Protocol B4371011

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

Statistical Analysis Plan
(SAP)

Version: **1**

Date: 20 Jan. 2021

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APPENDICES

1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
1 / 20 Jan 2021	Amendment 2 Protocol/Final v3.0_06 Mar 2019	Not Applicable (N/A)	N/A

2. INTRODUCTION

This statistical analysis plan (SAP) provides the detailed methodology for summary and statistical analyses of the data collected in Study B4371011. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

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 FDA 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, the FDA granted a Type C meeting to discuss the design of Pfizer's proposed AUS. Specifically, Pfizer and the FDA met once again to discuss and clarify issues surrounding the primary endpoint, subjects with "Ask a Doctor Before Use" conditions, methods to preselect for low reading ability, collecting concomitant NSAID use information during the Use Phase, and other important topics relevant to this study and the program. The study 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.

2.1. Study Objectives, Endpoints, and Estimates

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. • 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 (i.e., subjects who did not understand the dosing instructions on the package). • The proportion of subjects who exceed the maximum amount per dose (600 mg) on 1 or more occasions. • The proportion of subjects who exceed the maximum amount per dose (600 mg) on two or more occasions. • The proportion of subjects who exceed the maximum daily dose on 10 or more calendar days. • 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 (i.e., 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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2.2. 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 (including approximately 720 adults and 100 adolescents). For each of the first 4 risk groups (i.e., elderly consumers of >65 years of age, adults with GI bleeding risk, adults with CV adverse events risk, adults with history of severe pain), it is expected that a minimum of approximately 180 subjects will be recruited and enrolled, and within each risk group, approximately 30% will be low literacy based on the Rapid Estimate of Adult Literacy in Medicine (REALM) Test[1]. 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. 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. To allow for real-world, naturalistic medication use behaviors between parents/guardians and adolescent subjects, adolescent subjects and the parents/guardians of adolescent subjects will determine who will be responsible 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 based on their answer to this question at the end of the pharmacy Enrollment Visit: "Who usually decides how you (adolescent subject) will take OTC pain reliever medicines?" If the answer is the parent/guardian, the

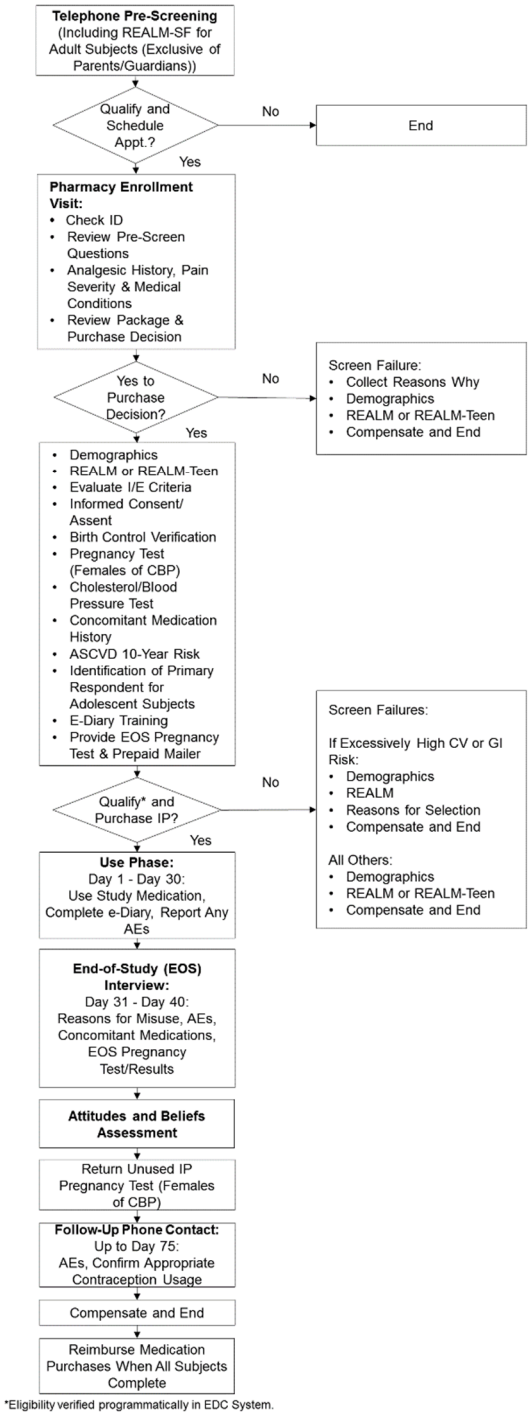
parent/guardian will be responsible for entering data and participating in all future assessments. If the answer is the adolescent subject, the adolescent subject will be responsible for entering data and participating in all future assessments. In cases where the parent/guardian and the adolescent report they "both" usually administer OTC pain reliever medications the adolescent takes, the parent/guardian and adolescent will be asked to decide which of them will have primary responsibility.

