FDA Briefing Document

Joint Meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee

and the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC)

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Division of Epidemiology II/Office of Surveillance and Epidemiology

Division of Biometrics VII/Office of Biostatistics

Division of Anesthesiology, Addiction Medicine, and Pain Medicine/Office of New Drugs

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee (AC). The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the findings of the completed extended-release/long-acting opioid analgesic (ER/LA OA) postmarketing requirements (PMRs) 3033-1 and 3033-2 to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the AC. The FDA will not issue a final determination on the issues at hand until input from the AC process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the AC meeting.

Table of Contents

Table of Tables

Table of Figures

Glossary

AADPAC	Anesthetic and Analgesic Drug Products Advisory Committee
AC	Advisory Committee
ACEs	adverse childhood experiences
ADF	abuse-deterrent formulation
ADHD	attention-deficit/hyperactivity disorder
BMI	body mass index
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CI	confidence interval
CNS	central nervous system
DMME	daily morphine milligram equivalent
DSaRM	Drug Safety and Risk Management
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
ED	emergency department
EHR	electronic health record
ER/LA	extended-release/long-acting
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FSR	final study report
GAD	generalized anxiety disorder
GEE	generalized estimating equations
HR	hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
IPW	inverse probability-weighted
IR/SA	immediate-release/short-acting
KPNW	Kaiser Permanente Northwest
MDD	major depressive disorder
LtOT	long-term opioid therapy
MME	morphine milligram equivalent

NDA	new drug application
NDI	National Death Index
NPV	negative predictive value
OA	opioid analgesic
OR	odds ratio
OOD	opioid-involved overdose or opioid overdose-related death
OPC	Opioid PMR Consortium
OPRM1	opioid receptor mu-1
OUD	opioid use disorder
OUD-H	heroin related opioid use disorder
OUD-P	prescription drug related opioid use disorder
PMR	postmarketing requirement
POMAQ	Prescription Opioid Misuse and Abuse Questionnaire
PPV	positive predictive value
PRISM-5-Op	Psychiatric Research Interview for Substance and Mental Disorders, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Opioid Version
PTSD	post-traumatic stress disorder
QMME	qualifying/quarterly morphine milligram equivalent
REMS	risk evaluation and mitigation strategy
SNP	single nucleotide polymorphism
SUD	substance use disorder
VUMC	Vanderbilt University Medical Center

1 Executive Summary and Draft Points for Consideration by the Advisory Committee (AC)

1.1 Purpose/Objective of the Advisory Committee Meeting

The Food and Drug Administration (FDA) is convening a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) to discuss the findings of the completed postmarketing requirement (PMR) studies 3033-1 and 3033-2 (FDA 2016b). These are epidemiologic studies that examined the risks of, and risk factors for, misuse, abuse,[1] addiction, and fatal and nonfatal opioid-involved overdose in patients with long-term use of opioid analgesics (OAs) for the management of chronic pain, including patients prescribed extended-release/long-acting (ER/LA) OAs. The ACs will be asked to discuss how these studies further extend our understanding of the safety of long-term OA use; the relevance and implications of the findings considering the evolving nature of the opioid crisis and prescribing landscape; and whether there are any novel findings that FDA should communicate to healthcare professionals, patients, and members of the public.

1.2 Context for Key Points to Be Discussed at the AC Meeting

Against a backdrop of increasing OA prescribing and rising prescription opioid-involved fatal overdoses, and based on a review of the available data, FDA determined in 2013 that more information was needed about the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of OAs for the management of chronic noncancer pain. Knowledge gaps included both quantitative estimates of risk and characterization of risk factors for these outcomes. In September 2013, using its authority under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act, FDA issued five PMRs (2065-1 through 2065-5) to all holders of ER/LA OA new drug applications (NDAs) to assess the risks of misuse, abuse, hyperalgesia, addiction, and overdose (four observational studies and one clinical trial) in patients using OAs long term for the management of chronic, noncancer pain, including patients using ER/LA OAs. In May 2014, FDA held a public scientific meeting, which the ER/LA OA companies attended, to solicit input from external experts on the design and conduct of these PMR studies (FDA 2014). Based on input from this meeting, the companies submitted a suite of protocols for studies to fulfill the PMRs. FDA determined that to better track all the individual studies proposed, it was necessary to release the 5 PMRs and reissue them as 11 PMRs (10 observational studies, 3033-1 to 3033-10, and 1 clinical trial, 3033-11). This expanded suite of PMRs included multiple studies to develop and validate outcome measurement instruments and algorithms for use in the two main observational PMRs, 3033-1 and 3033-2, which were designed to quantify the risk of, and identify possible risk factors for, misuse, abuse, addiction (operationalized in the PMR studies as moderate-to-severe opioid use

[1] The FDA defines *misuse* as the intentional use, for therapeutic purposes, of a drug in a manner other than as prescribed or by an individual for whom it was not prescribed. FDA defines *abuse* as the intentional, nontherapeutic use of a drug for its desirable psychological or physiological effects. FDA recognizes that certain language may perpetuate stigma and negative bias toward individuals who use substances or who have substance use disorders, potentially creating barriers to effective treatment. The abuse-related terminology used in labeling, and in this briefing document, is based on statutory (e.g., 21 U.S.C. 812(b)) and regulatory usage of these terms (e.g., 21 CFR 201.56(d)(1) and 201.57(c)(10)). FDA is committed to reducing stigma, expanding therapeutic options, and ensuring access to evidence-based treatment for individuals with substance use disorders.

disorder (OUD)) and opioid-related overdose and death associated with use of OAs long term for the management of chronic pain.[2]

FDA has reviewed the final study reports for PMR 3033-1, which examined the prevalence, incidence, and risk factors for misuse, abuse, and OUD using data prospectively collected from patients; and PMR 3033-2, which examined the incidence and risk factors for nonfatal and fatal overdose using administrative healthcare claims linked to mortality data. We are convening this AC meeting to discuss the findings of these two PMRs. PMR 3033-11, the clinical trial examining hyperalgesia, was discussed at an AC meeting on April 19, 2023, and is not a topic for discussion at the current AC meeting.

1.3 Brief Description of Points for Discussion at the AC Meeting

We are soliciting input from the ACs on their interpretation of the key findings from the main observational PMR studies, 3033-1 and 3033-2, considering study-design-related factors such as patient populations, exposure and outcome measurement, and analytic framework, as well as contextual factors such as the evolving opioid landscape and other information from published studies and clinical experience. We also ask the ACs to consider if there is a need for FDA to communicate any new findings, considering what is currently included in FDA-approved OA labeling.

Study 3033-1 had two components, a prospective study of two different patient cohorts with new long-term use of Schedule II OAs (one cohort with an additional requirement for new use of an ER/LA OA) and a cross-sectional study of patients who had used OAs, including at least one prescription for an ER/LA OA, for one year or longer. One aim of this study was to estimate the incidence and prevalence of misuse, abuse, and addiction (operationalized as moderate-to-severe OUD in the study) in these patient populations. A new questionnaire, the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), was developed and validated for use in this study. OUD was measured using an instrument also developed and validated for use in individuals with chronic pain on long-term OA therapy, based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria, called the Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version (PRISM-5-Op). The PRISM-5-Op is based on the earlier PRISM and PRISM-5, previously validated semistructured, clinician-administered interviews widely used to assess OUD and other substance use disorders using DSM criteria (Hasin et al. 1996; Hasin et al. 2020). The PRISM-5-Op made several changes to the PRISM-5 interview; most notably, questions were added on participants' history of prescription opioid use and probes and adjustments were added based on therapeutic vs. non-therapeutic intent of opioid use.

As shown in Table 1, opioid misuse (defined as the intentional use of a drug for a therapeutic purpose inappropriately outside label directions or in a way other than prescribed or directed by a healthcare practitioner) was the most frequently identified of the outcomes measured. Opioid abuse (defined as the intentional use of a drug for a nontherapeutic purpose, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect) was substantially less common. The incidence and prevalence of moderate-to-severe OUD were generally lower, but these estimates depended substantially on the OUD definition used. A pain-adjusted DSM-5-OUD definition of OUD (referred to in this document as pain-adjusted DSM-5-OUD)—which uses DSM-5 symptoms but counts them as positive only if endorsed in the context of using opioids for reasons other than pain (i.e., pain-adjusted

[2] While the focus of these studies was on noncancer pain, cancer patients whose illness was not terminal were eligible to be included.

criteria[3])—generated substantially lower estimates for OUD than using the standard DSM-5 criteria and definition (referred to in this document as DSM-5-OUD).

