully met if the lower-limit of the two-sided 95% confidence interval (CI) (calculated using the Wald Confidence Interval) for the correct performance rate is greater than the *a priori* performance standard of 90%. Adolescent performance for the Primary Endpoint will be presented descriptively. No inferential analysis on adolescents will be performed (descriptive only) and hence this group will not be compared to the performance threshold.<br><br>Values for all other dosing compliance endpoints will be calculated in similar fashion but will not be compared to any pre-specified performance threshold.<br><br>CCI [redacted]<br><br>Product misuse will be recorded by subjects in the electronic diary (which captures the date, time and number of tablets for each dosing occasion). For subjects whose electronic diary entries show misuse of the study medication (Primary Endpoint: exceeding the maximum daily dose, 1200 mg, on two or more calendar days, and relevant secondary endpoints related to dosing), data from the subject's full case report form (CRF) -(including the Enrollment Interview, electronic diary and EOS Interview) will be carefully reviewed to evaluate the benefit-risk balance, including potential mitigating factors. Mitigating factors are circumstances or considerations that result in reclassification of misuses to "acceptable" status, meaning the risk-benefit balance is judged to be favorable in spite of misuse. Two kinds of mitigation will be employed: pre-specified and post-study. Pre-specified mitigating |

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| | factors for the primary and relevant secondary endpoints related to dosing include: responses showing clear consultation with or direction from a healthcare practitioner (HCP) regarding observed patterns of misuse--, and severe pain, pain that is different than usual, or being larger or needing better/faster pain relief that would have otherwise led to using an opioid or other Rx analgesic, according to the subject. Because of wide variability in consumer behaviors and health conditions, not all mitigating factors can be pre-specified. Therefore, if other behavioral or health factors are identified and judged in post-study analysis to substantially impact the benefit-risk balance, associated misuses may likewise be mitigated to "acceptable" status. To ensure full transparency for reviewers, mitigation (both pre-specified and post-study) of individual misuses based on subjects' responses, together with the accompanying medical justification or rationale, will be carefully documented in the study report.<br><br>Subgroup analyses will be performed on subjects 1) at increased GI risk; 2) at increased CV risk; 3) >65 years age; and 4) with severe pain for the primary endpoint and secondary endpoints.<br><br>Adverse event (AE) summaries will include all events which initially occurred or worsened following initiation of treatment. AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA), System Organ Class (SOC) and Preferred Term (PT) designations and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to the study product. CCI [redacted] |

## SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the STUDY PROCEDURES and ASSESSMENTS sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

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

| Visit Identifier | Telephone Screening | Enrollment Visit | Resupply Pharmacy Visit | Day 30 | End of Study Telephone Interview[j] | Follow-Up Phone Contact (and Exit from Study) |
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| **Visit Window (Days)[a]** | **<1** | **1** | **1-30** | **30** | **31 (up to 40)** | **(up to 75)** |
| Pre-Screening Telephone Call | X | | | | | |
| Reading Level for Adults (REALM-SF Test)[b] | X | | | | | |
| Identification Verified | | X | | | | |
| Enrollment Screening and Medical Conditions to Confirm Eligibility | | X | | | | |
| Purchase Decision | | X | | | | |
| Analgesic Use History | | X | | | | |
| Demographics | | X | | | | |
| Reading Level for Adults (REALM Test) or Adolescents (REALM-Teen Test)[b] | | X | | | | |
| Inclusion and Exclusion Criteria[c] | X | X | | | | |
| Read and Sign Informed Consent (and Assent for Minors) | | X | | | | |
| Verification of Effective Birth Control[d] | | X | | | | X |
| Urine Pregnancy Test (if applicable) | | X | | | X | |
| Finger-Stick Cholesterol and Blood Pressure Tests[e] | | X | | | | |
| Subgroup Identification for At-Risk Populations | | X | | | | |
| Purchase Study Medication[f] | | X | X | | | |
| Subject Trained on Completion of Electronic Diary Entries[g] | | X | | | | |
| End of Study Pregnancy Test (if applicable) and Pre-Paid Mailer Provided | | X | | | | |
| Use Study Medication / Complete Electronic Diary / Record Concomitant Medications[h] | | X | → | X | | |
| Adverse Event and Medication Error Recording and Follow-Up[i] | | X | X | X | X | X |
| Electronic Diary Review[j] | | | | | X | |
| Focused Questions on Product Misuse | | | | | X | |

| Visit Identifier | Telephone Screening | Enrollment Visit | Resupply Pharmacy Visit | Day 30 | End of Study Telephone Interview[j] | Follow-Up Phone Contact (and Exit from Study) |
|---|---|---|---|---|---|---|
| **Visit Window (Days)[a]** | **<1** | **1** | **1-30** | **30** | **31 (up to 40)** | **(up to 75)** |
| Questions on Concomitant Analgesic Use (Concomitant Medication Use for Subjects Experiencing AEs) | | | | | X | |
| Conduct End of Study Urine Pregnancy Test (if applicable)[k] | | | | | X | |
| Attitudes and Beliefs (Self-Administered via the Electronic Diary Application at Completion of End of Study Telephone Interview)[l] | | | | | X | |
| Return Unused Medication (and Electronic Diary device if applicable) Via Mail[m] | | | | | X | |
| Exit from Study at Conclusion of Follow-Up Phone Contact | | | | | | X |
| Subject is Reimbursed for Purchase Price of Study Medication Following Last Subject Out[n] | | | | | | |

Abbreviations:
→ = ongoing/continuous event

REALM-SF = Rapid Estimate of Adult Literacy in Medicine – Short Form
REALM = Rapid Estimate of Adult Literacy in Medicine
REALM-Teen = Rapid Estimate of Adolescent Literacy in Medicine
AE = Adverse Event

a. Day relative to first purchase of study product on Day 1.

b. REALM-SF Test will assess reading grade level at screening for adult subjects. Adult subjects will have reading grade level confirmed via the REALM Test, and adolescent subjects will have reading grade level assessed via the REALM-Teen Test during the enrollment visit.

c. These are evaluated programmatically in the EDC system (based on pre-specified, protocol-defined, automatic edit checks), some at the initial telephone screening, and then all required criteria at the enrollment visit, prior to subject entry into the Use Phase (before medication purchase).

d. Conducted with male and female subjects.

e. Conducted with adult subjects (18 years and older) only.

f. Subjects (or the parents/guardians of adolescent subjects) will be allowed to purchase as much study medication as desired at the enrollment visit (up to 5 packages) after reading and signing the informed consent form. Subjects (or the parents/guardians of adolescent subjects or adolescent subjects) will also be allowed to purchase additional study medication (not to exceed a total of 5 packages for the study) from the pharmacy site if needed during the course of the 30-day study.

g. Diary entries are to be completed by the subject or the adolescent subject's parent/guardian if the adolescent subject does not usually self-administer oral OTC pain medication. The electronic diary will also capture information on concomitant medications taken in the 24-hour period before or the 24-hour period after each dose of the study medication.

h. As needed (determined by subject or the parents/guardians of adolescent subjects) from Day 1 to Day 30.

i. At any time during the 30-day study, subjects (or the parents/guardians of adolescent subjects) may contact the Investigator at the study site or may call the PEGUS 24-hour nurse line to report an AE. During the End-of-Study Telephone Interview and the Follow-up Phone Contact, subjects will be queried about AEs.

j. EOS Telephone Interview should take place shortly after Day 30 (ranging from Day 31 to Day 40) to ensure that all electronic diary entries have been transmitted, but at a time that reasonably allows for accurate subject recall about specific dosing instances. Subjects will be questioned to gather information on AEs, concomitant medications for subjects who experienced adverse event(s), subjects' use of the medication (and reasons for any deviations from the label directions), concomitant analgesic use, subject typical practices on following OTC dosing directions for analgesics, and any discussion the subject may have had with a physician or other healthcare professional about the study medication use.

k. After the last dose of study medication, female subjects of childbearing potential and at risk of pregnancy will self-administer the end of study pregnancy test that was provided to them at the Day 1 visit and report the result to the trained nurse interviewer during the End-of-Study Telephone Interview.

l. The Attitudes and Beliefs Questionnaire will be completed by subjects using the electronic-diary application within 10 days after completing the End-of-Study Telephone Interview.

m. Subjects will be instructed at End-of-Study Telephone Interview to discontinue all use of study medication and to use the provided mailing materials to return all unused study medication and electronic diary device (if applicable).

n. Once all subjects have exited the study, subjects, or the adolescent subject's parent/guardian will be reimbursed (at the same time) for the purchase price of study medication they purchased during the study. To maintain the naturalism of the study, subjects will not be notified in advance, at any time, that medication purchases will be reimbursed.

## 1. INTRODUCTION

Pfizer has developed an ibuprofen 600 mg immediate release/extended release (IR/ER) tablet formulation (Advil® 12 Hour) that approximates the early release characteristics of an ibuprofen 200 mg tablet with ER properties that are intended to maintain plasma concentrations adequate for analgesic efficacy over a 12-hour dosing interval. Pfizer submitted a CCI [redacted] to the United States (US) Food and Drug Administration (FDA) on 23 April 2014 for an ibuprofen 600 mg IR/ER tablet for over-the-counter (OTC) use, with the proposed trade name of Advil 12 Hour. Pfizer received a Complete Response Letter (CRL) on 23 February 2015 in which the Agency requested that Pfizer design a consumer program to: 1) evaluate subjects with low literacy to understand when and how they use the product, 2) identify individuals with medical conditions that may put them at greater risk for adverse effects when using nonsteroidal anti-inflammatory drugs (NSAIDs) and determine whether the labeling allows them to make appropriate decisions with regard to use of this product versus an IR product, 3) evaluate subjects with severe pain to determine if these individuals will deselect from using the product rather than taking more than the recommended dose when their pain is not relieved, and 4) understand additional measures that would discourage the behaviors of consumers who may override the label.

Following these discussions with FDA, Pfizer conducted extensive qualitative consumer research to understand the baseline motivators and behaviors behind consumer use and misuse within the analgesic category as well as follow-up interviews among a segment of the misusers in an earlier Advil 12 Hour Actual Use Study (AUS) (B4371008). On 09 March 2017, Pfizer met with the FDA to discuss the label development program and additional consumer research that would be needed leading up to a resubmission. In the meeting and official minutes, the FDA encouraged Pfizer to conduct a new AUS to characterize the misuse of Advil 12 Hour among those at increased risk, and to deeply understand the reasons for misuse. The Agency also provided feedback regarding which at-risk subpopulations should be studied including elderly consumers (>65 years of age), consumers with an increased risk of gastrointestinal (GI) bleeding or cardiovascular (CV) adverse events, consumers who experience severe pain, and low literacy subjects. Adolescents (12-17 years of age) should also be included for pediatric safety assessments, and the study should enroll a large proportion of frequent OTC analgesic users to increase the incidence of misuse. On 20 June 2018, FDA granted a Type C meeting to discuss the design of Pfizer's proposed AUS. Specifically, Pfizer and FDA met once again to discuss and clarify issues surrounding the primary endpoint, subjects with "Ask a Doctor Before Use" conditions, methods to pre-select for low reading ability, collecting concomitant NSAID use information during the Use Phase, and other important topics relevant to this study and the program. This protocol describes the AUS design and at-risk populations that will be employed to address the FDA's specific requests and advice for this critical component of the consumer research program.

### 1.1. Mechanism of Action/Indication

The product is a bi-layer, 600 mg ibuprofen tablet in which one layer contains 200 mg of ibuprofen as immediate release (IR) and the other layer contains 400 mg as extended release (ER). This bi-layer tablet formulation approximates the early-release characteristics of an ibuprofen 200 mg IR tablet combined with ER properties that maintain plasma concentrations adequate to provide 12 hours of analgesic efficacy.