The electronic diary will also capture information on concomitant medications to elucidate concurrent use of NSAIDs. 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 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 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.

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[2] 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. The individual (parent/guardian or adolescent subject) identified as the one who usually administers the 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. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

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). Only diary data during the 30-

Day Use Phase will be included for the analysis population for dosing compliance. All diary data, entered during the Use Phase or outside of this window, will be relevant for safety reporting.

3.1. Primary Endpoint(s)

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.

3.2. Secondary Endpoint(s) Dosing Compliance

Values for the following dosing compliance endpoints will be calculated in similar fashion to the Primary Endpoint (number of adult compliance-evaluable subjects exceeding the relevant dosing direction or dosing frequency, divided by the total number of adult compliance-evaluable subjects). The complement of this number (1-obtained proportion) will be calculated and will equal the total number of subjects with correct responses; however, these findings will not be compared to any pre-specified performance thresholds.

- Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period.
- 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 (i.e., subjects who did not understand the dosing instructions on the package).
- The proportion of subjects who exceed the maximum amount per dose (600 mg) on 1 or more occasions.
- The proportion of subjects who exceed the maximum amount per dose (600 mg) on two or more occasions.
- The proportion of subjects who exceed the maximum daily dose on 10 or more calendar days.
- 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 (i.e., 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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3.4. Baseline Variables

Cholesterol test results for all adult subjects will be recorded before enrollment into the study, including total cholesterol and HDL cholesterol.

A blood pressure (BP) test for all adult subjects will be conducted, and the results will be recorded before enrollment into the study, including systolic BP (mmHg) and diastolic BP (mmHg).

Subjects' 10-year atherosclerotic cardiovascular disease (ASCVD) risk will be calculated for all adult subjects (between the ages of 40 and 79 years old) before enrollment into the study.

3.5. Safety Endpoints

Section 3.3.3 displays safety compliance endpoints specified in the protocol. The incidence of adverse events (AEs) will be evaluated.

3.5.1. Adverse Events

All observed or volunteered events regardless of suspected causal relationship to the investigational product will be reported. All AEs will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT).

The time period for actively eliciting and collecting AEs and serious AEs (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 (i.e., 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 of investigational product.

A 3-tier approach will be used to summarize AEs. Under this approach, AEs are classified into 1 of 3 tiers. No Tier-1 events (pre-specified events of clinical importance) have been identified in the Safety Review Plan (SRP) for this product. However, for this study AEs included in the Targeted Medical Event (TME) list of the SRP (see Appendix 1) will be used to summarize these types of AEs. Different analyses will be performed for different tiers (see Section 6.6.1).

Tier 1 events: These are prespecified events of clinical importance and are maintained in a list in the product's SRP. For this study, TME in the SRP are considered as Tier-1 events.

Tier 2 events: These are events that are not Tier-1 but are "common." A MedDRA PT is defined as a Tier-2 event if there are at least 2% in any treatment group.

Tier 3 events: These are events that are neither Tier-1 nor Tier-2 events.