Table 1. PMR 3033-1: Incidence and Prevalence Estimates for Misuse, Abuse, and OUD

Estimate % (95% CI)	Misuse % (95% CI)	Abuse % (95% CI)	Moderate-to-Severe OUD	
			Pain-Adjusted DSM-5-OUD[1] % (95% CI)	DSM-5-OUD[2] % (95% CI)
Prospective ER/LA cohort:[3] 12-month incidence	22.8 (21.6, 24.0)	9.4 (7.7, 11.6)	1.4 (0.9, 2.3)	5.8 (4.5, 7.3)
Prospective LtOT cohort: 12-month incidence[4]	21.6 (18.3, 25.5)	8.6 (7.4, 10.0)	1.6 (0.9, 2.9)	3.4 (2.3, 5.1)
Cross-sectional study: prevalence	14.6 (12.6, 17.0)	6.0 (4.8, 7.6)	2.7 (1.8, 4.0)	6.3 (4.3, 9.1)

Source: FDA-generated figure adapted from data provided in Figure 4 and Supplemental Table 8, Final Report on the Cross-Sectional Study Results (prevalence); Tables 9a and 9b and Supplemental Tables 9a and 9b, Final Report on the Prospective Study Results (incidence).

[1] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[2] Moderate-to-severe DSM-5-OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[3] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[4] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR/SA, immediate-release/short-acting; LtOT, long-term opioid therapy; OA, opioid analgesic; OUD, opioid use disorder; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version

Study 3033-2 was a retrospective cohort study designed to estimate the 5-year cumulative incidence of opioid-involved overdose or opioid overdose-related death (OOD) in patients with new long-term use of Schedule II OAs (at least 70 of the 90 days prior to cohort start date, including ER/LA and/or immediate-release/short-acting (IR/SA) OAs). OOD was measured using an electronic healthcare data-based algorithm with linkage to the National Death Index database. The algorithm was validated prior to conducting these analyses. The 5-year cumulative incidence estimates for OOD in this population ranged from approximately 1.5% in two commercially insured populations and one managed-care population to approximately 4% in the fourth study site, Vanderbilt University Medical Center (VUMC), which was comprised of patients enrolled in Medicaid (Table 2). Incidence rates at the end of the 5-year follow-up ranged from approximately 3 per 1000 person-years at the commercially insured and managed-care sites to more than 8 per 1000 person-years at the Medicaid site (VUMC). The OOD incidence rate was highest during the first 3 months of follow-up, which started from the point the patient met the criteria for long-term OA use.

[3] Here, adjustment refers to modification of the standard DSM criteria, rather than statistical adjustment.

Table 2. PMR 3033-2: Cumulative Incidence and Incidence Rates of OOD

Study Site	5-year Cumulative Incidence[1] of OOD % (95% CI)	5-year Incidence Rate[2] of OOD (n per 1000 Person-Years) (95% CI)
HealthCore	1.49 (1.35, 1.63)	3.25 (2.99, 3.51)
KPNW	1.43 (1.19, 1.73)	3.11 (2.59, 3.74)
Optum	1.54 (1.27, 1.80)	3.34 (2.96, 3.76)
VUMC (Medicaid)	4.05 (3.85, 4.27)	8.31 (7.91, 8.71)

Source: FDA-generated table adapted from data provided in Healthcore, KPNW, Optum, and VUMC Site Table 8.2, Whiscon Summary Report.
[1] 5-year cumulative incidence = 1 - (Kaplan-Meier estimate of OOD-free survival through five years) * 100%.
[2] Five-year incidence rate = total number of OOD events at 5 years of follow-up ÷ person-years during 5 years of follow-up*1,000.
Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; VUMC, Vanderbilt University Medical Center

Together, these PMR studies provide ranges of quantitative estimates of the known serious risks of misuse, abuse, OUD, and overdose in different patient populations with long-term OA use. All these outcomes are currently described in the *Boxed Warning* and multiple other sections of OA labeling, although the labeling does not provide any quantitative estimates of these risks. Mitigation of these risks is also the overarching goal of an ongoing risk evaluation and mitigation strategy (REMS) (FDA 2024c). We are interested in the ACs' interpretation of the outcome estimates from PMRs 3033-1 and 3033-2 and whether any communication of new findings is warranted. We ask that committee members consider the study strengths and limitations, including the limited patient populations to which inferences can be made; foremost, the studies included only those with long-term use and therefore provided no information on risks associated with OA use less than 3-months in duration. The different study cohorts also had varying eligibility criteria, with a requirement of ER/LA OA use in some cohorts. As noted above, estimates for OUD depended substantially on the outcome definitions used (i.e., DSM-5-OUD versus pain-adjusted DSM-5-OUD), highlighting the complexity and challenges in identifying OUD in patients using OAs long-term for pain. Importantly, PMR 3033-2 was designed to capture only the first OOD event occurring during the follow-up period in patients without previous overdose events during the baseline or qualification periods, potentially excluding patients at particularly high risk for the outcome. The study also had substantial cohort attrition over the follow-up period, raising the possibility of biased estimates if patients who remained in the cohort and those who did not differed systematically in their risk of experiencing the outcome. OOD estimates were more than twice as high in populations receiving Medicaid as in those in the two commercially insured populations and one managed-care population, precluding the determination of a single risk estimate and serving as a reminder of the individual- and system-level factors that may converge to increase OA-related harms. Finally, in PMR 3033-2, much of the study period predated more recent changes in opioid prescribing practices and in the opioid crisis itself.

The PMR 3033-1 and 3033-2 studies also explored many potential risk factors for the respective outcomes of interest. We are interested in the ACs' interpretation of the risk factor analysis findings and input on whether any FDA communication of new findings is warranted. When the studies were designed, there was limited information about the risk factors for misuse, abuse, OUD, and OOD in patients using OAs long-term. Therefore, the risk factor analyses in these studies were exploratory, and not designed to evaluate prespecified causal relationships. Categories of risk factors included health- and pain-related factors, OA-related factors (e.g., dose, formulation, opioid moiety), and sociodemographic and genetic factors. The studies identified some factors that were associated with multiple outcomes of interest across multiple cohorts—most notably, having a personal history of a

substance use disorder (SUD), which was associated with all primary outcomes in both PMR studies. Some additional potential risk factors were significantly associated with one or more outcomes in one or more studies; in particular, having a mental health disorder (e.g., depression or psychosis) and use of central nervous system (CNS) active medications (e.g., benzodiazepines, antipsychotics). In addition, a higher opioid dose during the 90-day cohort qualification period was strongly and significantly associated with an increased risk of OOD in Study 3033-2, while in Study 3033-1, average daily opioid dose during the baseline period was associated with risk of misuse and abuse in some analyses, but not with OUD.

Other potential risk factors had variable associations across outcomes, study populations, and statistical models. In Study 3033-2, after controlling for differences in dose during the qualification period, predominant formulation (i.e., ER/LA vs IR/SA) was not associated with risk of OOD, but an exploratory analysis found that adding or switching from an IR/SA OA to an ER/LA OA (compared to adding or switching to another IR/SA OA) was associated with a modestly increased risk of OOD even after adjusting for differences in daily dose just before the add/switch event. However, adding or switching to an ER/LA OA also led to an increase in dose (compared to adding or switching to an IR/SA OA which resulted in a decrease in dose), suggesting that the dose increase, as opposed to a change in formulation, may have been the primary driver of the relatively increased OOD risk seen after adding or switching to an ER/LA OA. Several opioid moieties were associated with a greater risk of certain study outcomes than others (e.g., predominant use of hydromorphone during the baseline period was associated with greater risk of abuse than predominant use of oxycodone; and predominant use of morphine, oxycodone, and methadone during the baseline period were associated with greater risk of OOD than predominant use of hydrocodone), but these findings were not consistent across models, study cohorts, or outcomes.

The strongest and most consistent findings from the risk factor analyses are generally aligned with current OA labeling. The briefing document discusses several key methodologic considerations and limitations of the risk factor analyses and emphasizes that results do not have a causal interpretation. These considerations include, for example, limited statistical power to detect true associations in some analyses, potential for overadjustment or underadjustment in multivariable models, and the potential for chance associations. In addition, some important aspects of OA prescribing and risk were not considered in these studies (e.g., relationships between changes in dose or discontinuation of OAs and risks of overdose, suicide, or use of illicit opioids). Understanding these relationships has become more salient as opioid prescribing practices and the opioid crisis have evolved.

1.4 Draft Points for Consideration

1. Discuss your interpretation of the estimates of the incidence and prevalence of misuse, abuse, and OUD in patients using OAs long-term (PMR 3033-1).

   Please also comment on factors influencing your interpretation, e.g.,

   - Study strengths and limitations
   - Definitions and measurements of these outcomes, including the two different definitions of OUD (i.e., DSM-5-OUD, pain-adjusted DSM-5-OUD)
   - Generalizability and relevance to current patients using OAs in the evolving opioid landscape
   - Consistency of findings with other available evidence or clinical experience

2. Discuss your interpretation of the estimates of the incidence of fatal and nonfatal overdose in patients using OAs long-term (PMR 3033-2).