The clinical development program for Advil 12 Hour consisted of three pharmacokinetic (PK) studies comparing the formulation to 3 consecutive ibuprofen 200 mg doses, dosed every 4 hours, two dental pain extraction efficacy studies (one single and one multiple dose), and one AUS which included self-selection and compliance arms. These studies demonstrated that the product has a PK profile bioequivalent to that of 200 mg IR administered three times a day (TID) every 4 hours and provides sustained analgesic efficacy up to 12 hours following both single and multiple doses. The efficacy data support that the proposed product provides an onset of analgesia which is maintained for 12 hours.

The indications of Advil 12 Hour are "Pain reliever/Fever reducer." The uses identified in the proposed Drug Facts Label (DFL) are: for up to 12-hour relief of minor aches and pains due to: minor pain of arthritis, muscular aches, backache, menstrual cramps, toothache, headache, the common cold, and temporarily reduces fever.

### 1.2. Background and Rationale

Pfizer Consumer Healthcare (PCH) believes that an ibuprofen formulation that will provide a similar onset but longer duration of analgesic effect compared to currently marketed ibuprofen IR dosage forms will provide a benefit to consumers who dose more than once with an immediate release, short-acting analgesic to treat their painful condition. Market research studies indicate that OTC consumers often need to treat their pain symptoms with multiple doses of analgesics.[1,2]

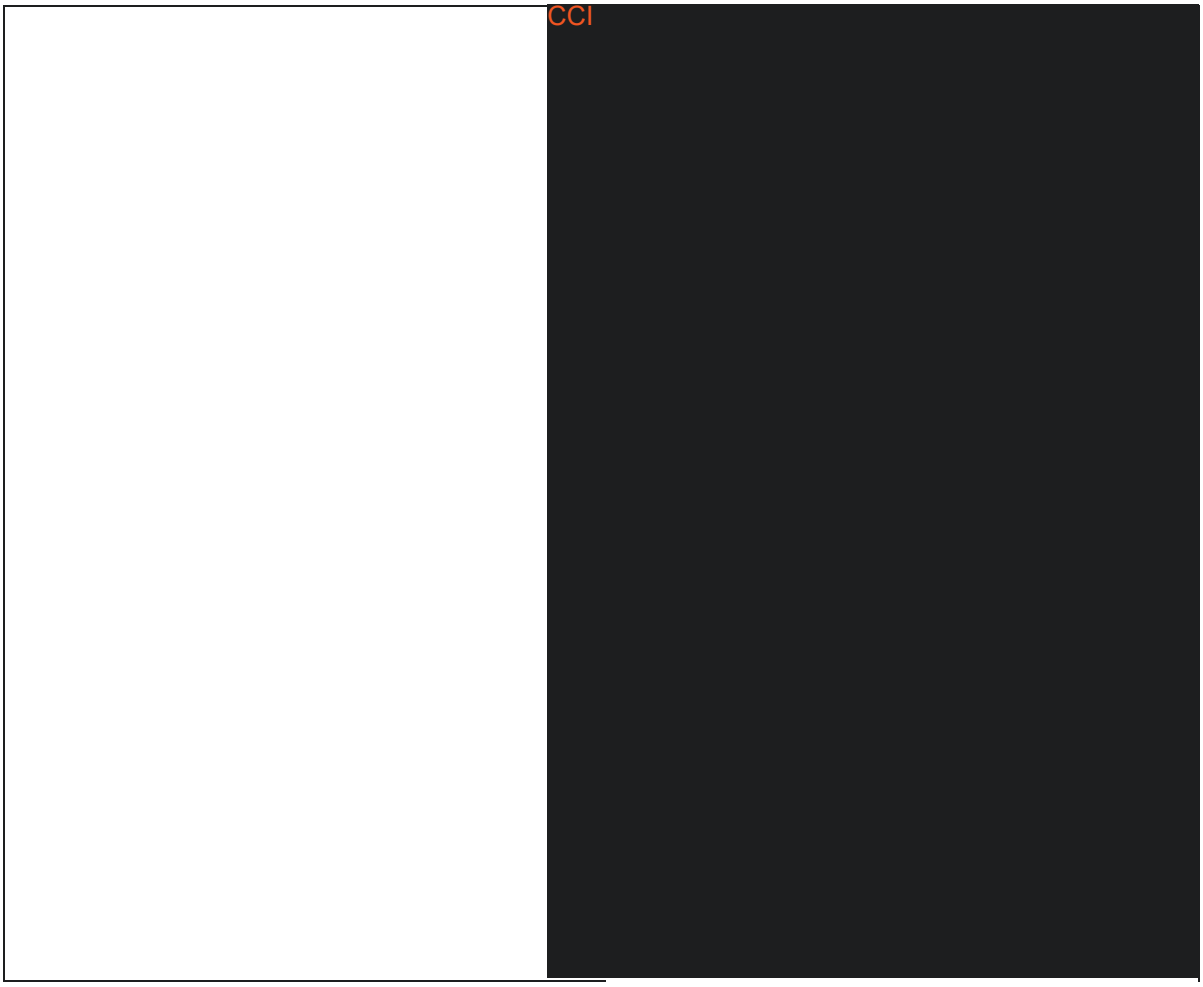
This study is being conducted to evaluate the extent to which consumers will appropriately use the ibuprofen 600 mg IR/ER tablets and comply with the dosing instructions (ie, 1 tablet every 12 hours, not to exceed 2 tablets per 24 hours) (total daily dose = 1200 mg ibuprofen). However, subjects will be free to take the medication (or not take it) according to their own (or in the case of the adolescent subject, the parent's/guardian's) understanding and decisions based on the Drug Facts Label and other packaging instructions throughout the 30-Day Use Phase.

Additional information for this compound may be found in the single reference safety document (SRSD), which for this study is the investigator's brochure (IB).

## 2. STUDY OBJECTIVES AND ENDPOINTS

The following primary and secondary endpoints will be evaluated.

| **Primary Objective:** | **Primary Endpoint:** |
|---|---|
| • Evaluate compliance with the labeled dosing directions for Advil 12 Hour, and understand why misuse occurred and if it was a conscious decision by the subject. | • Proportion of subjects who exceed the maximum daily dose (1200 mg) on two or more calendar days during the use period. |
| **Secondary Objectives:** | **Secondary Endpoints:** |
| • Evaluate the safety of Advil 12 Hour in unsupervised actual use and how it relates to misuse. | • Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period.<br>• Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period due to reasons categorized as unintentional misuse only (ie, subjects who did not understand the dosing instructions on the package).<br>• The proportion of subjects who exceed the maximum amount per dose (600 mg) on 1 or more occasions.<br>• The proportion of subjects who exceed the maximum amount per dose (600 mg) on two or more occasions.<br>• The proportion of subjects who exceed the maximum daily dose on 10 or more calendar days.<br>• The proportion of subjects who exceed the maximum daily dose on 7 or more calendar days.<br>• The proportion of subjects who take more than two doses (ie, more than two dosing occasions) on a calendar day.<br>• The proportion of subjects who re-dose in <12 hours, <10 hours and <8 hours on 1 or more occasions.<br>• The proportion of subjects who use the product on more than 10 consecutive days. |
| | CCI [redacted] |
| | [redacted] |




## 2.1. Rationale for Primary Endpoint Selection

The primary endpoint was selected based on input from the FDA, considerations of the study population, and the incremental CV and GI bleeding risk of misusing the study medication. The FDA indicated that a primary endpoint of interest was the proportion of subjects who exceed the maximum daily dose (1200 mg) (ie, misuse) even once. Pfizer has proposed the primary endpoint as the proportion of subjects who exceed the maximum daily dose on two or more calendar days, based on the justification of data from large, long-term clinical trials' (ie, TARGET,[3] CLASS,[4] and PRECISION[5]) CV and GI safety outcomes in subjects receiving prescription doses of ibuprofen. Based on these publications of controlled clinical trials on long-term use of prescription ibuprofen, it is conservatively estimated that each day of misuse would incur an incremental 0.0011% (1.1/100,000) risk of an -Antiplatelet Trialists' Collaboration (APTC)[6] non-hemorrhagic CV event, and an incremental 0.0014% (1.4/100,000) risk of upper GI bleeding compared to the estimated risk for 1200 mg ibuprofen per day. Therefore, two days of misuse for the proposed primary endpoint would not incur a clinically meaningful increase in the risk of a serious CV or GI outcome (2.2/100,000 and 2.8/100,000, respectively) compared to one day of misuse in an OTC population. Even if subjects were to misuse on 7 days, the incremental risks of a serious CV

or GI outcome would be 0.0077% (7.7/100,000) and 0.0098% (9.8/100,000), respectively, which qualify as "very rare" adverse events (less than 0.01% or 1/10,000) according to the World Health Organization (WHO) (International Conference on Harmonisation (ICH) Council for International Organizations of Medical Sciences (CIOMS) guidance). For these reasons, Pfizer considers the proposed primary endpoint of the proportion of subjects who exceed the maximum daily dose on two or more calendar days among these at-risk study populations to be a highly sensitive endpoint to assess OTC suitability and represents a minimal incremental clinical risk for those consumers who exceed this threshold frequency of misuse.

## 3. STUDY DESIGN

This will be an open-label, multicenter, 30-day, unsupervised AUS among targeted (at-risk) -adult and adolescent consumers designed to mimic an OTC-like environment. More specifically, "at-risk" consumers, as discussed with the FDA, will comprise elderly consumers (>65 years of age), consumers with an increased risk of gastrointestinal (GI) bleeding or cardiovascular (CV) adverse events, consumers who experience severe pain, low literacy subjects, and adolescents (younger than the age of majority in their state, hereafter referred to as "12-17 years of age," although some sites may also designate 18-year-olds as younger than the age of majority, according to state requirements). The total number of subjects expected to enroll into the study is approximately 820. Sites will be pharmacies in diverse geographic locations around the US. Prospective adult subjects will be recruited via general population and targeted risk condition advertising--- (although subjects will not be informed as to specific health conditions for which they are being recruited), while adolescents will be recruited using targeted, outbound pre-recruiting telephone calls. Subjects (or the parents/guardians of prospective adolescent subjects) responding to the advertisements or recruitment calls will be initially screened by telephone, and eligibility will subsequently be verified in-person at the pharmacy site.