3.5.2. Laboratory Data

Not applicable.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to releasing the database and classifications will be documented per Vendor's (PEGUS) standard operating procedures (SOPs). The populations of interest are defined as follows:

Population	Description
Screening	Potential subjects who respond to the recruitment advertising, call the toll-free number, and begin the screening process.
Enrollment	Subjects who upon fulfilling the phone screen interview (and meet study inclusion criteria), schedule a face-to-face interview at the pharmacy site, appear at their scheduled interview, and make a purchase decision.
Purchasers	Subjects who purchase the study medication.
Adult Compliance–Evaluable	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.
Adolescent Users	Subjects less than age of majority (based on state of residence) that report at least one dose (dosing occasion with 1 or more tablets) of the study medication in the electronic diary application.
Safety	All subjects who sign informed consent and purchase the product.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The primary endpoint analysis will be the Wald test of binary endpoints which will be performed to calculate the two-sided 95% confidence interval (CI). 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 in the Adult Compliance-Evaluable Population 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.

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

For all binary endpoints, frequency and proportion will be calculated. Additionally, a 95% CI will be calculated for the primary endpoint based on Wald and Exact tests, the latter being a secondary analysis method.

5.2.2. Analyses for Categorical Endpoints

For categorical endpoints, descriptive statistics will be provided (number and %).

5.2.3. Types of Data to be Analyzed

Data regarding subjects' use of the study medication is to be captured in an electronic diary, including the date, time, number of tablets taken, and other information for each dosing occasion. Per the protocol, the primary and secondary endpoint results are to be calculated from diary data and as well as clarified or mitigated diary data, which will lead in some cases to the generation of four sets of statistical tables as described below.

Analysis Set Number	Brief Description	Detailed Description
1	Original Data	Data exactly as recorded by subjects into their electronic diary.
2	Clarified Data	Data clarified by the nurses during the EOS interview under very specific pre-specified conditions when subjects spontaneously identified dosing occasion-specific entry errors in their original electronic diary data.
3	Corrected/Mitigated Data – Incorrect or Impossible Diary Entries	Clarified data (Set 2) **plus** misuses mitigated for additional diary entries judged to be incorrect or impossible based on subjects' clear verbatim responses in the EOS interview.

4	Mitigated Data – Pre-Specified Factors	Corrected data (Set 3) **plus** circumstances or considerations resulting in reclassification of misuses to "acceptable" status, meaning the risk-benefit balance is judged to be favorable by the subject despite misuse. Pre-specified mitigations (see Protocol Mitigation Plan under Section 9.3.1) include: 1. Clear consultation with or direction from a healthcare practitioner (HCP). 2. Subjects who indicate they would have taken an opioid or other Rx analgesic if they had not taken another dose. 3. Subjects who indicated they would have misused acetaminophen or other OTC analgesics. 4. Subjects who re-dose earlier due to scheduling restrictions in order to prevent pain from returning.

Analysis Set 3 incorporates both the subject-initiated data entry clarifications (implemented by the nurses at the EOS Interview) and post-study mitigations for diary entries determined to be incorrect or impossible. Analysis Set 3 therefore represents the subjects' actual dosing behaviors, with self-reported errors and self-evident diary entry errors removed. Analysis Set 4 builds on Analysis Set 3 by adding pre-specified mitigation factors to put occasions of misuse into context.

5.3. Methods to Manage Missing Data

All missing data will be considered missing, and no statistical procedures will be employed to estimate or impute missing data.

6. ANALYSES AND SUMMARIES

6.1. Primary Endpoint(s)

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.

6.1.1. Main Analysis

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

A 95% two-sided CI for the primary endpoint will be calculated using the Wald test. 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%.

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Additional calculations will be performed using a 2-sided Exact Test for the 95% CIs for both primary and secondary endpoints only.

No sensitivity analyses will be performed.

6.2. Secondary Endpoint(s)

Like the primary endpoint, secondary endpoints will be calculated as the number of adult compliance-evaluable subjects meeting the specified definition divided by the total number of adult compliance evaluable subjects, and the complement of this number will be the correct performance rate. Secondary endpoint findings will not be compared to any pre-specified performance thresholds.