   Please also comment on factors influencing your interpretation, e.g.,

   - Study strengths and limitations
   - Definition of opioid overdose outcome, including timing of ascertainment and potential for bias due to attrition
   - Heterogeneity of results across study populations, particularly those with Medicaid versus commercial insurance
   - Generalizability and relevance to current patients using OAs in the evolving opioid landscape
   - Consistency of findings with other available evidence or clinical experience

3. Discuss your interpretation of the risk factor analyses in PMRs 3033-1 and 3033-2 and what you see as the most important findings.

   Please also comment on factors influencing your interpretation, e.g.,

   - Strengths and limitations of risk factor analyses
   - Definitions and measurement of risk factors, particularly OA-related risk factors (e.g., dose, ER/LA versus IR/SA formulation)
   - Consistency of findings with other available evidence or clinical experience

4. Given your interpretation of the findings from these studies and what is currently in FDA-approved OA labeling, are there any novel findings that you believe FDA should communicate to healthcare providers, patients, and other members of the public?

2 Introduction and Background

Morphine, the first opium derivative, was first commercially marketed in the United States in the early 1800s, followed by codeine and heroin. By the early 1900s, opioid addiction was considered to be a major public health crisis, and, in response, narcotics control legislation was passed at both the state and federal levels. After the approval of hydrocodone in 1943, and methadone in 1947, the following decades saw the approval of new IR/SA OAs, including, for example, oxycodone (1950), propoxyphene (1957), and later, hydromorphone (1984), and tramadol (1995). In 1987, FDA approved morphine sulfate extended-release tablets, under the brand name MS Contin. Fentanyl, a potent synthetic opioid originally approved as an injectable solution in 1968, was approved in 1990 as an extended-release transdermal patch under the brand name Duragesic. In 1995, the FDA approved OxyContin, the first extended-release oxycodone product to be approved for marketing.

In the early 1990s, the medical community increasingly began prescribing OAs for the management of both acute and chronic noncancer pain. The estimated number of prescriptions dispensed for OAs in the United States increased from approximately 112 million prescriptions in 1992 to a peak of 263 million prescriptions in 2012 (Figure 1). The large majority of prescriptions were for IR/SA OAs, but on average, ER/LA OA prescriptions had higher total morphine milligram equivalents (MMEs) of opioid per prescription compared to IR/SA OAs. In 2013, the estimated aggregate, average MMEs per ER/LA OA prescription was 3,672 MMEs, compared to 705 MMEs per IR/SA OA prescription (Appendix Figure 9).

During the late 1990s and early 2000s, FDA began receiving and analyzing increasing numbers of reports of significant problems related to the misuse and abuse of prescription opioid products. Meanwhile, public health officials were seeing an alarming rise in fatal overdoses involving prescription opioids. FDA used regulatory authorities available at the time to require labeling changes, including the addition of boxed warnings to alert prescribers to these risks, and to issue warning letters (FDA 2003) citing manufacturers' violative promotional and advertising materials. In 2010, FDA also approved a reformulated version of OxyContin that was designed to deter abuse by nasal and injection routes. Approvals followed for other OA products (mostly ER/LA) with similar properties.

In 2007, Congress passed the Food and Drug Administration Amendments Act (FDAAA), giving the FDA new safety authorities. FDA could now require safety-related postmarketing studies or clinical trials (i.e., postmarketing requirements, or PMRs[4]) and safety labeling changes. FDAAA also authorized the FDA to require that manufacturers develop and implement REMS when necessary to ensure that the benefits of a medication outweigh its risks. In July 2012, FDA approved the ER/LA OA REMS program (FDA 2022), which included a requirement for manufacturers to make available to prescribers free training programs on safe ER/LA OA prescribing, following an FDA-approved blueprint (FDA 2018a).

Against the backdrop of increasing OA prescribing and growing awareness of serious harms related to these medications, in May 2012, FDA hosted a public scientific workshop with the National Institutes of Health to discuss chronic noncancer pain (FDA 2012). The purpose of this workshop was to identify knowledge gaps and research needs in several areas related to the treatment of chronic noncancer pain, including the appropriate population(s) for treatment, duration of therapy, and the optimal management of OA therapy. At this meeting, participants expressed concern about the safety of longer-duration and higher-dose OA therapy and discussed the need for more information on the risks of misuse, abuse, addiction, overdose, and death associated with long-term[5] use of OAs for chronic noncancer pain.

To further examine the available evidence and to assess knowledge gaps, FDA conducted a review of the published literature (Pratt et al. 2013) on these risks. Based on the results of this review and input from multiple public scientific meetings and hearings, FDA concluded that more data were needed to inform clinicians and patients about the known serious risks of misuse, abuse, hyperalgesia, addiction, overdose, and death associated with the long-term use of OAs. One finding of the FDA literature review was that the available evidence suggested an association between higher OA doses and risk of overdose; ER/LA OAs were generally available in higher dosage strengths, compared to immediate-release products, and were, on average, prescribed at higher daily doses for patients with chronic noncancer pain (Miller et al. 2015).

[4] Under FDAAA, postmarketing studies and clinical trials can be required to assess a known serious risk related to the use of the drug, assess signals of serious risk related to the use of the drug, or identify an unexpected serious risk when available data indicate the potential for a serious risk.

[5] There is no universally accepted definition of long-term use, although many studies have used three months, or 90 days, as a marker of long-term, or chronic, use.

In September 2013 (FDA 2013), FDA issued five PMRs (four observational studies and one clinical trial) to holders of ER/LA OA NDAs, requiring that they do the following (excerpted in relevant part):

1. Conduct one or more studies to provide quantitative estimates of the serious risks of and evaluate risk factors for misuse, abuse, addiction, overdose, and death associated with long-term use of OAs for management of chronic pain among patients prescribed ER/LA OAs (PMR 2065-1).
2. Develop and validate measures of misuse, abuse, addiction, overdose, and death, which will be used to inform the design and analysis of PMR 2065-1 (PMR 2065-2).
3. Conduct a study to validate coded medical terminologies used to identify opioid-related adverse events (misuse, abuse, addiction, overdose, death) in any existing postmarketing databases to be employed in the studies. These validated codes will be used to inform the design and analysis of PMR 2065-1 (PMR 2065-3).
4. Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. These validated codes will be used to inform the design and analysis for PMR 2065-1 (PMR 2065-4).
5. Conduct a clinical trial to estimate the serious risk for the development of hyperalgesia following use of ER/LA opioid analgesics for at least one year to treat chronic pain (PMR 2065-5).

Note that PMR 2065-5, a clinical trial that was released and reissued in amended form in 2016, is not a topic of discussion for this AC meeting.

The PMRs were issued to each ER/LA OA NDA holder, but FDA encouraged the companies to work together to complete the required studies. The NDA holders subsequently formed the Opioid PMR Consortium (OPC) to collaborate on fulfillment of the PMRs. In May 2014, FDA held a public scientific meeting, which the OPC attended, to discuss design considerations for the PMR studies (FDA 2014). During this discussion and during protocol development, it became apparent that multiple, separate investigations would be necessary to address multiple aspects of the study questions described in the four observational PMRs. To be able to track each of the studies individually, the 4 observational PMRs were released and reissued as 10 separate PMRs (see Table 3) in February 2016 (FDA 2016b).[6]

Under the reissued PMRs, the main observational PMR studies, and the subject of this AC meeting, were PMRs 3033-1 and 3033-2. Together, these studies were intended to provide a more comprehensive understanding of the incidence of, and risk factors for, misuse, abuse, addiction (operationalized as moderate-to-severe OUD), and fatal and nonfatal overdose in patients on long-term OA therapy for the management of chronic pain, including those prescribed ER/LA OAs. PMR studies 3033-3 through 3033-10 were foundational studies, intended to inform the design and conduct of the two main PMR studies,[7] to be completed prior to conducting PMR studies 3033-1 and 3033-2. Instruments developed and validated in PMR studies 3033-3, 3033-4, and 3033-5 were used to prospectively measure misuse, abuse, and addiction outcomes in PMR 3033-1. Electronic healthcare data-based algorithms developed in PMR 3033-6 were used to measure fatal and nonfatal overdose outcomes in PMR 3033-2. Algorithms

[6] The clinical trial, PMR 3033-11, was also released and reissued, but remains as a single PMR.

[7] FDA's reviews of the final study reports for PMR studies 3033-3 through 3033-5 and PMR studies 3033-7 through 3033-10 are available online at: https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-extended-release-and-long-acting-opioids. PMR study 3033-6 cannot be fulfilled until the review of PMR study 3033-2 has been finalized, as the OOD algorithm in PMR study 3033-6 underwent further testing as part of PMR study 3033-2. The final study report for PMR study 3033-6 (OOD algorithm) was reviewed by FDA, but the review is not available publicly until the PMR is fulfilled.

developed and evaluated in PMR studies 3033-7 (electronic healthcare data-based algorithms for abuse and addiction) and 3033-8 through 3033-10 (doctor and pharmacy shopping algorithms) did not perform sufficiently well to be used as outcome measures in the main observational PMR studies and will not be discussed further.