Adult subjects and the parents/guardians of adolescent subjects who qualify will answer questions related to the subject's attitudes toward, and usage of, oral OTC and prescription pain medications and will have the opportunity to purchase and use the study medication based only on their reading of the Drug Facts Label (DFL) and other information on the package. Following the initial purchase decision, subjects (or the parent/guardian of adolescent subjects) will provide informed consent and complete additional evaluations for inclusion/exclusion as well as assessment of risk group classification(s) for adult subjects (see Section 3.1). Eligible subjects (or the parents/guardians of eligible adolescent subjects) are then permitted to purchase as much study medication as desired (up to 5 packages) at the start of the study. Data regarding subjects' use of the study medication will be captured in an electronic diary. CCI [redacted]

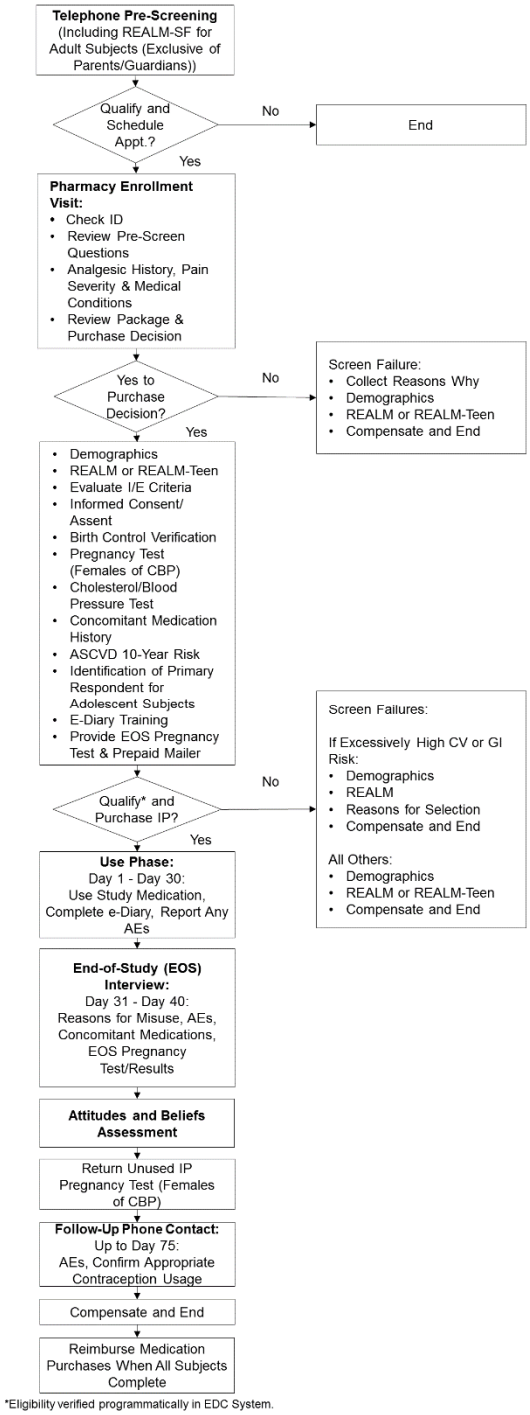
CCI [redacted]

The electronic diary will also capture information on concomitant medications to elucidate concurrent use of NSAIDs (see Section 6.4). Subjects (and either the parents/guardians of adolescent subjects or adolescent subjects, depending on which is responsible to make entries in the electronic diary and participate in all other assessments) may return to the pharmacy site at any point during the 30-Day Use Phase to purchase additional study medication (not to exceed a total of 5 packages for the study). Finally, between Days 31 and 40, subjects (or the parents/guardians of adolescent subjects) will provide detailed explanatory information about the subject's reasons for misuse, as well as information about adverse events (AEs), in an end-of-study (EOS) telephone -interview; the EOS telephone interview will be audio-recorded in order to capture subjects' verbatim responses. The EOS telephone interview will be followed by a self-administered Attitudes and Beliefs electronic questionnaire (to be completed within 10 days after the EOS telephone interview) and participation will end.

Note that for adolescent subjects 12-17 years of age, the initial telephone screening and pharmacy enrollment visit assessments (with the exception of the REALM-Teen Test[7] and instances where the investigator may exercise judgment to determine if the parent/guardian and/or adolescent subject should both be present for and respond to questions in the birth control verification discussion or other sensitive content areas) will be directed to and managed by the parent/guardian, who answers for and on behalf of the adolescent subject, and must be present to enroll the adolescent into the study and purchase study medication. The individual (parent/guardian or adolescent subject) identified as the one who usually administers the oral OTC pain reliever medications the adolescent takes will have the primary responsibility to administer the study medication and subsequently participate in remaining study assessments including completion of the electronic diary, the EOS telephone interview and the self-administered Attitudes and Beliefs electronic questionnaire.

Figure 1 is a visual representation (schematic) of the study.

## Figure 1. Study Schematic




## 3.1. Risk Group Classifications

Of special interest for this study are consumers with key "Ask a Doctor Before Use" conditions from the proposed DFL, especially those with factors for elevated cardiovascular and gastrointestinal bleeding risk. The adult portion of the study sample will consist entirely of subjects who: 1) have a history taking oral OTC analgesics at least 5 doses/month on

average during the past 3 months, and 2) are from the following special at-risk populations of interest (which are not mutually exclusive):

1. **Cardiovascular (CV) Risk**: In order to ensure that subjects for this group to be included in the study are at increased risk for cardiovascular disease, a 10-year risk for atherosclerotic cardiovascular disease (ASCVD) assessment will be used for adult subjects. The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Prevention Guidelines Tool CV Risk Calculator, which is a companion tool to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk, will be used for this calculation. Subjects in the 40-79-year age bracket will only be eligible for inclusion in the CV Risk Group if they have a score of 5% to <20% for 10-Year ASCVD risk. The <20% upper threshold for 10-year ASCVD risk is selected to be high enough to enable enrollment of older consumers (who naturally have higher 10-year risk scores as a function of age regardless of other contributing factors) as requested by the FDA, while still conservatively excluding those with the highest levels of risk (ie, ensures subjects 40-79 years of age will have no more than a 1 in 5 estimated baseline risk for a first ASCVD event in 10 years). It should be noted that a <20% upper limit for 10-Year ASCVD risk will result in no more than 0.082% *additional* baseline risk in 30 days (the length of the Use Phase) for any individual subject in the study versus a 10% ASCVD upper limit, or about a 1 in 1217 additional risk in 30 days. This 0.082% additional baseline risk derives from the assumption that if the additional 10% ASCVD risk (by increasing from 10% to <20%) is evenly distributed across 10 years, any 30-day period (the length of the Use Phase) will represent 30 days/3650 days x 10% ASCVD risk in 10 years = 0.082%. All subjects will have their high-density lipoprotein (HDL) and total cholesterol levels assessed on-site using a finger-prick test and will have these values entered into the Risk Calculator (programmed in the electronic data capture (EDC) System), along with the subject's systolic blood pressure reading. In order to avoid having subjects with significant concurrent cardiovascular disease who would be at unacceptably high risk for a CV adverse event (AE) enrolled into the study, subjects with the following clinical conditions, which place them at excessively high risk for ASCVD as defined by the 2013 ACC/AHA Guidelines on the Assessment of Atherosclerotic Cardiovascular Risk, will not be included in the study: clinically established coronary heart disease; cerebrovascular disease; peripheral artery disease; abdominal aortic aneurysm; and chronic kidney disease. Subjects who have experienced a prior non-fatal cardiovascular disease event (angina, heart failure, heart disease, heart attack or stroke/transient ischemic attack) or have had heart surgery or who currently have uncontrolled high blood pressure (either by self-report or measured systolic blood pressure higher than 180 mmHg or diastolic pressure higher than 120 mmHg at the time of the enrollment interview) will also be excluded from the study.

2. **Gastrointestinal (GI) Bleeding Risk**: Subjects for this group will be considered to be at moderate risk for gastrointestinal bleeding and eligible for inclusion in the study if they have at least one but no more than two of the following risk factors: age >65 years; a previous history of uncomplicated ulcer within one year of the study

enrollment date; concurrent use of oral corticosteroids; or concurrent use of a low dose aspirin regimen.[8] Subjects with concurrent or recent (within 30 days) use of anticoagulants, a prior history of complicated peptic ulcer, or a GI bleeding event requiring hospitalization or blood transfusion will be excluded from the study.

3. **History of Severe Pain**: Subjects who report at enrollment that they experienced 5 or more episodes of pain they rate as "severe" during the preceding month.

4. **>65 Years of Age:** Subjects who report their age at the time of enrollment to be greater than 65 years of age.

Note that these at-risk groups are not mutually exclusive. Because of substantial overlap in these frequently co-morbid conditions, subjects from the at-risk groups are not recruited in any specific, fixed proportions. Approximately 30% of each adult at-risk group (groups 1-4 above) will be classified as low- literacy based on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test[9] in order to evaluate dosing compliance and other important behaviors among subjects at increased risk due to low health literacy. Among adult subjects, heavy oral OTC pain reliever users (ie, those who report taking an average of 30 or more doses per month on average in the 3 months preceding enrollment) will be enrolled in approximately a 2:1 ratio with moderate users (5-29 doses in the previous 3 months).

**Additional Cohort of Interest:**

Adolescent subjects will be included for pediatric compliance and safety assessments.

1. **Adolescent Subjects (12-17 years of age):** Subjects who report their age at the time of enrollment to be 12-17 years.

## 4. SUBJECT ELIGIBILITY CRITERIA

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

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study. Eligibility questions that involve only straightforward collection of subjects' self-reports may be administered by any trained and designated member of the investigator's study team (including non-pharmacist study coordinators). Exclusion criteria questions that require additional judgment or understanding to recognize potential risks or clinical issues, or that involve sensitive discussions (such as birth control verification) must be administered by a registered pharmacist (either the investigator or another pharmacist from the study team).

The specific criteria that must be evaluated by a study pharmacist (and not by a non-pharmacist member of the study team) are: Exclusion Criteria Numbers 6 through 10 and 15 (see Section 4.2).

### 4.1. Inclusion Criteria

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

1. Male or female 18 years of age or older, has history of using oral OTC analgesics at OTC dose levels, defined as taking at least 5 doses/month on average during the past 3 months, and qualifies for inclusion in at least one risk group category, including cardiovascular, gastrointestinal bleeding, history of severe pain (≥5 episodes in last month) or >65 years of age (see Groups 1-4 in Section 3.1).

   OR

   Male or female 12-17 years of age and has history of using oral OTC analgesics at OTC dose levels, defined as taking at least 5 doses/month on average during the past 3 months.

2. Evidence of a personally signed and dated informed consent document (ICD), and in the case of minor adolescent subjects (12-17 years of age or adolescent subjects residing in states where the age of majority is > than 18), an assent document, indicating that the subject and where applicable a legally acceptable representative/parent(s)/legal guardian has been informed of all pertinent aspects of the study.

3. Willing and able to comply with scheduled visits, treatment plan, and other study procedures.

4. Willing (or in the case of adolescent subjects, the parent/guardian is willing) and able to purchase study medication.

5. Agrees the product purchased is for subject's own use and not to be shared.

6. Willing (or in the case of adolescent subjects, the parent/guardian is willing) and able to provide contact information for follow-up purposes.

### 4.2. Exclusion Criteria

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

1. Subject (or parent/guardian, if applicable) cannot read, speak, and/or understand English.

2. Trained or employed as a healthcare professional.

3. Subject or someone else in the household is employed by a pharmaceutical company, medical practice or hospital, pharmacy, managed care or health insurance organization or a contract research organization.

4. Investigator site staff members directly involved in the conduct of the study and their family members, site staff members otherwise supervised by the investigator, or potential subjects who are Pfizer employees, including their family members, directly involved in the conduct of the study.

5. Participation in other studies involving investigational drug(s) within 6 months prior to study entry and/or during study participation.

6. Known hypersensitivity to ibuprofen, aspirin, or any other NSAIDs.

7. Subjects with the following clinical conditions which place them at excessively high risk or have ≥20% 10-year risk for atherosclerotic cardiovascular disease (ASCVD), as defined by the 2013 ACC/AHA Guidelines on the Assessment of Atherosclerotic Cardiovascular Risk, will not be included in the study: clinically established coronary heart disease; cerebrovascular disease; peripheral artery disease; abdominal aortic aneurysm; and chronic kidney disease. Subjects who have experienced a prior non-fatal cardiovascular disease event (angina, heart failure, heart disease, heart attack, stroke/transient ischemic attack) or have had heart surgery or who currently have uncontrolled high blood pressure (either by self-report or by measured systolic blood pressure higher than 180 mmHg or diastolic pressure higher than 120 mmHg at the time of the enrollment interview), will also be excluded from the study.

8. Subjects with concurrent or recent (within 30 days) use of anticoagulants, a prior history of complicated peptic ulcer, or a gastrointestinal bleeding event requiring hospitalization or blood transfusion.

9. Other acute or chronic medical or psychiatric condition including recent (within the past year) or active suicidal ideation or behavior or laboratory abnormality that may increase the risk associated with study participation or investigational product (IP) administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

10. Pregnant female subjects; breastfeeding female subjects; and male and female subjects of childbearing potential who are unwilling or unable to use a highly effective method of contraception as outlined in this protocol for the duration of the study and for 28 days after the end of their 30-Day Use Phase or, for subjects who use the investigational product after Day 30, 28 days after the last recorded dose of investigational product.