6.2.1. Proportion of subjects who exceed the maximum daily dose (1200 mg) on one or more calendar days during the use period

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.2. 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 (i.e., subjects who did not understand the dosing instructions on the package)

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.3. The proportion of subjects who exceed the maximum amount per dose (600 mg) on 1 or more occasions

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.4. The proportion of subjects who exceed the maximum amount per dose (600 mg) on two or more occasions

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.5. The proportion of subjects who exceed the maximum daily dose on 10 or more calendar days

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.6. The proportion of subjects who exceed the maximum daily dose on 7 or more calendar days

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.7. The proportion of subjects who take more than two doses (i.e., more than two dosing occasions) on a calendar day

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

6.2.8. The proportion of subjects who re-dose in <12 hours, <10 hours, and <8 hours on 1 or more occasions

Frequency and proportion for each re-dose scenario category will be calculated based on the Adult Compliance-Evaluable Population.

6.2.9. The proportion of subjects who use the product on more than 10 consecutive days

Frequency and proportion will be calculated based on the Adult Compliance-Evaluable Population.

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6.4. Subset Analyses

Subgroup analysis for the primary and secondary endpoints will be performed based on normal and low literacy subgroups, adolescent users, and 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 rates for these subsets will be presented descriptively including 95% confidence intervals. No inferential analyses will be performed, and hence these results will not be compared to the performance threshold.

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

Cholesterol test results including total cholesterol and HDL cholesterol will be summarized with descriptive statistics based on the Purchasers, Adult Compliance-Evaluable Population, Safety Population, and within each at-risk subpopulation.

BP test results including systolic BP (mmHg) and diastolic BP (mmHg) will be summarized with descriptive statistics based on the Purchasers, Adult Compliance-Evaluable Population, Safety Population, and within each at-risk subpopulation.

Subject's 10-year ASCVD risk will be summarized with descriptive statistics based on the Purchasers, Adult Compliance-Evaluable Population, Safety Population, and within each at-risk subpopulation.

6.5.2. Study Conduct and Subject Disposition

A summary of the disposition of subjects (including Screening, Enrollment, Purchasers, Adult Compliance-Evaluable Population, Adolescent Users, and Safety Population) and reasons for exclusion from these populations will be provided (e.g., the reason that a subject was screened or participated in the enrollment interview but not a purchaser). The number and percentage of subjects included in each analysis population will be summarized.

6.5.3. Excessively High CV or GI risk

Self-reported reasons why subjects with excessively high CV or GI risk decided to purchase the product will be presented descriptively for the study report.

6.5.4. Study Treatment Exposure

Study treatment exposure will be counted from the first day in Use Phase to last day in Use Phase (Day 1 to Day 30), or up to the date subject discontinues. Summary statistics will be provided for treatment exposure for the Adult Compliance-Evaluable Population, Adolescent Users, and Safety Population, including packages of study medication purchased.

The analysis will also descriptively summarize medication purchase behaviors, as well as any self-reported reasons why subjects attempted to purchase more than 5 packages of study medication during the study and subjects who attempt to purchase more than 5 packages will be described based on any relevant characteristics.

6.5.5. Concomitant Medications and Nondrug Treatments

Concomitant medications will be summarized using the preferred drug name from WHODrug for the Safety Population.

Concomitant non-drug treatment or procedures will be listed.

6.6. Safety Summaries and Analyses

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

6.6.1. Adverse Events

AEs will additionally be summarized using a 3-tier approach. No Tier-1 events (pre-specified events of clinical importance) have been identified in the SRP for this product. However, for this study AEs included in the TME list of the SRP (see Appendix 1) will be used to summarize these types of AEs as follows:

Tier-1: pre-specified AEs of clinical importance, which are maintained in a list in the product's SRP (see Appendix 1 for the complete list of TME AEs. For this study TMEs in the SRP are considered as Tier-1 events);

Tier-2: AEs that are not Tier-1 but are "common." A MedDRA PT is defined as a Tier-2 event if its frequency is at least 2% in any treatment group;

Tier-3: AEs that are neither Tier-1 nor Tier-2 events.