Table 3. ER/LA OA Observational PMRs

Main Observational PMRs	
PMR	**Description**
3033-1	A prospective, observational study designed to quantify the serious risks of misuse, abuse, and addiction associated with long-term use of OAs for management of chronic pain among patients prescribed ER/LA OAs. This study must address at a minimum the following specific objectives: • Estimate the incidence of misuse, abuse, and addiction associated with long-term use of OAs for chronic pain. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of misuse, abuse, and addiction. • Evaluate and quantify other risk factors for misuse, abuse, and addiction associated with long-term use of OAs for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships.
3033-2	An observational study designed to measure the incidence and predictors of opioid overdose and death (OOD), as well as opioid abuse/addiction, using patient health records, insurance claims, and death records. This study must address at a minimum the following specific objectives: • Estimate the incidence of abuse/addiction, overdose, and death associated with long-term use of OAs for chronic pain. Stratify overdose by intentionality wherever possible. Examine the effect of product/formulation, dose and duration of opioid use, prescriber specialty, indication, and other clinical factors (e.g., concomitant psychotropic medications, personal or family history of substance abuse, history of psychiatric illness) on the risk of abuse/addiction, overdose, and death. • Evaluate and quantify other risk factors for abuse/addiction, overdose, and death associated with long-term use of OAs for chronic pain, including but not limited to the following: demographic factors, psychosocial/behavioral factors, medical factors, and genetic factors. Identify confounders and effect modifiers of individual risk factor/outcome relationships. Stratify overdose by intentionality wherever possible.
Foundational/Supportive PMRs	
PMR	**Description**
3033-3	A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.
3033-4	An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term OA use.
3033-5	An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving OAs for chronic pain.
3033-6	An observational study to develop and validate an algorithm using coded medical terminologies and other electronic healthcare data to identify opioid-related overdose and death.
3033-7[1]	An observational study to develop and validate an algorithm using coded medical terminologies to identify patients experiencing prescription opioid abuse or addiction, among patients receiving an ER/LA OA.

3033-8[1]	An observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.
3033-9[1]	An observational study using a validated patient survey to evaluate the association between doctor/pharmacy shopping outcomes and self-reported misuse and abuse.
3033-10[1]	An observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.

Source: Food and Drug Administration. Release from Postmarketing Requirement and New Postmarketing Requirement letter. Available at: https://www.fda.gov/media/95546/download. Accessed December 5, 2024.

[1] Algorithms developed and evaluated in PMR studies 3033-7 through 3033-10 did not perform sufficiently well to be used as outcome measures in the main observational PMR studies.

Abbreviations: ER/LA, extended-release/long-acting; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire

PMR study 3033-11 required "a clinical trial to estimate the serious risk for the development of hyperalgesia following the long-term use of high-dose ER/LA opioid analgesics for at least one year to treat chronic pain. Include an assessment of risk relative to efficacy." This study is on a separate timeline and will not be discussed as part of the current AC meeting.

PMRs 3033-1 and 3033-2 were originally scheduled to be completed by March 2020; however, in 2017, the OPC informed FDA that if using the original eligibility criteria, which required that patients were initiating treatment with an ER/LA OA, recruitment for PMR 3033-1 would not be completed until 2028. This delay was attributed to a decline in new prescriptions for ER/LA OAs and an unexpectedly high percentage of patients being ineligible for inclusion due to terminal illness. To address this challenge, the study end date was extended by 1 year (from March 2020 to March 2021), a new study site was added, eligibility criteria were modified (e.g., patients were required to have no Schedule II or ER/LA OA use for six months, rather than one year, prior to the study start), and a second cohort of patients initiating long-term therapy with any Schedule II OA was added. Following additional delays due to the COVID-19 pandemic, the PMR 3033-1 final study reports (FSRs) were submitted in January 2023. PMR 3033-2, which underwent a protocol modification to incorporate updates to the eligibility criteria to parallel those for PMR 3033-1 (e.g., expansion of inclusion criteria to include long-term use of IR/SA OAs), was completed in June 2021. Many of the study reports, including the FSRs for the main studies, PMRs 3033-1 and 3033-2, were followed by multiple information requests from FDA and submissions of amended results and study reports. Appendix Figure 7 is a timeline of significant milestones for the observational PMR program.

2.1 The Changing Opioid Landscape

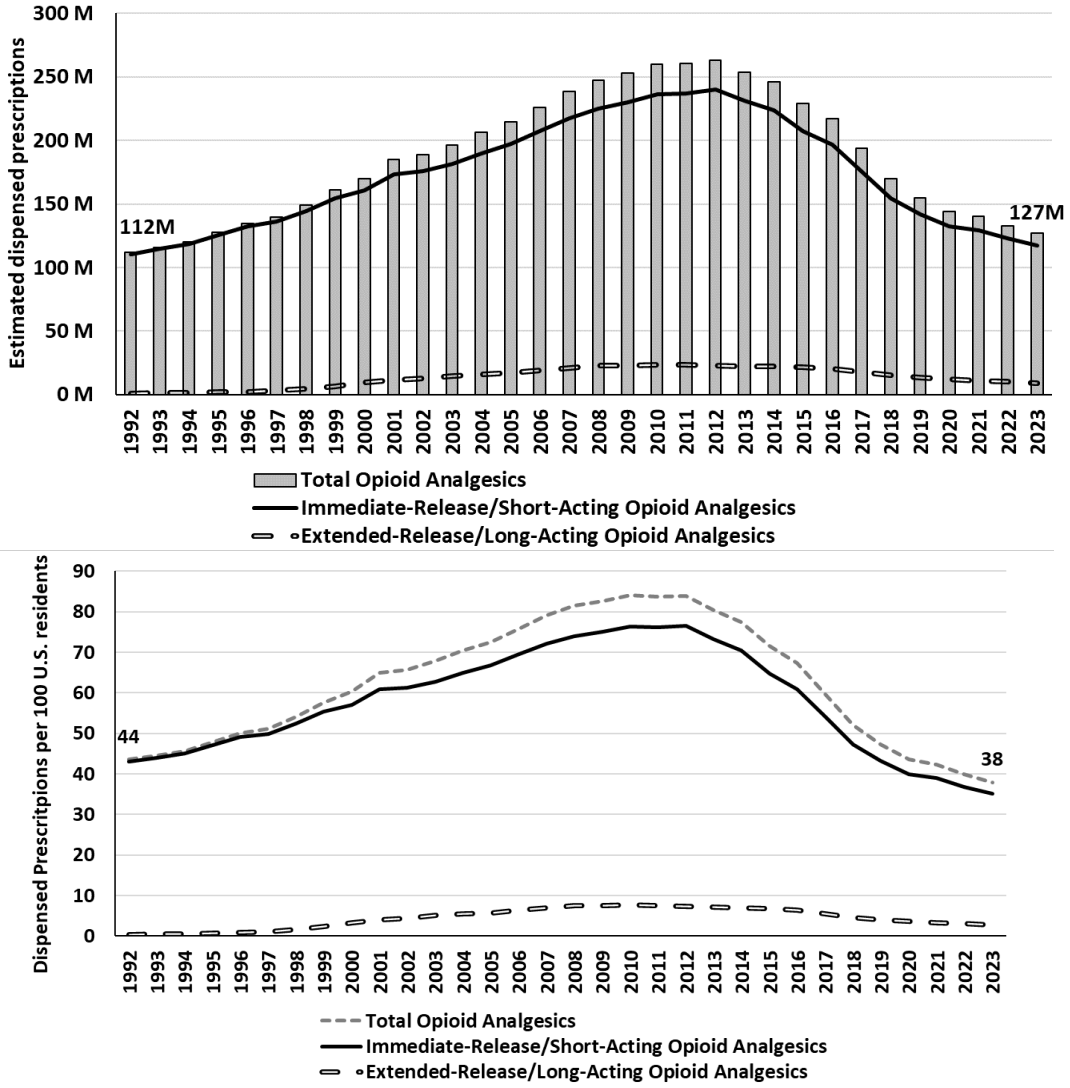
Trends and Current Patterns of OA Prescribing

The OA prescribing landscape has changed since these PMRs were issued in 2013. At that time, prescription OA dispensing had recently reached peak levels, and fatal overdoses and OUD involving prescription opioids were devastating communities (Volkow and Blanco 2021). As shown in the top panel of Figure 1, prescription OA dispensing increased substantially from 1992 through 2012.[8] At the

[8] See Appendix Section 6.2 for additional FDA analyses of drug utilization patterns to provide context for the changing opioid landscape. Several aspects of OA drug utilization were evaluated: the magnitude of use in the United States, which formulations (e.g., IR/SA, ER/LA) were commonly used and how they were used, how many

height of OA prescribing in 2012, there were approximately 263 million prescriptions dispensed in the United States, of which 22.8 million (8.7%) were for ER/LA OA products.[9] By 2023, outpatient pharmacy dispensing of OAs had decreased to 127 million prescriptions, of which 9.3 million (7.3%) were for ER/LA OA products. Adjusting for population growth, the number of OA prescriptions dispensed per 100 U.S. residents was lower in 2023 than in 1992 (Figure 1, bottom panel).