11. 18 years of age or older and classified as normal-literacy (REALM Test score ≥61) after the normal literacy group quotas (approximately 70% of adult subjects) are full or refuses to complete the REALM Test (note there is no corresponding literacy exclusion criterion for adolescent subjects based on REALM Teen score).

12. 18 years of age or older and classified as moderate (less frequent) oral OTC pain reliever user (<30 doses per month on average in the preceding 3 months) after the moderate user group quotas (approximately 33% of adult subjects) are full.

13. Not capable of swallowing a vitamin-sized tablet.

14. Refuses to participate in required assessments (such as urine pregnancy, finger-stick cholesterol or blood pressure tests, or unable or unwilling to comply with electronic diary procedures).

The following additional exclusion criteria will be applied for adolescent subjects only (12-17 years of age):

15. Has developmental or learning disabilities that, in the judgment of the parent/guardian or the investigator, would interfere with study participation.

16. Another adolescent child from the family is already enrolled into the study, or parent/guardian does not agree that only one adolescent child from the family or household will be enrolled into the study.

### 4.3. Randomization Criteria

Not Applicable (N/A). This is a single-treatment study.

### 4.4. Lifestyle Requirements

#### 4.4.1. Contraception

In this study, male and female subjects who are of childbearing potential will receive ibuprofen, which has been associated with premature closure of the ductus arteriosus. Subjects who are, in the opinion of the investigator, sexually active and at risk for pregnancy with their partner(s) must agree to use a method of highly effective contraception throughout the study and for at least 28 days after the end of their 30-Day Use Phase or for subjects who use the investigational product after Day 30, for 28 calendar days after their last recorded dose. The investigator or his or her designee, in consultation with the subject, will confirm that the subject has selected an appropriate method of contraception for the individual subject from the list of permitted contraception methods (see below) and will confirm that the subject has been instructed in their consistent and correct use. At time points indicated in the Schedule of Activities, the investigator or designee will inform the subject of the need to use a highly effective method of contraception consistently and correctly and document the conversation, and the subject's affirmation, in the subject's case report form (CRF). In addition, the investigator or designee will instruct the subject to call immediately if the

selected contraception method is discontinued or if pregnancy is known or suspected in the subject or partner.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of hormonal methods of contraception associated with inhibition of ovulation (eg, oral, inserted, injected, implanted, transdermal), provided the subject or male subject's female partner plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper-containing intrauterine device (IUD).

3. Male condom or female condom used WITH a separate spermicide product (ie, foam, gel, film, cream, or suppository). For countries where spermicide is not available or condom plus spermicide is not accepted as highly effective contraception, this option is not appropriate.

4. Male sterilization with absence of sperm in the post-vasectomy ejaculate.

5. Bilateral tubal ligation/bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

6. Abstinence, if this is the preferred and usual lifestyle of the subject (conditional upon agreement to use an acceptable method of birth control if subject becomes sexually active).

7. Same-sex partner (conditional upon agreement to use an acceptable method of birth control if subject becomes sexually active with a member of the opposite sex).

### 4.5. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational product identifiers, subject study numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for

advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigator site.

## 5. STUDY TREATMENTS

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

For this study, the investigational product is ibuprofen 600 mg IR/ER tablets (Advil 12 Hour).

### 5.1. Allocation to Treatment

This is a single-treatment study; all eligible subjects or the parents/guardians of prospective adolescent subjects will be provided the opportunity to purchase and use ibuprofen 600 mg IR/ER tablets.

### 5.2. Breaking the Blind

Not Applicable (N/A). This is an open-label study.

### 5.3. Subject Compliance

Subjects will use the medication based only on their reading of the Drug Facts Label (DFL) and other information on the package (ie, use of the study drug is not protocol-driven). Data regarding subjects' use of the medication will be captured in an electronic diary -application either on the subject's own device (eg, smart phone, tablet or personal computer) or on a smart phone provided for use in the study. Subjects (or the parent/guardian of an adolescent subject) will be instructed by the study staff at the enrollment visit how to use the electronic diary to report their use of the medication throughout the 30-Day Use Phase.

### 5.4. Investigational Product Supplies

#### 5.4.1. Dosage Form(s) and Packaging

Ibuprofen 600 mg IR/ER (provided with the proposed trade name Advil 12 Hour) will be provided as tablets for oral administration. The 600 mg tablets will be supplied in 40 count packages and labeled according to local regulatory requirements.

#### 5.4.2. Preparation and Dispensing

The investigational product will be dispensed at the end of the Enrollment Visit. A qualified staff member will dispense the investigational product via unique container numbers in the packages provided, recording dispensation in the Electronic Data Capture (EDC) system. The subjects or the parents/guardians of prospective adolescent subjects may purchase up to a maximum of 5 total packages of the investigational product at any time during their 30-Day

Use Phase. The subject/caregiver should be instructed to maintain the product in the package provided throughout the course of the Use Phase.

### 5.5. Administration

This is an observational study with no other protocol-directed dosing. Subjects will use (or the parent/guardian of adolescent subjects will administer) the investigational product according to their own understanding of the directions on the DFL. The DFL directs users to "swallow the tablet of investigational product whole – do not crush, chew, split or dissolve."

### 5.6. Investigational Product Storage

The investigator or an approved representative, eg, pharmacist, will ensure that all investigational products are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Investigational products should be stored in their original containers and in accordance with the labels.

Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the product label.

Site systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all site storage locations. This should be captured from the time of investigational product receipt throughout the study. Even for continuous-monitoring systems, a log or site procedure that ensures active evaluation for excursions should be available. The intent is to ensure that the minimum and maximum temperature is checked each business day to confirm that no excursion occurred since the last evaluation and to provide the site with the capability to store or view the minimum/maximum temperature for all non-working days upon return to normal operations. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure they are maintained in working order.

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

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

Temperatures occurring outside of the specified storage range of 20°-25°C (68°-77°F) will be recorded and reported to Pfizer. IP will not be quarantined unless the reported temperature excursion is outside the documented stability range of 15°-30°C (59°-86°F). Receipt of materials, door opening and closing, and other routine handling operations where the products are briefly out of the temperature range described in the labeling are not considered excursions and do not need to be reported.

### 5.7. Investigational Product Accountability

The investigator site must maintain adequate records documenting the receipt, use, loss, or other disposition of the investigational product supplies. All investigational products will be accounted for using a drug accountability form/record. All unused IP and/or empty study drug packaging must be returned to the contract research organization (CRO) by the subject at the end of the trial. A pre-paid United States Postal Service (USPS) envelope will be provided to subjects at the end of the pharmacy enrollment visit for return of unused IP and empty packaging.

#### 5.7.1. Return or Destruction of Investigational Product Supplies

The sponsor or designee will provide guidance on the return or destruction of unused investigational product (eg, at the site). If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

### 5.8. Concomitant Treatment(s)

There are no prohibited prior treatments. Subjects currently using anticoagulants will be excluded from the study prior to purchasing study medication (see Section 4.2).

## 6. STUDY PROCEDURES

### 6.1. Study Sites

Approximately -30 retail pharmacies will be chosen as study sites. These sites represent an environment or setting in which consumers customarily seek and purchase their over-the-counter medications, and trained study staff and pharmacist-Investigators will manage all subject enrollment and medication purchase interactions. The sites will be selected from diverse areas of the US to provide geographic and demographic diversity. Some sites may be selected in areas of lower socio-economic status to improve recruitment of low- literacy subjects. Each site will be required to have a private office or a suitable semi-private area where the study will be carried out confidentially and without distraction. The study area at the site will be equipped with all necessary computer equipment and a high-speed Internet connection to accommodate the electronic data capture (EDC) system.

### 6.2. Recruitment Methods

To ensure adequate recruitment for the specific targeted groups requested by the FDA, multiple recruitment methods are anticipated.

- **General Population Advertising (Pain Indication Only):** General population advertisements, such as direct mail postcards, print, radio or targeted digital media to the geographic areas surrounding the study pharmacy sites will be used to generate interest. The advertisements will feature a general pain indication ("Do you use over-the-counter pain relievers to treat aches and pains?") with a toll-free number for prospective subjects to call. These advertisements are expected to capture a substantial proportion of the needed elderly subjects (>65 years of age), and a portion of this advertising may be targeted to households with socioeconomic factors loosely correlated with lower-literacy and households with children 12-17 years of age.

- **Targeted Advertising**: Because of the need to recruit adult subjects with highly-specific risk conditions (CV risk, GI bleeding risk, and severe pain sufferers), additional media advertisements, potentially including postcards, print, radio or targeted digital media, will be employed to target consumers who: 1) have pain usually treated with oral OTC pain relievers, and 2) also have relevant risk factors for inclusion in the target group (for example, "Do you use over-the-counter pain relievers to treat aches and pains? And, are you 65 years of age or older: …?" or "Do you suffer from severe pain?").

- **Targeted Outbound Pre-Recruiting:** Because adolescents are: 1) less likely than adults to use pain relievers on a regular basis, and 2) less likely to see standard recruitment advertising and consider themselves candidates for inclusion in a study, specialized recruitment vendors located near the pharmacy study sites will conduct outbound pre-recruiting telephone calls to parents/guardians from existing market research databases to identify those with adolescents who would be interested in participating. Additional targeted outbound pre-recruiting (possibly including other direct methods) may also be used to supplement recruitment for low- literacy subjects.

### 6.3. Telephone Pre-Screening

Prospective subjects (or parents/guardians of subjects) who become aware of the study via recruitment advertising will respond to the advertisement by calling a telephone number or (if available) visiting a website address to see if they qualify to participate in the study. Both the telephone number and the website address will route subjects to speak with a trained interviewer in the CRO call center, where potential subjects (or parents/guardians of minor subjects) will be pre-screened for initial eligibility criteria (all data will be entered into the study EDC system).

The parents/guardians of prospective adolescent subjects or other subjects identified by way of targeted outbound pre-recruiting will likewise be directed (by the recruiter) to visit a study website address or call the toll-free number at the CRO call center to see if they qualify to participate in the study.

Because a large proportion of each adult subgroup, approximately 30%, will need to be low literacy (AUSs often have naturally occurring low- literacy incidence rates of approximately 12-15%), evaluation of prospective adult subjects for literacy will be completed by telephone at the time of initial screening. This will be accomplished using the Rapid Estimate of Adult Literacy in Medicine-Short Form (REALM-SF) Test, an abbreviated version of the REALM Test consisting of an excerpt of only 7 words from the full assessment that are demonstrated to have high correlation to results of the REALM Test when dichotomized to an $8^{th}/9^{th}$ reading grade level split.[10] Words from the REALM-SF will be made available to prospective subjects for the telephone pre-screening via a simple website address subjects can enter into the browser of their smartphone, tablet, or personal computer, or by other electronic or non-electronic means. Once accessed, this list will display only the 7 words from the REALM-SF Test. The interviewer will give instructions for completing the test verbally over the telephone, after which the prospective subject will read the words aloud, and scoring of the REALM-SF words will be documented in the EDC system exactly as it would be if administered in- person. REALM-SF scores of zero to 6 correspond to $3^{rd}$ to $8^{th}$ grade reading levels (low health literacy), whereas a score of 7 corresponds to $9^{th}$ grade or higher reading levels (normal health literacy). This pre-screening for reading ability will help ensure adequate representation of poor readers within each of the adult at-risk groups without the significant inefficiency incurred by conducting the REALM Test only in-person at the sites. Note that neither adolescent subjects, nor their accompanying parents/guardians, will be screened for literacy at the time of the initial telephone screening and scheduling call. Subjects who are qualified based on their REALM-SF score and other eligibility criteria will have an enrollment visit scheduled at the nearest pharmacy study site, and their contact information will be collected in the subject scheduling system.