It should be recognized that most studies are not designed to reliably demonstrate a causal relationship between the use of a pharmaceutical product and an adverse event or a group of adverse events. Except for select events in unique situations, studies do not routinely employ formal adjudication procedures for the purpose of event classification. As such, safety analysis is generally considered as an exploratory analysis and its purpose is to generate hypotheses for further investigation. The 3-tier approach facilitates this exploratory analysis.

7. INTERIM ANALYSES

No formal interim analysis will be conducted for this study. However, as described in Section 9.6 of the protocol this is an open-label study, and the sponsor may conduct

unblinded reviews of the data during the course of the study, among other possible purposes, to support clinical development.

8. REFERENCES

1. Murphy PW, Davis TC, Long SW, Jackson RH, and Decker BC. Rapid estimate of adult literacy in medicine (REALM): a quick reading test for patients. J of Reading 1993;37(2)124-30.

2. Davis TC, Wolf MS, Arnold CL, Byrd RS, Long SW, Springer T, Kennen E, Bocchini JA. Development and validation of the Rapid Estimate of Adolescent Literacy in Medicine (REALM Teen): a tool to screen adolescents for below grade reading in health care settings. Pediatrics. 2006 Dec 1;118(6):e1707 14.

9. APPENDICES

Appendix 1. Target Medical Event List

Target Medical Event Term	Code	Level (PT, SMQ1)
Cardiac failure	10007554	PT
Cerebral artery occlusion	10008089	PT
Deafness	10011878	PT
Gastrointestinal haemorrhage	10017955	PT
Hypersensitivity	10020751	PT
Hypertension	10020772	PT
Hypoacusis	10048865	PT
Myocardial infarction	10028596	PT
Overdose	10033295	PT
Pruritus	10037087	PT
Rash	10037844	PT
Renal failure	10038435	PT
Acute generalised exanthematous pustulosis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Bullous haemorrhagic dermatosis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Cutaneous vasculitis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Dermatitis bullous	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Dermatitis exfoliative	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Dermatitis exfoliative generalised	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Drug reaction with eosinophilia and systemic symptoms	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Epidermal necrosis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Erythema multiforme	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Erythrodermic atopic dermatitis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Exfoliative rash	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Oculomucocutaneous syndrome	20000020	Severe cutaneous adverse reactions SMQ1 narrow
SJS-TEN overlap	20000020	Severe cutaneous adverse reactions SMQ1 narrow

Target Medical Event Term	Code	Level (PT, SMQ1)
Skin necrosis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Stevens-Johnson syndrome	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Target skin lesion	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Toxic epidermal necrolysis	20000020	Severe cutaneous adverse reactions SMQ1 narrow
Toxic skin eruption	20000020	Severe cutaneous adverse reactions SMQ1 narrow

Source: Ibuprofen Safety Surveillance Review plan V14 Dated 30 Jan 2019
PT = Preferred Term; SMQ = Standard Medical Query

Appendix 2. Data Derivation Details

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 2.1. Definition and Use of Visit Windows in Reporting

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 2.2. Endpoint Derivations

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 2.3. Definition of Protocol Deviations That Relate to Statistical Analyses/Populations

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 3. Data Set Descriptions

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 4. Statistical Methodology Details

[Reference should be made to final Programming Specifications and Other Descriptions]

Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
APTC	Antiplatelet Trialists' Collaboration
ASCVD	atherosclerotic cardiovascular disease
AUS	actual use study
BP	blood pressure
CI	confidence interval
CSR	clinical study report
CRL	complete response letter
CV	cardiovascular
DFL	drug facts label
EOS	end-of-study
ER	extended release
FDA	Food and Drug Administration (United States)
GI	gastrointestinal
IR	immediate release
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
N/A	not applicable
NDA	New Drug Application
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PT	preferred term
REALM	Rapid Estimate of Adult Literacy in Medicine
REALM-Teen	Rapid Estimate of Adolescent Literacy in Medicine
Rx	prescription
SAE	serious adverse event
SAP	statistical analysis plan

Abbreviation	Term
SMQ	standard medical query
SOC	system organ class
SOP	standard operating procedure
SRP	safety review plan
TME	targeted medical event
US	United States