Figure 1. Nationally Estimated Number of Opioid Analgesic Prescriptions Dispensed From Retail and Mail-Order Pharmacies, by Formulation, Total (Top) and Per 100 U.S. Residents (Bottom), 1992 Through 2023 Annually



Sources: IQVIA National Prescription Audit™, U.S. Launch edition, data years 1992-2023, data extracted July 2024; U.S. Census, www.census.gov. Note: Results in this figure may differ from results in other figures due to different data sources used.
Abbreviations: M, millions; U.S., United States

patients received longer-term therapy compared to acute OA therapy, types and specialties of the practitioners who prescribed opioids analgesics, and for which medical conditions these products were commonly prescribed.

[9] See Appendix Section 6.2.4 for a list of ER/LA OA products included in FDA's analyses. These products may differ from products classified as ER/LA OA in the PMR studies.

FDA analyses found that from 2019 to 2023, based on office-based healthcare practitioner survey data for adult patients, both ER/LA and IR/SA OAs were primarily used to treat conditions associated with the musculoskeletal and connective tissue systems, such as back pain (Appendix Table 24). In a large sample of patients starting ER/LA OA therapy in 2023, the most common ER/LA OA starting daily doses dispensed to patients without evidence of ER/LA OA prescriptions in the prior 12 months were 26 to 30 MMEs per day (34% of patients), followed by 56 to 60 MMEs per day (17%) (Appendix Figure 10). These 2023 data were similar to patterns seen in 2018, and in both time periods very few patients received ER/LA OA prescriptions for doses higher than 120 MMEs per day for their first ER/LA OA prescription.

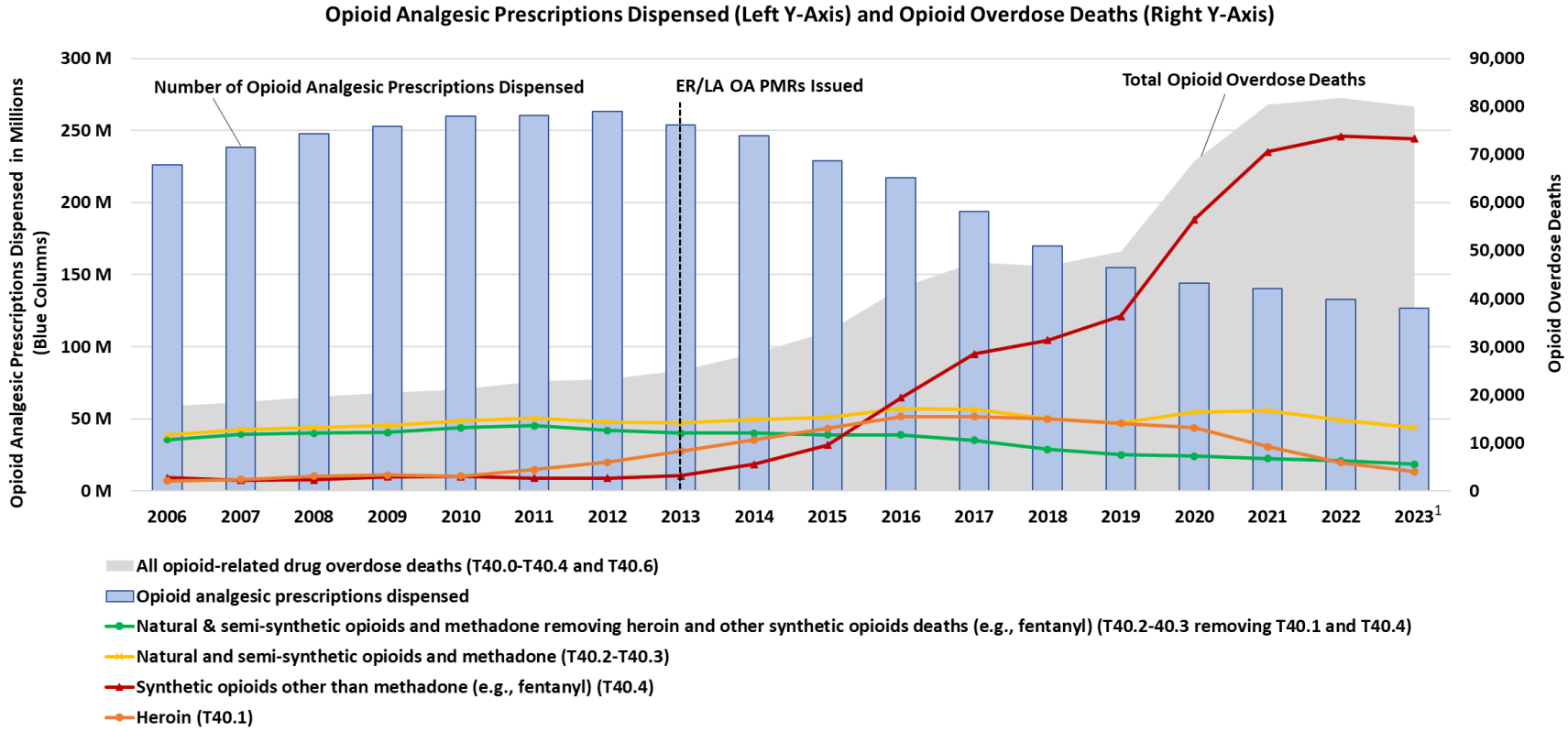
Among patients starting ER/LA OA therapy in 2023, 38% appeared not to have received a prior IR/SA OA prescription, compared to 42% in 2018 (Appendix Table 25). However, these percentages may be overestimates as patients could have received prior IR/SA OA therapy in other settings not captured in these data (e.g., inpatient care, dispensing from pharmacies outside the data sample). In another large sample of patients starting OA therapy in 2021 or 2022, 83% of patients had presumed short-term OA therapy while 17% had presumed long-term therapy (Appendix Table 26).[10] Among those patients with presumed long-term OA therapy, 0.7% received predominantly ER/LA OA prescriptions, 2.5% received multiple IR/SA OA and ER/LA OA prescriptions, and approximately 97% received predominantly IR/SA OA prescriptions. ER/LA OAs dispensed in 2023 were most commonly prescribed by nurse practitioners and physician assistants, followed by general practitioners, and anesthesiologists and pain medicine specialists (Appendix Table 27).

Trends in Opioid Overdose Deaths

While OA prescribing fell after 2012, opioid-involved overdose deaths continued to rise sharply, with the increase largely attributable to illicitly manufactured opioids—first heroin, then potent synthetic opioids, primarily fentanyl (Figure 2). In 2013, when the ER/LA OA PMRs were issued and the number of OA prescriptions dispensed was near the peak, there were 14,145 prescription opioid-involved (i.e., natural and semisynthetic opioids, and methadone) overdose deaths. Most of these deaths involved prescription opioids without involvement of heroin or synthetic opioids other than methadone. Since then, the total number of prescription opioid-involved overdose deaths have remained fairly stable, but as of 2023, more than half of the prescription opioid-involved overdose deaths also involved synthetic opioids other than methadone (e.g., fentanyl) or heroin. In recent years, the vast majority of opioid-involved overdose deaths involved synthetic opioids other than methadone, primarily illicitly manufactured fentanyl.

[10] Presumed short-term OA therapy defined as two or fewer ER/LA opioid analgesic prescriptions and/or two or fewer IR opioid analgesic prescriptions during the 1-year follow-up. Presumed long-term OA therapy defined as three or more ER/LA opioid analgesic prescriptions or three or more IR opioid analgesic prescriptions during the 1-year follow-up.

Figure 2. Nationally Estimated Number of Prescriptions for OAs Dispensed From U.S. Outpatient Pharmacies and Opioid-Involved Overdose Deaths in the United States, 2006 Through 2023[1]



Sources: Prescription dispensing data from IQVIA, National Prescription Audit™; data years 2006-2023; data extracted November 2024. Overdose death data from the Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2022, and from provisional data for year 2023, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed at https://wonder.cdc.gov/mcd.html on November 18, 2024.

[1] 2023 data from CDC WONDER are provisional and subject to change.

Abbreviations: CDC, Centers for Disease Control and Prevention; M, million; OA, opioid analgesic; U.S., United States

2.2 Selected Additional FDA Regulatory Actions to Address OA Safety

Concurrently with issuing the ER/LA OA PMRs in 2013, FDA also required class-wide safety labeling changes for ER/LA OAs, including additions to the *Boxed Warning* further highlighting the risks of addiction, abuse, misuse, overdose, and death, as well as risks of fatal respiratory depression following a dose increase or if not swallowed whole, accidental exposure in children, and neonatal opioid withdrawal syndrome:

> "TRADENAME exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk before prescribing and monitor regularly for development of these behaviors or conditions. Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation or following a dose increase. Instruct patients to swallow TRADENAME (formulation) whole to avoid exposure to a potentially fatal dose of (active opioid). Accidental consumption of TRADENAME, especially in children, can result in fatal overdose of (active opioid). For patients who require opioid therapy while pregnant, be aware that infants may require treatment for neonatal opioid withdrawal syndrome. Prolonged use during pregnancy can result in life-threatening neonatal opioid withdrawal syndrome."