### 6.4. Pharmacy Enrollment Visit

Upon arrival at the pharmacy study site, subjects (or parents/guardians of prospective adolescent subjects) will participate in the following enrollment visit steps or procedures:

1. Identity for the subject (or the parent/guardian of adolescent subjects) will be verified from government-issued identification (ID) against contact information contained in the scheduling system.

2. For adolescent subjects 12-17 years of age, the study staff will confirm that the adolescent is accompanied by a parent or guardian. Legal guardians will be required to provide proof of guardianship. The initial telephone pre-screening and pharmacy enrollment visit assessments (with the exception of the REALM-Teen Test[7] and instances where the investigator may exercise judgment to determine if the parent/guardian and/or adolescent subject should both be present for and respond to questions in the birth control verification discussion or other sensitive content areas) will be directed to and managed by the parent/guardian, who will answer for and on behalf of the adolescent subject, and must be present to enroll into the study and purchase study medication.

3. Explicit consent to gather personal information will be elicited and documented.

4. Next, the pre-screening questions answered initially by telephone will be re-asked by the study site personnel to ensure the subject currently meets all required initial eligibility criteria. Questions at this stage will also collect information about the frequency of subjects' oral OTC pain reliever use in the 3 months prior to enrollment to define or identify heavy/frequent users (those taking 30 or more doses on average per month in the preceding 3 months) and the nature of subjects' usual pain, including severity, to define or identify self-reported frequent, severe pain sufferers (5 or more episodes of severe pain in the preceding month). Additional questions regarding medical conditions will also be asked at this stage to identify those with unacceptably high GI or CV risk ("Ask a Doctor Before Use" conditions). Responses to these questions will also help identify subgroups for at-risk populations.

5. After verification of initial screening information, those who qualify (either the subject or the parent/guardian of adolescent subjects) will be given the Advil 12 Hour package and instructed to read the product information. After reviewing the DFL and other information on the outside of the package, the subjects (or the parents/guardians of adolescent subjects) will be asked if they would like to purchase the product today for their own (or their child's own) use for $5.00 per package of 40 tablets.

6. Adult subjects who decline to purchase will be asked the reasons why they did not want to purchase and will provide basic demographic information and complete the REALM Test, after which participation will end, and subjects will be compensated. The parents/guardians of adolescent subjects who decline to purchase for their adolescent subject will be asked the reason why, provide basic demographic information and will complete the Rapid Estimate of Adolescent Literacy in Medicine (REALM-Teen) Test administered to descriptively characterize their health literacy level, after which participation will end, and the parents/guardians of the adolescent subject will be compensated.

7. Subjects (or parents/guardians of adolescent subjects) who decide to purchase the product will be asked to provide a brief history of the subject's analgesic use, including brands taken of both oral OTC and prescription medications, followed by collection of basic demographic information and the REALM Test for adults and the REALM-Teen Test for adolescent subjects. After the normal literacy group quotas (approximately 70% of adult subjects) are full, adult subjects who score as normal literacy on the REALM Test will end their participation at this point and be compensated.

8. Next, additional eligibility questions will be asked (see Exclusion Criteria 4, 9, and 13 (and if an adolescent subject, see 15 and 16) in Section 4.2). Inclusion and exclusion criteria are evaluated programmatically in the EDC system (based on pre-specified, protocol-defined, automatic edit checks), some at the initial telephone screening, and then remaining required criteria at the enrollment visit. Exclusion criteria questions that require additional judgment or understanding to recognize potential risks or clinical issues, or that involve sensitive discussions (such as birth control verification), must be administered by a registered pharmacist (either the investigator or another pharmacist from the study team).

9. Subjects (or the parent/guardian of adolescent subjects) who are qualified will be asked to review and sign the informed consent document, which will be administered, signed and documented electronically. Adolescent subjects (12-17 years of age, or older in states where the age of majority >18 years) will be asked to sign to indicate their assent. As part of the informed consent process, adolescent subjects- will be instructed that if they do not wish to participate in order not to disclose to their parent/guardian that they are sexually active, they may opt-out without being required to disclose the reason.

10. After this, the adequacy of birth control methods will be verified, and females of childbearing potential will self-administer (or in the case of young adolescent female subjects, an accompanying parent/guardian may be allowed to assist) an in-stream urine-based pregnancy test to ensure they are not pregnant.

11. At this stage, all subjects 18 or older will have a finger-stick cholesterol test (to measure total cholesterol and HDL) and blood pressure measurement. Results from these tests will be entered with other previous data into the ASCVD 10-Year Risk Calculator in the EDC System (as described in Item 1 in Section 3.1). Next, all subjects will be asked to provide additional contact information necessary for study participation (which will be entered into an administrative database), after which subjects' responses to all relevant health and other eligibility questions will be evaluated programmatically in the EDC System to determine if any exclusion criteria apply, or alternatively if the subject qualifies to continue to the study medication purchase transaction.

12. Adult subjects with excessively high CV or GI risk (screen failures, as defined in Items 7 and 8 in Section 4.2) who decide to purchase the product will provide basic demographic information, complete the REALM Test, and then answer questions about why they thought the medication would be appropriate for them to purchase even though they have an "Ask a Doctor Before Use" condition from the DFL (to enable descriptive analysis of the reasons). All other subjects who do not qualify to purchase will provide basic demographic information and complete the REALM Test (adults) or REALM-Teen Test (adolescents). Following these questions, participation will end, and subjects (or the parents/guardians of adolescent subjects) will be compensated.

13. Subjects (or the parents/guardians of adolescent subjects) who qualify to purchase the study medication will be given access to an electronic medication use diary- application either on the subject's (or, in the case of adolescent subjects, the parent's/guardian's) own device (eg, smart phone, tablet, or personal computer) or on a smart phone provided for use in the study. Subjects (or parents/guardians of minor subjects) will be instructed by the study staff at the enrollment visit how to use the electronic diary to report their use of the study medication throughout the 30-Day Use Phase.

14. The electronic diary will also capture information on concomitant medications to elucidate concurrent use of NSAIDs (see Section 6.4). To avoid sensitizing subjects to the purpose of concomitant medications data collected or influencing their behaviors surrounding concomitant NSAID use in any way, subjects will be instructed at the end of the enrollment visit to enter information for all concomitant medications (not limited to

NSAIDs) taken in the 24-hour period before or the 24-hour period after each dose of the study medication. The concomitant medications form in the electronic diary application will present instructions to reaffirm the relevant time windows for concomitant medication reporting before and after each dose of the study medication, and subjects will see these instructions each time they proceed to enter a concomitant medication dose. However, the electronic diary application will **not** present proactive prompts or reminders to subjects to make concomitant medication entries (to avoid inadvertently influencing their behaviors or perceptions of expectations for their behaviors during the study). Specifically, the electronic diary will elicit information about the medication name, date and time of dose and dose amount for each concomitant medication taken by the subject. To minimize the overall reporting burden, subjects will be instructed to enter dosing information for *routine* concomitant medications (regimens initially reported at enrollment) in the electronic diary only if they take them differently than normal. Otherwise, routine medications reported at enrollment, including NSAIDs, will be assumed to be ongoing, concomitant medications during the Use Phase. The 24-hour windows before and after doses of the study medication reflect that:

- The concomitant NSAIDs of interest are those taken in close enough temporal proximity to the study medication to result in additive NSAID over-exposure risk.

- Most prescription and oral OTC NSAID pain relievers have meaningful plasma concentration levels (and therefore dosing intervals) ≤24 hours, and therefore 24 hours is the relevant window for concomitant medication collection *before* study medication use.

- The study medication, Advil 12 Hour, has a 12-hour dosing interval. However, 24 hours is conservatively selected as the relevant window for concomitant medication collection *after* study medication use: 1) to reduce the conceptual burden that would be imposed on subjects by having different windows before and after, and 2) to avoid prompting or suggesting "12 hours" to subjects in any way during the Use Phase, since this value corresponds to a key medication use compliance endpoint.

15. Subjects (or the parent/guardian of adolescent subjects) who qualify will purchase the study medication and are permitted to purchase as much study medication as desired (up to 5 packages) at the start of the study. If they purchase less than 5 packages initially, they will be allowed to purchase additional study medication from the research site at a resupply visit, if desired, during the course of -their 30-Day Use Phase, not to exceed a total of 5 packages for the study. While the parents/guardians of adolescent subjects must be present to enroll into the study and purchase study medication initially at the enrollment -visit, to ensure needed realism, adolescent subjects- who are assigned the responsibility to complete the electronic diary and participate in all future assessments may purchase additional medication, unattended, during the course of their 30-Day Use Phase, up to the maximum of 5 packages. Any attempts by subjects (or the parents/guardians of adolescent subjects) to purchase more than 5 packages of the study medication during the study will be recorded in the study database.

16. Female subjects of childbearing potential and at risk of pregnancy will be provided an end of study pregnancy test (to self-administer after the last dose of study medication and report the result to the nurse interviewer during the End-of-Study Telephone Interview) together with a pre-paid mailer to return the study product and study-issued electronic diary device (if one is provided), and the enrollment visit will end.

### 6.5. Resupply Pharmacy Visit

For subjects who purchased less than 5 packages of study medication at their pharmacy enrollment visit, they may return to the pharmacy to purchase additional study medication at a resupply visit, if desired, during the course of their 30-Day Use Phase, not to exceed a total of 5 packages for the study.

### 6.6. 30-Day Use Phase

After leaving the pharmacy research site, subjects will use the product as needed (determined by the subject or the parents/guardians of adolescent subjects), based on their own understanding of the DFL and packaging information (ie, use of the study medication is not protocol-driven) from Day 1 to Day 30 (Use Phase). The electronic diary will be designed to send periodic (weekly, at 7-day intervals after study medication purchase) reminders to record any use of the product as soon as subjects take it. These reminders will include consistent messaging for all subjects.

In the electronic diary, subjects (or the parents/guardians of adolescent subjects) will record each dose of medication taken, including date, time, and number of tablets for each dosing occasion and will also enter additional information about the pain they were treating (for example, type and severity) to help characterize their reasons for dose selection. They will also be asked situational questions (eg, where they were, who were they with, what were they doing) at the time of dosing and what they would have taken if they did not have the study medication to use. The purpose of these situational questions is to: 1) help accurately characterize the reasons for subjects' behaviors, as well as 2) provide context to aid subjects in remembering what they did and why later during the End-of-Study (EOS) Interview questions. The electronic diary will also help capture information on concomitant medications to elucidate concurrent use of NSAIDs as described in Step 14 in Section 6.4.

At any time during the 30-Day Use Phase, subjects (or the parents/guardians of adolescent subjects) may contact the Investigator at the pharmacy site or may call the PEGUS 24-hour nurse line to report an adverse event.

#### 6.6.1. End-of-Study Telephone Interview

After the end of the 30-Day Use Phase (Days 31 to 40), a nurse from the CRO will conduct an end-of-study (EOS) interview. The telephone interview should take place shortly after Day 30 to ensure that all electronic diary entries have been transmitted, but at a time that reasonably allows for accurate subject recall about specific dosing instances. For adolescent subjects, either the parent/guardian or the adolescent subject will complete the EOS Interview, as designated by the question regarding who typically administers medications at the end of the Enrollment Visit. Subjects (and/or the parents/guardians of adolescent

subjects) will be questioned to gather information on AEs, concomitant medications for subjects who experienced adverse event(s), subjects' use of the study medication (and reasons for any deviations from the label directions), concomitant analgesic use, subjects' typical practices on following oral OTC dosing directions for analgesics, end-of-study pregnancy test results for female subjects of childbearing potential and at risk of pregnancy, and any discussion the subject may have had with a physician or other healthcare professional about the study medication use (see DCI Section 22). To facilitate a careful, in-depth behavioral assessment of subjects' reasons for misusing Advil 12 Hour, the following procedures will be employed for this final interview in person or via telephone:

- At the end of the 30-Day Use Phase, a simple tabular summary of all doses taken by the subject will be generated. This dosing summary report may include information such as the date and time of dose, number of tablets, type of pain treated and pain severity for each dosing occasion recorded in the electronic diary. The report may highlight individual occasions on which misuse occurred, defined as taking: 1) more than 2 tablets per calendar day, 2) more than 1 tablet per dosing occasion (or distinct dosing occasions with identical date-time values), or 3) a dose <12 hours after the most recent previous dose. Individual electronic diary entries (dosing occasions) may be flagged for more than one type of misuse.