Since 2013, FDA has taken and continues to take actions to address the evolving opioid crisis. During the period in which these studies were underway and being evaluated, FDA continued to implement changes to both the ER/LA OA REMS program and to product labeling. One of the more significant labeling actions took place in March 2016, when FDA required multiple changes to class-wide labeling for both IR/SA and ER/LA OAs (FDA 2018b). The Drug Safety Communication issued with this action described multiple labeling updates related to serotonin syndrome, androgen deficiency, and adrenal insufficiency. FDA also harmonized the labeling language regarding addiction, abuse, misuse, overdose, and death across ER/LA and IR/SA OA products. This was a significant change insofar as it was the first time that both IR/SA and ER/LA OAs displayed the same *Boxed Warning* on these safety issues.

As part of the 2016 safety labeling action, FDA also added new language to the *Boxed Warning* for all OAs, cautioning about the concomitant use of opioids with benzodiazepines or other CNS depressants (FDA 2018b).

> "Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of TRADENAME and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate."

That same year, FDA convened a joint meeting of the AADPAC and DSaRM ACs to discuss the ER/LA OA REMS (FDA 2016a). Based on discussion at that meeting, on September 28, 2017, FDA notified all application holders of ER/LA and IR/SA OAs that the REMS was being expanded to include OAs that were expected to be used in the outpatient setting that were not already covered by another REMS program. The REMS modification also included revisions to the FDA Blueprint for Healthcare Provider Education which was subsequently approved in September 2018. The strategy in this REMS is education and is intended to improve the broader healthcare team's understanding of how to manage pain and the role of OAs along with nonpharmacologic and non-opioid analgesics in pain management. The FDA Blueprint contains a high-level outline of the core education messages that must be included in the educational program developed under the OA REMS (e.g., continuing education). The FDA Blueprint focuses on the

fundamentals of acute and chronic pain management and provides a contextual framework for safe prescribing as well as a primer on OUD and disposal of OAs. The core messages are directed to prescribers, pharmacists, and nurses, but are also relevant for other healthcare providers who participate in the management of pain. The training is not intended to be exhaustive nor a substitute for a more comprehensive pain management course (FDA 2018a).

In 2019, FDA became aware of harms occurring to patients whose OAs were suddenly discontinued or whose dose was rapidly decreased and determined that serious signs and symptoms, such as withdrawal symptoms, uncontrolled pain, psychological distress, and suicide, necessitated additional labeling changes (FDA 2019). With this action, FDA required and implemented new language on tapering of OAs, providing new instruction for prescribers in the *Dosage and Administration* section of labeling. The same year, FDA also released draft guidance for industry describing the benefit-risk assessment framework that FDA uses to assess the risks and benefits of OAs, including consideration of the broader public health effects such as the risks of misuse, abuse, OUD, accidental exposures, and overdose (June 2019).

The next year, in 2020, FDA took the step of requiring that labeling for OAs used in the outpatient setting include language about the availability of the overdose reversal agent, naloxone (FDA 2020a). According to the new labeling, prescribers are encouraged to discuss the availability of naloxone with every patient for whom they are considering prescribing an opioid. Since this update, naloxone has also become more widely available, following FDA's approval on March 29, 2023, of the first naloxone product to be available without a prescription.

In 2022, CDER conducted a comprehensive examination of approved labeling for OAs and in April 2023, required changes to the prescribing information for both IR/SA and ER/LA OAs, including the following (FDA 2023b):

- Updates for all OAs stating that the risk of overdose increases as the dose increases.
- Updates for IR/SA OAs stating these products should not be used for an extended period unless the pain remains severe enough to require them and alternative treatments continue to be inadequate, and that many acute pain conditions treated in the outpatient setting require no more than a few days of an opioid pain medicine. This may include pain occurring with a number of surgical conditions or musculoskeletal injuries.
- Updates to the approved use for ER/LA OAs to recommend they be reserved for severe and persistent pain that requires an extended treatment period with a daily opioid pain medicine and for which alternative treatment options are inadequate.
- Adding a new warning about opioid-induced hyperalgesia for both IR/SA and ER/LA OAs. This includes information describing the symptoms that differentiate opioid-induced hyperalgesia from opioid tolerance and withdrawal.

In addition to the changes bulleted above, this labeling action also included changes to *Section 9.2, Abuse*. The section was standardized across many OAs to further clarify the potential for misuse and abuse, which can lead to the development of substance use disorder, including addiction. This section of labeling goes on to explain that all patients treated with OAs require careful and frequent reevaluation for signs of misuse, abuse, and addiction, and that the risk of addiction exists even when the OA is appropriately used. The section concludes by advising the prescriber to conduct proper assessments of the patient, adhere to proper prescribing practices, and periodically reevaluate therapy while also noting that measures, such as proper storage, can limit abuse of opioids.

For details regarding this action as well as a description of other labeling changes made, please refer to the April 13, 2023, Drug Safety Communication (FDA 2023b). An example of the current label for IR/SA OAs (oxycodone hydrochloride capsules) can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/200534s014lbl.pdf. An example of the current label for ER/LA OAs (MS Contin) can be found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/019516s058lbl.pdf.

In October 2024, FDA approved a modification to the OA REMS to require manufacturers provide pre-paid drug mail-back envelopes upon request to pharmacies and other dispensers of OAs to reduce the risk of misuse, abuse, and accidental exposures that may result from excess OAs in the home (FDA 2023a; FDA 2024a). This action was implemented on March 31, 2025 (FDA 2023a; FDA 2024a).

Recognizing the evolving nature of the overdose crisis, FDA continues to evaluate and adjust its approach according to the latest available science and data. In addition to these regulatory actions, FDA has taken many other actions, for example, convening AC meetings and public workshops, recommending changes to scheduling of opioid drugs under the Controlled Substances Act, approving products to treat OUD and to reverse opioid overdoses, publishing research, issuing various communications, and collaborating with other agencies and organizations to address the opioid crisis. These are documented in FDA's Overdose Prevention Activities Timeline (FDA 2024d). The FDA also developed the Overdose Prevention Framework, consisting of four overarching priorities to address the public health emergency as it continues to evolve:

- Supporting primary prevention by eliminating unnecessary initial prescription drug exposure and inappropriate prolonged prescribing.
- Encouraging harm reduction through innovation and education.
- Advancing development of evidence-based treatments for substance use disorders.
- Protecting the public from unapproved, diverted, or counterfeit drugs presenting overdose risks.

2.3 Unintended Consequences of Actions to Address the Opioid Crisis

Efforts to address the evolving opioid crisis, including any potential future regulatory actions that may result from the findings of these PMR studies, must consider the potential for unintended consequences, as even well-intentioned actions can result in unintended harms. Many initiatives, interventions, and legislative actions have been taken at the federal, state, and local levels to address the opioid crisis. While many of these efforts have focused on limiting initial OA prescriptions for acute pain, efforts have also been made to limit the quantity or dose of IR/SA or ER/LA OA prescribed for patients with long-term use of OAs for the management of chronic noncancer pain, such as those included in these PMRs. For example, the Centers for Disease Control and Prevention (CDC) issued the CDC Guideline for Prescribing Opioids for Chronic Pain – United States in 2016 (Dowell et al. 2016), which recommended that clinicians avoid increasing daily doses beyond certain thresholds for chronic noncancer pain. The CDC updated the guideline in November 2022 (Dowell et al. 2022), providing modified recommendations on the treatment of acute, subacute, and chronic pain in adults. Many institutions across the United States have also developed guidelines for OA prescribing (Mayo Clinic 2018; Gazelka et al. 2020; The Overdose Prevention Engagement Network 2024; The University of Michigan and Michigan Opioid Collective 2024); the majority of states have passed legislation limiting OA prescriptions for acute pain, and many state Medicaid agencies also have requirements intended to limit OA prescribing (Seitz et al. 2022). A number of these additional institutional and state prescribing

limits are targeted toward long-term OA use or use of ER/LA OAs, including daily dose or prescription quantity limits and prior authorization requirements for higher daily doses, use of ER/LA OAs, or the number of prescriptions received over a certain period of time.

While OA prescribing decreased steeply as a result of these and other interventions, unintended consequences have been observed. For example, misapplication of the 2016 CDC Guideline contributed to patient harms such as rapid opioid tapers and abrupt discontinuation of opioids without shared decision-making between patients and practitioners, dismissal of patients from physicians' practices followed by the inability to find a new provider, extension to patient populations not covered in the 2016 CDC guideline, and application of the guideline's recommendations for OAs to medications for OUD (Demidenko et al. 2017; Dowell et al. 2019; FDA 2019). Published studies and public comments reported significant adverse consequences of these various actions, including increased stigmatization, quality-of-life challenges with untreated pain, job loss, and transition to illicit substance use (Seitz et al. 2022).

3 Methods and Results for PMRs 3033-1 and 3033-2

3.1 PMR 3033-1: Prospective and Cross-Sectional Studies of Opioid Misuse, Opioid Abuse, and OUD

PMR 3033-1 was designed to measure the incidence and prevalence of misuse, abuse, and addiction (operationalized as moderate-to-severe OUD) among patients with chronic pain on long-term OA therapy. PMR 3033-1 had two components: a prospective study (henceforth, prospective PMR 3033-1) and a cross-sectional study (henceforth, cross-sectional PMR 3033-1). These component studies assessed the same outcomes and risk factors for these outcomes (with some exceptions). The study populations are described in detail in Sections 3.1.3 to 3.1.6, but briefly, the prospective study included two separate cohorts from multiple U.S. healthcare systems comprising: 1) patients with new use of ER/LA OA therapy for at least 28 continuous days followed by an additional ER/LA OA prescription within 7 days, and 2) patients with new use of an ER/LA OA or a Schedule II IR/SA for at least 70 days out of the 90-day period prior to recruitment into the cohort. The cross-sectional study included patients from the same healthcare systems (with one exception) on long-term OA therapy for at least 1 year, with at least one ER/LA OA prescription. The shared outcomes and risk factors are described in detail in Sections 3.1.1 and 3.1.2, while the statistical methods and results are described separately for the prospective study (Sections 3.1.3 and 3.1.4) and cross-sectional study (Sections 3.1.5 and 3.1.6).

3.1.1 Outcomes Assessed in PMR 3033-1 Studies

The primary outcomes assessed in the cross-sectional and prospective PMR 3033-1 studies were past-three-month opioid misuse, past-three-month opioid abuse, and past-year OUD. These were measured as incident conditions (newly occurring during the study period) in the prospective study and prevalent conditions (present at the time of a single study assessment) in the cross-sectional study. Several secondary and sensitivity outcomes were also assessed, including a composite of the three primary outcomes and multiple ways of operationalizing OUD, as described below.

Opioid Misuse and Abuse Outcome Measures

At the time the ER/LA OA PMRs were issued, there was no generally accepted patient-reported measurement instrument that assessed misuse and abuse behaviors. Therefore, the OPC, with input

from FDA, chose to modify the Self-Reported Misuse, Abuse, and Diversion of Prescription Opioids questionnaire, which was developed to identify and monitor prescription opioid misuse, abuse, and diversion, for use in PMR 3033-1 (Coyne et al. 2021a). The resulting questionnaire, the POMAQ, was designed to assess current and past patient behaviors related to prescription OA misuse and abuse.

The POMAQ uses the same definitions of opioid misuse and abuse as the Analgesic, Anesthetic, and Addiction Clinical Trials, Translations, Innovations, Opportunities, and Networks public-private partnership (Smith et al. 2013), which align with current definitions recommended by FDA (July 2019). Misuse is defined as intentional use of a drug for a therapeutic purpose (i.e., to reduce an aversive symptom or state) inappropriately outside label directions or in a way other than prescribed or directed by a health care practitioner (e.g., using a drug for a condition different from that for which the drug was prescribed, taking more of a drug than prescribed, using a drug at different dosing intervals than what was prescribed, or taking a drug prescribed for someone else). Abuse is defined as the intentional use of a drug for a nontherapeutic purpose, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect. To assess opioid misuse and abuse, the POMAQ asks whether various drug use behaviors indicative of misuse or abuse occurred within the past 12 months, and if so, whether they occurred in the past 3 months. If the behavior occurred in the past 3 months, individuals are asked the reason(s) for the behavior from a prespecified list (with the option to choose other and specify another reason), as well as the frequency of the behavior over the past 1 month (i.e., none, 1 time, 2 to 5 times, 6 to 10 times, 11 to 15 times, more than 15 times). Appendix 6.3 contains the POMAQ.

The POMAQ was validated in PMR 3033-3, which assessed comprehension and face validity (i.e., if the instrument questions actually measured what they were supposed to measure), and PMR 3033-4 (Kornegay et al. 2019), which assessed content validity (i.e., the extent to which an instrument measures the concept of interest) and reproducibility (i.e., the extent to which an instrument produces the same result when used repeatedly under the same circumstances). Based on review of the validation study findings, FDA concurred that the POMAQ was acceptable for use in the ER/LA OA PMR studies.

OUD Outcome Measures

Historically, diagnostic criteria for OUD were designed and tested in an era when most harmful opioid use was illicit (heroin), and diagnostic interview tools based on these criteria were not evaluated in patients prescribed opioids chronically for pain. Currently, the DSM-5 is the standard for diagnosing substance use disorders. To measure OUD in PMR 3033-1, the OPC developed the PRISM-5-Op. The PRISM-5-Op is based on the PRISM and the PRISM-5, previously validated semistructured, clinician-administered interviews widely used in clinical and research settings to assess OUD using DSM criteria (Hasin et al. 1996; Hasin et al. 2020). The standard DSM-5 definition of OUD is based on 11 diagnostic criteria (9 behavioral and 2 physiological). The DSM-5 distinguishes between mild, moderate, and severe substance use disorders (defined as having 2 to 3, 4 to 5, or 6 to 11 of the listed criteria, respectively).

The PRISM-5-Op was developed for use in a population similar to those included in the PMR 3033-1 studies (i.e., individuals with chronic pain on long-term OA therapy), collecting additional information on

opioid use associated with the DSM-5 criteria. Specifically, the PRISM-5-Op made the following changes to the PRISM-5 interview:

- The prescription opioid module was moved to the beginning.
- Questions were added on participants' history of prescription opioid use.
- Probes and adjustments were added based on therapeutic vs. non-therapeutic intent.

The PRISM-5-Op was evaluated in PMR 3033-5 (Hasin et al. 2022), which considered three definitions of OUD based on the 11 DSM-5 diagnostic criteria for OUD and the new information collected by the modified instrument:

1. **Unadjusted:** The 11 DSM-5 criteria were rated positive if present, without regard to any extenuating circumstances.
2. **DSM-5-adjusted (referred to as DSM-5-OUD in this briefing document):** Similar to the unadjusted definition, but withdrawal and tolerance were not rated positive if they occurred among patients who used OAs only as prescribed.
3. **Fully adjusted (referred to as pain-adjusted DSM-5-OUD in this briefing document):** In addition to the DSM-5 adjustment for withdrawal and tolerance criteria, eight of the remaining nine criteria were rated positive only if the respondent indicated a reason for opioid use other than the treatment of pain (i.e., "pain-adjusted"). In addition, the final criterion, persistent desire or repeated attempts to quit/cut down, was rated positive only if the patient had made more than one attempt to quit/cut down.

In PMR 3033-1, "addiction," one of the primary outcomes specified in the PMR 3033-1 language, was operationalized based on the definitions of OUD described above. The PRISM-5-Op was the measurement tool. The PRISM-5-Op is able to determine a probable diagnosis of OUD based on the standard DSM-5 definition (referred to as "DSM-5-OUD" in this briefing document), as well as a measure that makes certain adjustments to the standard criteria based on additional information collected, primarily accounting for whether the reason for opioid use was pain-related or not; referred to as "pain-adjusted DSM-5-OUD" in this briefing document.[11] These original DSM-5 criteria, and the modified "pain-adjusted" criteria, are listed in Table 4. Of note, "pain-adjusted" in this context does not refer to statistical adjustment, but rather an adjustment to the DSM-5 criteria themselves.

As described above, binary measures of OUD can be determined using a designated threshold for number of criteria. The moderate-to-severe threshold (i.e., four or more criteria) was used to define the primary OUD outcome in PMR 3033-1. More specifically, the primary outcome in PMR 3033-1 was "moderate-to-severe pain-adjusted DSM-5-OUD," defined as meeting four or more pain-adjusted criteria related to prescription opioids *or* two or more criteria related to heroin.[12] Moderate-to-severe DSM-5-OUD, defined as meeting four or more standard DSM-5-OUD criteria related to prescription opioids (i.e., without considering whether pain was the reason for prescription opioid use) *or* two or more related to heroin, was considered a secondary OUD outcome definition in PMR 3033-1.

[11] This outcome was referred to as "PRISM-5-Op OUD" in the Final Study Report for PMR 3033-1 but was changed for clarity and to be more consistent with updated terminology used by the OPC in their briefing materials for this meeting.

[12] Patients meeting two or more DSM-5 criteria due to heroin use were included in all severity thresholds of OUD, including moderate-to-severe OUD.