- The dosing summary report will be provided to the subject (and/or the parent/guardian of adolescent subjects) for review and discussion before the time of the EOS Interview. At enrollment or subsequently, subjects may elect for (or be assigned) 1 of 3 options to complete the EOS Interview:

    1. Electronic diary data for the final interview will be provided to the subject (and/or the parent/guardian of adolescent subjects) in advance of the EOS interview (typically after Day 30 via email). This is the recommended or preferred method. The diary data will be password protected to avoid inadvertently disclosing personal health information to anyone other than the subject. Once the dosing summary report has been received by the subject, the nurse will call the subject by telephone (or alternatively, in some cases, may schedule an in-person appointment) to complete the EOS interview. Alternatively, the subject (and/or the parent/guardian of adolescent subjects) can call the nurses directly during specific hours of the week.

    2. For subjects with no access to email or who prefer to be interviewed at the site, an appointment for the EOS interview may be scheduled at the pharmacy site. Appointment times will coincide with nurse hours at the CRO. The subject will arrive at the pharmacy, return any unused study medication, using a computer at the site, and call the nurse by telephone from the site to complete the EOS Interview.

    3. A printed paper copy of the dosing summary report will also be sent to the subject via regular mail, and the EOS Interview will be conducted by telephone.

- When the EOS Interview is initiated with the subject (or parent/guardian of the adolescent subject), if misuses are evident from the electronic diary, the interviewer will review the relevant information from the dosing summary report with attention to each prioritized, specific occasion or day with misuse. CCI [redacted]

- Subjects whose diaries indicate that study medication was taken but for whom no misuse occurred will skip questions regarding reasons for misuse, but will still participate in other relevant parts of the EOS Interview, including an assessment of adverse events and medication error recording and follow-up as well as concomitant analgesic use or concomitant medication use for subjects experiencing adverse events and end-of-study pregnancy test results for female subjects of childbearing potential. Subjects whose diaries show no recorded uses of study medication will be asked questions regarding why the medication was not taken. If the subject reports that study medication was taken but not recorded in the electronic diary, the interviewer will ask general questions (not occasion-specific) regarding what types of pain were treated, how the subject took the medication (typical number of tablets per day, tablets per dose and frequency of dosing) and whether the subject (or the parent/guardian of adolescent subjects) talked to a doctor or other HCP about Advil 12 Hour during the study.

Subjects will be instructed at the conclusion of the End-of-Study Telephone Interview to discontinue all use of study medication, use the provided mailing materials to return all unused study medication and electronic diary device (if applicable), and to report the results of their end-of-study pregnancy test (females of childbearing potential). Unused study medication and other materials will be returned using a pre-addressed, postage-paid mailing envelope provided at enrollment. Subjects who are physically able to have children and who are sexually active will also be reminded (and provided the date) of the instruction to use birth control consistently and correctly at the conclusion of the End-of-Study Telephone Interview.

Once the subject has started the EOS Interview, subjects (and/or the parent/guardian of adolescent subjects) will no longer be able to make additional entries in their electronic diary and also will be provided with a form in the electronic dairy to self-administer (via mobile device) a final questionnaire about their attitudes and beliefs relating to pain reliever medications. The Attitudes and Beliefs Questionnaire will be completed by subjects using the electronic-diary application within 10 days after completing the End-of-Study Telephone Interview. This will include questions about usual oral OTC pain reliever dosing practices, the stability of subjects' (or the parents/guardians of adolescent subjects) daily routines, size and orderliness of their households, subjects' height and weight, and finally rating scales for agreement with multiple statements about the reasons for various medication usage patterns or decision-making practices.

### 6.6.2. Follow-Up Phone Contact (Up to Day 75)

Follow-up contact will be completed at least 28 calendar days, and up to 35 calendar days after the end of the subject's 30-Day Use Phase or, for subjects who use the investigational product after Day 30, for at least 28 (and up to 35) calendar days after the last recorded dose of investigational product to capture any potential adverse events (see Section 8.1.4) and to confirm appropriate contraception usage (see Section 4.4.1). The date of last administration of the investigational product will be identified by the nurse interviewer at the EOS Interview, who will verify with the subject whether the last administration corresponds with the date of the latest dosing occasion recorded in the diary or, if applicable, another date of administration that was not recorded by the subject. Contact with the subject will be made via a phone call, and study participation will end.

## 6.7. Reimbursement for Study Medication Purchase

Once all subjects have exited the study, all subjects will be reimbursed (at the same time) for the purchase price of study medication they purchased during the study. To maintain the naturalism of the study, subjects will not be notified in advance, at any time that their medication purchases will be reimbursed.

## 6.8. Subject Withdrawal or Early Termination

### 6.8.1. Withdrawal of Consent:

Subjects who request to discontinue receipt of study treatment will remain in the study and must continue to be followed for protocol specified follow-up procedures. If subjects who request to discontinue their participation are willing to complete follow-up procedures, the EOS telephone interview would be conducted as soon as possible and the Follow-Up Phone Contact will be conducted 28-35 calendar days after the date they request to discontinue. The only exception to this is when a subject specifically withdraws consent for any further contact with him or her or persons previously authorized by the subject to provide this information. Subjects should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the CRF by the investigator, as to whether the withdrawal is only from further receipt of investigational product or also from study procedures and/or post-treatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the subject is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety (see also the Withdrawal from the Study Due to Adverse Events, (Section 8.1.3) or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study site.

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

### 6.8.2. Lost to Follow-Up:

All reasonable efforts must be made to locate subjects to determine and report their ongoing status. This includes follow-up with persons authorized by the subject as noted above. Lost to follow-up is defined by the inability to reach the subject after a minimum of two documented phone calls, faxes, or e-mails as well as lack of response by the subject to one registered mail letter. All attempts should be documented. If it is determined that the subject has died, the site will use locally permissible methods to obtain the date and cause of death. The site staff and representative will consult publicly available sources, such as public health registries and databases, in order to obtain updated contact information. If, after all attempts, the subject remains lost to follow-up, then the last-known-alive date as determined by the investigator should be reported and documented in the subject's medical records.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's record. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product, request that the subject complete the EOS Interview, if applicable, and follow up with the subject regarding any unresolved adverse events (AEs).

## 7. ASSESSMENTS

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

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

### 7.1. Health Literacy Assessment

The REALM-SF Test will be used to estimate reading grade level for adult subjects during pre-screening. The REALM-SF score corresponds to 4 grade-equivalent reading levels as shown in Table 1 below. A score of 6 or less (a reading level of eighth grade or lower) will be used to identify subjects that potentially fall into the low literacy subgroup.

**Table 1. REALM-SF Test Grade-Equivalent Reading Levels**

| REALM-SF Score | Grade-Equivalent Reading Level |
|---|---|
| 0 | Third and below |
| 1-3 | Fourth to sixth |
| 4-6 | Seventh to eighth |
| 7 | Ninth and above |

The REALM Test will be used to confirm measured reading grade level for adult subjects at the enrollment visit and will be the measure of functional health literacy used for this study. The REALM score corresponds to 4 grade-equivalent reading levels as shown in Table 2 below. A score of 60 or less (a reading level of eighth grade or lower) will define the low-literacy subgroup.

**Table 2. REALM Test Grade-Equivalent Reading Levels**

| REALM Score | Grade-Equivalent Reading Level |
|---|---|
| 0-18 | Third and below |
| 19-44 | Fourth to sixth |
| 45-60 | Seventh to eighth |
| 61-66 | Ninth and above |

The REALM-Teen Test will be used to measure reading grade level for all adolescent subjects. The REALM-Teen score corresponds to 5 grade-equivalent reading levels as shown in Table 3 below. No low-literacy subgroup will be defined for adolescents. Instead, subjects' reading levels will be presented descriptively.

**Table 3. REALM-Teen Test Grade-Equivalent Reading Levels**

| REALM-Teen Score | Grade-Equivalent Reading Level |
|---|---|
| 0-37 | Third and below |
| 38-47 | Fourth to fifth |
| 48-58 | Sixth to seventh |
| 59-62 | Eighth to ninth |
| 63-66 | Tenth and above |

The health literacy tests will be scored in the EDC system. Adult subjects may be excluded based on REALM Test score if literacy quotas have been reached (see Section 4.2).

### 7.2. Pregnancy Testing

For female subjects of childbearing potential, a urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed on Day 1 before enrollment into the study (purchase of study medication) and at the end of the study (or as soon as possible after early-withdrawal) to confirm the subject has not become pregnant during the study. A pregnancy test kit will be provided to the subject at the pharmacy enrollment visit (or may be sent to the subject as a replacement towards the end of the study), so the subject can self-administer a pregnancy test following the last dose of study medication.

Also, following the enrollment visit, an additional pregnancy test will be conducted for any female subjects who elect to return to the pharmacy for the first purchase of the study medication within 3 calendar days of the original enrollment visit (to ensure they have not become pregnant during the intervening days). The result will be documented in the Data Collection Instrument (DCI).

A negative pregnancy test result is required before the subject may receive the investigational product. Pregnancy tests will also be done whenever 1 menstrual cycle is missed during the active treatment period (or when potential pregnancy is otherwise suspected). Pregnancy tests may also be repeated if requested by institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations.

Urine pregnancy tests must be sensitive to at least 25 mIU/mL and will be conducted with the test kit provided approved by the sponsor in accordance with instructions provided in its package insert. Subjects who have missed a menstrual period or who show an indeterminate or positive result on the urine test may not further progress in the study until pregnancy is ruled out using further diagnostic testing (eg, a negative quantitative serum pregnancy test conducted at a certified laboratory).

In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of investigational product and from the study.

### 7.3. Finger-Stick Cholesterol Test

After informed consent but before enrollment into the study (purchase of study medication), subjects 18 years of age and older will be required to complete a finger-stick cholesterol test. The purpose of this assessment is to determine if subjects are at increased risk for cardiovascular disease to qualify for at-risk group inclusion (see Section 3.1).

The finger-stick cholesterol test will be conducted by a trained member of the study staff using a commercially-available analyzer (CardioChek® Plus or similar). Lipid panel results, including total cholesterol and HDL cholesterol, will be entered directly into the EDC System by study staff at time of the test. Subjects who refuse to complete the test will be excluded from participation.

### 7.4. Blood Pressure Test

After informed consent but before enrollment into the study (purchase of study medication), subjects 18 years of age and older will be required to complete a blood pressure test. The purpose of this assessment is to determine if subjects are at increased risk for cardiovascular disease to qualify for at-risk group inclusion and also to rule out those with unacceptably high risk for a CV adverse event (see Section 3.1).

The blood pressure test will be conducted by a trained member of the study staff using a commercially-available blood pressure testing device. Blood pressure results, including systolic and diastolic blood pressure values, will be entered directly into the EDC System by study staff at time of the test. Subjects who refuse to complete the test will be excluded from participation.

Blood pressure will be assessed in a sitting position with both feet flat on the floor and back supported, after the subject has been seated for at least 10 minutes. Subjects should be instructed not to speak during measurements. The left (or if this is not possible, then the right) arm will be used for any given subject when measuring blood pressure. At the discretion of the trained member of the study staff, blood pressure measurements may be repeated to confirm the measurement (eg, due to subject movement, abnormal measurement, etc.). When repeated measurements are necessary, a total of 3 measurements, at least 5 minutes apart, will be made, and the lowest systolic and diastolic values from these three measurements will be entered into the EDC System.

### 7.5. 10-Year Risk for Atherosclerotic Cardiovascular Disease (ASCVD) Assessment

The 2013 ACC/AHA Prevention Guidelines Tool CV Risk Calculator, which is a companion tool to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk, will be used to calculate adult subjects' 10-year risk for ASCVD. A Risk Calculator will be programmed in to the EDC system to calculate each subject's 10-year ASCVD risk. Values entered into the Risk Calculator will include age, gender, race, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for high blood pressure (yes/no), diabetes (yes/no), and current smoking status (yes/no). Subjects in the 40-79-year age bracket will only be eligible for inclusion in the CV Risk Group if they have a score of ≥5% and <20% for 10-Year ASCVD risk (see Section 3.1).

### 7.6. Rater Qualifications

Not applicable.

## 8. ADVERSE EVENT REPORTING

### 8.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF and for reporting safety events on the Clinical Trial (CT) Serious Adverse Event (SAE) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) non-serious adverse events (AEs); and (3) exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| SAE | All | All |
| Non-serious AE | All | None |
| Exposure to the investigational product under study during pregnancy or breastfeeding, and occupational exposure | All (regardless of whether associated with an AE), **except occupational exposure** | Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE) |

All observed or volunteered events regardless of suspected causal relationship to the investigational product will be reported as described in the following paragraphs.

Events listed in the table above that require reporting to Pfizer Safety on the CT SAE Report Form within 24 hours of awareness of the event by the investigator **are to be reported regardless of whether the event is determined by the investigator to be related to an investigational product under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer Safety must be made immediately, irrespective of the extent of available event information. This time frame also applies to additional new (follow-up) information on previously forwarded reports. In the rare situation that the investigator does not become immediately aware of the occurrence of an event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the event.

For each event, the investigator must pursue and obtain adequate information both to determine the outcome and to assess whether it meets the criteria for classification as an SAE (see the Serious Adverse Events, Section 8.2.3 below). In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the CRF. In general, this will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety. Any pertinent additional information must be reported on the CT SAE Report Form; additional source documents (eg, medical records, CRF, laboratory data) are to be sent to Pfizer Safety **ONLY** upon request.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

### 8.1.1. Additional Details on Recording Adverse Events on the CRF

All events detailed in the table above will be recorded on the AE page(s) of the CRF. It should be noted that the CT SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology, and the same AE term should be used on both the CRF and the CT SAE Report Form for reporting of SAE information.

### 8.1.2. Eliciting Adverse Event Information

The investigator is to record on the CRF all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian. In addition, each study subject/parent(s)/legal guardian will be questioned about the occurrence of AEs in a non-leading manner.

### 8.1.3. Withdrawal from the Study Due to Adverse Events (see also the Subject Withdrawal section)

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

When a subject withdraws from the study because of an SAE, the SAE must be recorded on the CRF and reported, as appropriate, on the CT SAE Report Form, in accordance with the Requirements section above.

### 8.1.4. Time Period for Collecting AE/SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each subject begins from the time the subject provides informed consent, which is obtained before the subject's participation in the study (ie, before undergoing any study-related procedure and/or receiving investigational product), through and including a minimum of 28 calendar days after the end of the subject's 30-Day Use Phase or, for subjects who use the investigational product after Day 30, for at least 28 calendar days after the last recorded dose.

For subjects who are screen failures, the active collection period ends when screen failure status is determined.

#### 8.1.4.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a subject during the active collection period are reported to Pfizer Safety on the CT SAE Report Form.

SAEs occurring in a subject after the active collection period has ended are reported to Pfizer Safety if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product must be reported to Pfizer Safety.

Follow up by the investigator continues throughout and after the active collection period and until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

#### 8.1.4.2. Recording Non-Serious AEs and SAEs on the CRF

During the active collection period, both non-serious AEs and SAEs are recorded on the CRF.

Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

### 8.1.5. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship on the CRF, and report such an assessment in accordance with the SAE reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally, the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor. If the investigator's causality assessment is "unknown but not related" to investigational product, this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the CT SAE Report Form and in accordance with the SAE reporting requirements.

### 8.1.6. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## 8.2. Definitions

### 8.2.1. Adverse Events

An AE is any untoward medical occurrence in a study subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include, but are not limited to:

- Abnormal test findings;

- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

Additionally, AEs may include signs and symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

### 8.2.2. Abnormal Test Findings

Abnormal objective test findings should be recorded as AEs when any of the following conditions are met:

- Test result is associated with accompanying symptoms; and/or
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or
- Test result leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require recording as an AE.

### 8.2.3. Serious Adverse Events

A serious adverse event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Or that is considered to be:

- An important medical event.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization; however, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### 8.2.4. Hospitalization

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility, or any prolongation of an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit is assessed for medical importance.

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;

- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of a persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as SAEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an SAE. For example, an acute appendicitis that begins during the reporting period should be reported if the SAE requirements are met, and the resulting appendectomy should be recorded as treatment of the AE.

### 8.3. Severity Assessment

| On the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows: | |
|---|---|
| MILD | Does not interfere with subject's usual function. |
| MODERATE | Interferes to some extent with subject's usual function. |
| SEVERE | Interferes significantly with subject's usual function. |

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

## 8.4. Special Situations

### 8.4.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported to Pfizer Safety by the investigator as described in previous sections and will be handled as SAEs in the safety database.

### 8.4.2. Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt, are termed “adaptors.” In some subjects, transaminase elevations are a harbinger of a more serious potential outcome. These subjects fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as drug-induced liver injury (DILI). Subjects who experience a transaminase elevation above 3 times the upper limit of normal (× ULN) should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a subject presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) precede total bilirubin (TBili) elevations (>2 × ULN) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and TBili values will be elevated within the same lab sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the subject’s individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a TBili value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

- For subjects with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

    - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

    - Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least 1 × ULN **or** if the value reaches >3 × ULN (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The subject should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment.

In addition to repeating measurements of AST and ALT and TBili, laboratory tests should include albumin, creatine kinase (CK), direct and indirect bilirubin, gamma-glutamyl transferase (GGT), prothrombin time/international normalized ratio (INR), total bile acids, alkaline phosphatase and acetaminophen drug and/or protein adduct levels. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

### 8.4.3. Exposure to the Investigational Product During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the investigational product under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

#### 8.4.3.1. Exposure During Pregnancy

For both unapproved/unlicensed products and for marketed products, an exposure during pregnancy (EDP) occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;
    - An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
- A male has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a subject or subject's partner becomes or is found to be pregnant during the subject's treatment with the investigational product, the investigator must report this information to Pfizer Safety on the CT SAE Report Form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) to Pfizer Safety using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP supplemental form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the investigational product.

Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

#### 8.4.3.2. Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated SAE, to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug's administration, the SAE is reported together with the exposure during breastfeeding.

#### 8.4.3.3. Occupational Exposure

An occupational exposure occurs when, during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an AE.

An occupational exposure is reported to Pfizer Safety within 24 hours of the investigator's awareness, using the CT SAE Report Form, regardless of whether there is an associated SAE. Since the information does not pertain to a subject enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed CT SAE Report Form is maintained in the investigator site file.

### 8.4.4. Medication Errors

Other exposures to the investigational product under study may occur in clinical trial settings, such as medication errors.

| Safety Event | Recorded on the CRF | Reported on the CT SAE Report Form to Pfizer Safety Within 24 Hours of Awareness |
|---|---|---|
| Medication errors | All (regardless of whether associated with an AE) | Only if associated with an SAE |

Medication errors may result in this study from the administration or consumption of the investigational product by the wrong subject.

Medication errors include:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject;
- Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF which is a specific version of the AE page.

In the event of a medication error, the sponsor should be notified immediately.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and non-serious, is recorded on an AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a CT SAE Report Form **only when associated with an SAE**.

## 9. DATA ANALYSIS/STATISTICAL METHODS

Detailed methodology for summary and statistical analyses of the data collected in this study is outlined here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

## 9.1. Sample Size Determination

### Overall Sample Size (Adult Risk Groups):

Overall sample size for the combined adult risk groups (cardiovascular risk, gastrointestinal bleeding risk, history of severe pain and >65 years of age) is driven primarily by power considerations. The following assumptions are used to construct the sample size calculation:

- Subject recruitment will be structured in a way to ensure that heavy pain reliever users (ie, those who report taking 30 or more doses on average per month in the 3 months preceding enrollment) will represent approximately two-thirds (67%) of the overall adult sample.

- Based on the Primary Endpoint (exceed >1200 mg per day on 2 or more days), the composite misuse rate (for combined heavy and moderate users in the study, in the proportions postulated above) is assumed to be of 6.6%, for a correct performance (ie, correct daily dosing compliance) rate of 93.4%.

- An *a priori* performance threshold of 90% is selected for the Primary Endpoint. The lower limit of the 95% confidence interval (CI) for the obtained value for correct performance for the Primary Endpoint among the full adult Compliance-Evaluable Population must exceed this threshold value for success.

- Power should be at least 85%.

- Two-sided normal approximation z test for binomial proportion, alpha=.05.

Utilizing these assumptions, an overall sample of at least 620 compliance-evaluable adult subjects will yield 85% power to demonstrate superiority of the Primary Endpoint correct performance finding over the *a priori* performance threshold.

### Individual Adult Group Sizes:

For each of the first 4 risk groups (adults with cardiovascular risk, gastrointestinal bleeding risk, history of severe pain or >65 years of age) it is expected that a minimum of approximately 180 subjects will be recruited and enrolled in order to yield at least 155 who are compliance-evaluable for the analysis. Note, however, that because of substantial natural comorbidity (overlap) for these risk conditions, the at-risk groups are not mutually exclusive and many or most subjects will qualify for inclusion in more than one group, so that the sum of the individual subgroup counts will be expected to exceed the total adult subject count. If any individual risk group fails to fill adequately, additional measures (such as more targeted recruitment advertising or excluding potential subjects who belong only to other, over-full risk groups) may be employed. Any procedures used to manage risk group representation will be documented in the study report.

**Adolescent Group Size:**

It is expected that the study will recruit a total of approximately 100 adolescent subjects to ensure approximately 80 will be evaluable for the endpoint analysis (note the enrolled-to-evaluable attrition rate for adolescents is expected to be somewhat larger than for adults). For the Adolescent Group, a sample of 80 compliance-evaluable subjects is expected to be adequate to describe or characterize dosing compliance and other important behaviors as well as the underlying reasoning processes for this specific cohort of potential users of the ultimate approved product.

While reading grade level will be measured for adolescents (based on the REALM-Teen Test) and summarized descriptively, adolescent subjects will not be classified as low- or normal- literacy for the study.

Similarly, adolescents entering the study will not be required to have any specific risk factors, history of severe pain or history of heavy pain reliever use.

**Total Sample Size Requirements:**

The total number of subjects expected to enroll into the study is 820 (including approximately 720 adults and 100 adolescents). Accordingly, the number of subjects expected to be screened by telephone is 14,409, of whom approximately 7,029 would meet all initial screening criteria and schedule an enrollment visit appointment. Among these, it is expected that 3,046 would visit a participating pharmacy research site, and 820 would meet all eligibility criteria, purchase study medication and enter the Use Phase. Finally, among enrolled subjects it is expected approximately 700 would be available for the dosing compliance endpoint analysis (compliance-evaluable subjects are those that take at least one dose of study medication and record it in the electronic diary), including approximately 620 adults and 80 adolescents.

## 9.2. Dosing Compliance Analysis

### 9.2.1. Analysis of the Primary Endpoint

The analysis population for dosing compliance is composed of subjects that report at least one dose (dosing occasion with 1 or more tablets) of the study medication in the electronic diary application (Adult Compliance-Evaluable Population). The Primary Endpoint (proportion of subjects who exceed the maximum daily dose, 1200 mg, on two or more days during the use period) will be calculated as:

> Adult compliance-evaluable subjects exceeding 1200 mg/day on ≥2 days, divided by the total number of adult compliance-evaluable subjects.

The complement of this number (1 – obtained proportion) will be calculated. This is the correct performance rate.

Subgroup analysis for the primary endpoint will be performed on subjects within each of the at-risk populations: 1) increased CV risk; 2) increased GI risk; 3) a history of severe pain; and 4) >65 years age. The correct performance rate for adolescent subjects will be presented descriptively; no inferential analysis on adolescent subjects will be performed.

### 9.2.2. Performance Threshold Selection and Rationale

The Primary Endpoint will be considered successfully met if the lower-limit of the two-sided 95% CI (calculated using the Wald Confidence Interval) for the correct performance rate is greater than the *a priori* performance standard of 90%. Adolescent performance for the Primary Endpoint will be presented descriptively. No inferential analysis on adolescents will be performed and hence it will not be compared to the performance threshold.

This performance threshold for the Primary Endpoint is selected to be highly conservative. Based on the power calculations noted in Section 9.1, a minimum of 93.4% of compliance evaluable subjects will need to exhibit correct performance to be successful for this endpoint. This high standard is to provide robust assurance regarding the utility of the proposed labeling refinements and the ability of consumers to correctly dose based on the directions for Advil 12 Hour.

### 9.2.3. Analysis of Secondary CCI [redacted] Dosing Compliance Endpoints

Values for all other dosing compliance endpoints will be calculated in similar fashion to the Primary Endpoint (number of compliance-evaluable subjects exceeding the relevant dosing direction or dosing frequency, divided by the total number of adult compliance-evaluable subjects). However, Secondary CCI [redacted] Endpoint findings will not be compared to any pre-specified performance thresholds. The SAP will provide a detailed description of the calculation methods for all endpoints.

Subgroup analysis for the secondary endpoints will be performed on subjects within each of the at-risk populations: 1) increased CV risk; 2) increased GI risk; 3) a history of severe pain; and 4) >65 years age.

CCI [redacted]

CCI

[redacted]

CCI

CCI

[redacted]

CCI

[redacted]

### 9.4. Safety Analysis

Adverse event (AE) summaries will include all events which initially occurred or worsened following initiation of treatment. AEs will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) designations and classified according to their severity (mild, moderate, or severe) and relationship (related or not related) to the study product. CCI

[redacted]

CCI

[redacted]

CCI

[redacted]

### 9.6. Interim Analysis

No formal interim analysis will be conducted for this study. However, as this is an open-label study, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose-escalation decisions, facilitating pharmacokinetic (PK)/pharmacodynamic (PD) modeling, and/or to support clinical development.

### 9.7. Data Monitoring Committee

Not applicable (N/A).

## 10. QUALITY CONTROL AND QUALITY ASSURANCE

Pfizer or its agent will conduct periodic monitoring visits during study conduct to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification. This verification may also occur after study completion.

During study conduct and/or after study completion, the investigator site may be subject to review by the IRB/EC, and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

The investigator(s) will notify Pfizer or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with Pfizer or its agents to prepare the investigator site for the inspection and will allow Pfizer or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the subject's study records. The investigator will promptly provide copies of the inspection findings to Pfizer or its agent. Before response submission to the regulatory authorities, the investigator will provide Pfizer or its agents with an opportunity to review and comment on responses to any such findings.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

# 11. DATA HANDLING AND RECORD KEEPING

## 11.1. Case Report Forms/Electronic Data Record

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

A CRF is required and should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital or the physician subject chart. In these cases, data collected on the CRFs must match the data in those charts.

In some cases, the CRF may also serve as the source document. In these cases, a document should be available at the investigator site and at Pfizer that clearly identifies those data that will be recorded on the CRF, and for which the CRF will stand as the source document.

A Data Management Plan (DMP) will be created to describe the data management system and define procedures for security, user acceptance testing, data validation (edit specifications, queries and self-evident corrections), coding and database lock.

## 11.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent[/assent] documents, copies of all CRFs, safety reporting forms, source documents and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes and telephone call reports). The records should be retained by the investigator according to the ICH guidelines, according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution or an independent third party arranged by Pfizer.

Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## 12. ETHICS

### 12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent/assent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

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

### 12.2. Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, legal and regulatory requirements and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), ICH Guideline for Good Clinical Practice, and the Declaration of Helsinki.

### 12.3. Subject Information and Consent

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

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by numerical codes based on a numbering system provided by Pfizer in order to de-identify study subjects. The investigator site will maintain a confidential list of subjects who participated in the study, linking each subject’s numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects’ personal data consistent with applicable privacy laws.

The informed consent/assent documents and any subject recruitment materials must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent/assent documents used during the informed consent process and any subject recruitment materials must be reviewed and approved by Pfizer, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject, or parent(s) or legal guardian if a minor, is fully informed about the nature and objectives of the study and possible risks associated with participation.

Whenever consent is obtained from a subject's legally acceptable representative/parent(s) or legal guardian, the subject's assent (affirmative agreement) must subsequently be obtained when the subject has the capacity to provide assent, as determined by the IRB/EC. If the investigator determines that a subject's decisional capacity is so limited he/she cannot reasonably be consulted, then, as permitted by the IRB/EC and consistent with local regulatory and legal requirements, the subject's assent may be waived with source documentation of the reason assent was not obtained. If the study subject does not provide his or her own consent, the source documents must record why the subject did not provide consent (eg, minor, decisionally-impaired adult), how the investigator determined that the person signing the consent was the subject's legally acceptable representative, the consent signer's relationship to the study subject (eg, parent, spouse), and that the subject's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

If the study includes minor subjects who reach the age of majority during the study, as recognized under local law, they must reconsent as adults to remain in the study. If the enrollment of emancipated minors is permitted by the study age criteria, the IRB/EC, and local law, they must provide documentation of legal status to give consent without the permission of a parent or legal guardian.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject or the parent(s) or legal guardian and the subject's assent, when applicable, before any study-specific activity is performed, unless a waiver of informed consent has been granted by an IRB/EC. The investigator will retain the original of each subject's signed consent/assent document.

Coded subject information may be used to advance scientific research and public health in other projects that will occur in the future. At this time, Pfizer cannot anticipate the specific details of any future research projects. The privacy and confidentiality of subjects would be maintained. The subject would acknowledge this via the subject's signature on the consent/assent document.

### 12.4. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

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

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

## 13. DEFINITION OF END OF TRIAL

### 13.1. End of Trial in All Participating Countries

End of trial in all participating countries is defined as last subject last visit (LSLV).

## 14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or investigational product safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of 600 mg IR/ER ibuprofen at any time.

If a study is prematurely terminated, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects within 7 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 15. PUBLICATION OF STUDY RESULTS

### 15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the European Clinical Trials Database (EudraCT), and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial US Basic Results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a Pfizer product, regardless of the geographical location in which the study is conducted. US Basic Results are submitted for posting within 1 year of the primary completion date (PCD) for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

PCD is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the prespecified protocol or was terminated.

EudraCT

Pfizer posts European Union (EU) Basic Results on EudraCT for all Pfizer-sponsored interventional studies that are in scope of EU requirements. EU Basic Results are submitted for posting within 1 year of the PCD for studies in adult populations or within 6 months of the PCD for studies in pediatric populations.

www.pfizer.com

Pfizer posts Public Disclosure Synopses (clinical study report synopses in which any data that could be used to identify individual patients has been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the US Basic Results document is posted to www.clinicaltrials.gov.

### 15.2. Publications by Investigators

Pfizer supports the exercise of academic freedom and has no objection to publication by the principal investigator (PI) of the results of the study based on information collected or generated by the PI, whether or not the results are favorable to the Pfizer product. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, the investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure of the results of the study (collectively, "publication") before it is submitted or otherwise disclosed.

The investigator will provide any publication to Pfizer at least 30 days before it is submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study-, or Pfizer product-related information necessary to the appropriate scientific presentation or understanding of the study results.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all investigator sites, and that any subsequent publications by the PI will reference that primary publication. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, the investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, the institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the CSA between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the CSA.

If there is any conflict between the CSA and any attachments to it, the terms of the CSA control. If there is any conflict between this protocol and the CSA, this protocol will control as to any issue regarding treatment of study subjects, and the CSA will control as to all other issues.

## 16. REFERENCES

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## ABBREVIATIONS

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

| Abbreviation | Term |
|---|---|
| ACC | American College of Cardiology |
| AE | adverse event |
| AHA | American Heart Association |
| ALT | alanine aminotransferase |
| APTC | -Antiplatelet Trialists' Collaboration |
| ASCVD | atherosclerotic cardiovascular disease |
| AST | aspartate aminotransferase |
| AUS | Actual use study |
| CI | Confidence interval |
| CIOMS | Council for International Organizations of Medical Sciences |
| CK | creatine kinase |
| CRF | case report form |
| CRL | Complete response letter |
| CRO | Contract research organization |
| CSA | clinical study agreement |
| CSR | clinical study report |
| CT | Clinical trial |
| CTA | clinical trial application |
| CTCAE | Common Terminology Criteria for Adverse Events |
| CV | cardiovascular |
| DCI | data collection instrument |
| DFL | Drug Facts label |
| DILI | drug-induced liver injury |
| DMC | data monitoring committee |
| DMP | data management plan |
| EC | ethics committee |
| EDC | Electronic data capture |
| EDP | exposure during pregnancy |
| EOS | end of study |
| ER | extended release |
| EU | European Union |
| EudraCT | European Clinical Trials Database |
| FDA | Food and Drug Administration |
| FSH | follicle-stimulating hormone |
| GCP | Good Clinical Practice |
| GGT | gamma-glutamyl transferase |
| GI | gastrointestinal |
| HCP | Healthcare practitioner |
| HDL | high-density lipoprotein |
| IB | Investigator's brochure |

| Abbreviation | Term |
|---|---|
| IBU | ibuprofen |
| ICD | Informed consent document |
| ICH | International Conference on Harmonisation |
| ID | identification |
| IND | investigational new drug application |
| INR | international normalized ratio |
| IP | investigational product |
| IR | immediate release |
| IRB | institutional review board |
| IRC | internal review committee |
| IUD | intrauterine device |
| LFT | liver function test |
| LSLV | last subject last visit |
| MedDRA | Medical Dictionary for Regulatory Activities |
| N/A | not applicable |
| NDA | new drug application |
| NSAIDS | nonsteroidal anti-inflammatory drugs |
| OTC | Over the counter |
| PACL | Protocol Administrative Change Letter |
| PCD | primary completion date |
| PCH | Pfizer Consumer Healthcare |
| PD | Pharmacodynamics(s) |
| PI | principal investigator |
| PK | pharmacokinetic |
| PT | preferred term |
| REALM | Rapid Estimate of Adult Literacy in Medicine |
| REALM-SF | Rapid Estimate of Adult Literacy in Medicine – Short Form |
| REALM-Teen | Rapid Estimate of Adolescent Literacy in Medicine |
| Rx | prescription |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SOC | System organ class |
| SOP | standard operating procedure |
| SRSD | single reference safety document |
| SUSAR | suspected unexpected serious adverse reaction |
| TBili | total bilirubin |
| TID | Three times a day |
| ULN | upper limit of normal |
| URL | universal resource locator |
| US | United States |
| USPS | Unites States Postal Service |
| WHO | World Health Organization |