Table 4. Definition of Moderate-to-Severe OUD Used in PMR 3033-1 Studies, Using DSM-5 Criteria for OUD and Additional Information Collected by the PRISM-5-Op

Scoring Used in PMR 3033-1	DSM-5 Substance Use Criteria	Criteria for DSM-5-OUD Definition	Criteria for Pain-Adjusted DSM-5-OUD Definition (Primary OUD Definition in PMR 3033-1)
≥4 criteria related to prescription opioid use *Or* ≥2 criteria related to heroin use[1]	Tolerance[2]	Positive only if this occurs when opioids were taken **other than as prescribed** (e.g., more than prescribed or without a prescription)[3]	Positive only if this occurs when opioids were taken **other than as prescribed** (e.g., more than prescribed or without a prescription)[3]
	Withdrawal or use to avoid withdrawal[2]	Positive only if this occurs when opioids were taken **other than as prescribed** (e.g., more than prescribed or without a prescription)[3]	Positive only if this occurs when opioids were taken **other than as prescribed** (e.g., more than prescribed or without a prescription)[3]
	Persistent desire or repeated attempts to quit/cut down	Positive if there is a persistent desire even without attempts to quit or cut down	Positive only if patient made repeated unsuccessful **attempts** to quit/cut down
	Social/interpersonal problems due to use	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Neglected major roles to use	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Used larger amounts/longer	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Much time spent using	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Continued use despite physical or psychological problems	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Activities given up to use	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Craving	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]
	Use in physically hazardous situations	Positive **regardless of reason**	Positive only if this occurs for a **nonpain reason**[4]

Source: FDA-generated table adapted from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Washington, DC, American Psychiatric Association, and PMR 3033-1 Protocol 1a, Amendment 2.

[1] Patients meeting two or more DSM-5 criteria due to heroin use were included in all severity thresholds of OUD.

[2] The DSM-5 recommends not diagnosing OUD in individuals using opioids as prescribed when the only criteria met were tolerance and/or withdrawal.

[3] "Taking as prescribed" criterion not relevant for heroin use disorder.

[4] Nonpain reasons include: to feel high, to feel less depressed/nervous/angry, to help sleep (other than pain relief), to prevent or treat withdrawal, to feel relaxed or mellow, because you saw something that reminded you of the medication.

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FDA, Food and Drug Administration; OUD, opioid use disorder; PMR, postmarketing requirement; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid version

The PMR 3033-5 study included a series of analyses to assess the validity of the different OUD definitions as measured by the PRISM-5-Op (i.e., unadjusted, DSM-5-OUD [also referred to as DSM-5-adjusted], and pain-adjusted [also referred to as fully adjusted] DSM-5-OUD definitions). Two groups of patients were recruited for the study. The first group, considered at "high risk" of OUD, consisted of patients in treatment for addiction and who currently had or in the past had an OA prescription for chronic pain. The second group, considered at "low risk" of OUD, included patients with a current prescription for OAs for chronic pain, recruited from pain or physical rehabilitation clinics. Most analyses were conducted among a combined sample of the low-risk and high-risk groups. The results of the validation analyses are summarized below.

- Test-retest reliability (i.e., reproducibility): Test-retest reliability was moderate to substantial for each unadjusted, DSM-5-adjusted, and fully adjusted binary criterion and for each binary measure of OUD based on these criteria. Reliability was excellent for the unadjusted, DSM-5-adjusted, and fully adjusted dimensional (i.e., continuous) measures of OUD. For both binary and dimensional measures, the fully adjusted version had the highest reliability, though the difference was only statistically significant for the dimensional measure.
- Dimensionality: In exploratory factor analysis, for all three criteria sets (unadjusted, DSM-5-adjusted, and fully adjusted), a one-factor solution had the best fit (i.e., the 11 criteria formed a unidimensional factor), with all the criteria contributing substantially. In confirmatory factor analysis, the fully adjusted criteria set showed the greatest total test information (i.e., how well the criteria set measures the underlying trait, in this case, OUD).
- Expert clinician ratings based on the Longitudinal Expert All Data procedure: The PRISM-5-Op results were compared to evaluations by addiction and pain medicine experts. Using these ratings as the standard, most PRISM-5-Op binary ratings (individual criteria and binary measure, both DSM-5-adjusted and fully adjusted) showed excellent sensitivity, specificity, positive predictive value, negative predictive value, and agreement in this population of patients using prescription opioids for pain.
- Testing whether the relationships between the unadjusted and adjusted OUD measures differed between high-risk and low-risk populations: If the adjustments to the DSM-5 definition were valid, we would expect differences between unadjusted and adjusted criteria and between unadjusted and adjusted binary outcomes to be greater in low-risk (pain treatment) than high-risk (addiction treatment) respondents. The results showed statistically significant evidence that this was the case, supporting the validity of the PRISM-5-Op fully adjusted criteria and binary measure for measuring OUD in patients using prescription opioids for pain.
- Multitrait-multimethod validators: This analysis assessed the strength of association between each OUD definition and several validators which had predicted associations with OUD. Focusing on the dimensional (i.e., continuous) OUD measures, the fully adjusted measure had stronger associations with the multitrait-multimethod validators than did the unadjusted or DSM-5-adjusted measures. Findings were similar for the binary OUD measures, although power was reduced in these analyses, leading to fewer statistically significant results. The study investigators concluded that, overall, these findings supported the fully adjusted measures having the strongest validity as a measure of OUD in a population of patients using opioids for pain.

Based on the findings of the validation study, FDA concurred that the PRISM-5-Op measures of OUD demonstrated adequate validity and reliability and were appropriate for use in PMR 3033-1. Nonetheless, FDA reviewers had questions about the interpretation of findings from this novel instrument that resulted in the pain-adjusted DSM-5-OUD measure in comparison to DSM-5-OUD

measure. Therefore, the DSM-5-OUD definition (as in Table 4) was included as a secondary outcome in PMR 3033-1. In addition to the primary OUD definition, which used a threshold of four or more criteria, other thresholds of two or more criteria (i.e., "any OUD") and six or more criteria (i.e., "severe OUD") were also analyzed. Some limited additional analyses were also conducted to examine OUD involving prescription opioids (i.e., OUD-P) and OUD involving heroin (i.e., OUD-H), independently.

Composite Outcome Measure

In addition to these outcomes of misuse, abuse, and OUD, a composite outcome definition was created that included patients with any of the three primary outcomes (misuse, abuse, or moderate-to-severe pain-adjusted DSM-5-OUD). The composite outcome was considered a secondary outcome.

3.1.2 Potential Risk Factors Assessed in Study 3033-1

The following potential risk factors for misuse, abuse, or OUD were examined. Information for identifying risk factors was obtained from electronic health records (EHR), claims data, self-reported questionnaire data, and interview data. Information on how each potential risk factor was defined and operationalized, and the timeframes during which each potential risk factor was assessed, can be found in Appendix Table 28.

- Sociodemographic factors: age, sex, race, ethnicity, annual household income, highest education level, insurance type (Medicaid versus other), predominant place of care (e.g., integrated care, fee-for-service).
- OA-related factors:[13] predominant opioid moiety, predominant OA formulation (ER/LA or IR/SA), average daily OA dose in MMEs, use of an abuse-deterrent formulation (ADF) OA, duration of Schedule II OA therapy.[14]
- Substance Use Disorder (SUD) history: any nonopioid/non-nicotine SUD (past year *and* prior to past year),[15] baseline outcome status (i.e., past-year *and* prior to past year OUD-H and OUD-P as measured at baseline via the pain-adjusted DSM-5-OUD definition with the PRISM-5-Op, past-3-month opioid misuse as measured at baseline via the POMAQ, past-3-month opioid abuse as measured at baseline via POMAQ).[16]
- Health and pain-related factors: number of emergency department (ED) visits in the past year, number of inpatient stays in the past year, concomitant medication use (antidepressants, antipsychotics, benzodiazepines, buprenorphine, gabapentinoids, muscle relaxers, naloxone, sedative hypnotics, stimulants), number of pain conditions recorded in EHR, Elixhauser Comorbidity Index, body mass index (BMI), fibromyalgia (from patient-reported symptoms), pain severity, pain interference, physical capability, mental capability.
- Mental health and social factors: major depressive disorder (MDD), attention-deficit/hyperactivity disorder (ADHD), borderline personality disorder, generalized anxiety disorder (GAD), post-

[13] For the prospective 3033-1 study, the opioid-related factors were collected during the baseline period, which occurred in the 6 months prior to the patient's baseline interview.
[14] Duration of Schedule II OA therapy during the baseline period was considered only in the prospective 3033-1 study, but not in the cross-sectional 3033-1 study.
[15] SUDs were assessed both as individual disorders and combined (i.e., any nonopioid/non-nicotine SUD) in the unadjusted and demographically adjusted analyses. Only the combined risk factor (any nonopioid/non-nicotine SUD) was assessed in the fully adjusted analyses.
[16] Baseline outcome status was considered only in the prospective 3033-1 study, but not in the cross-sectional 3033-1 study.

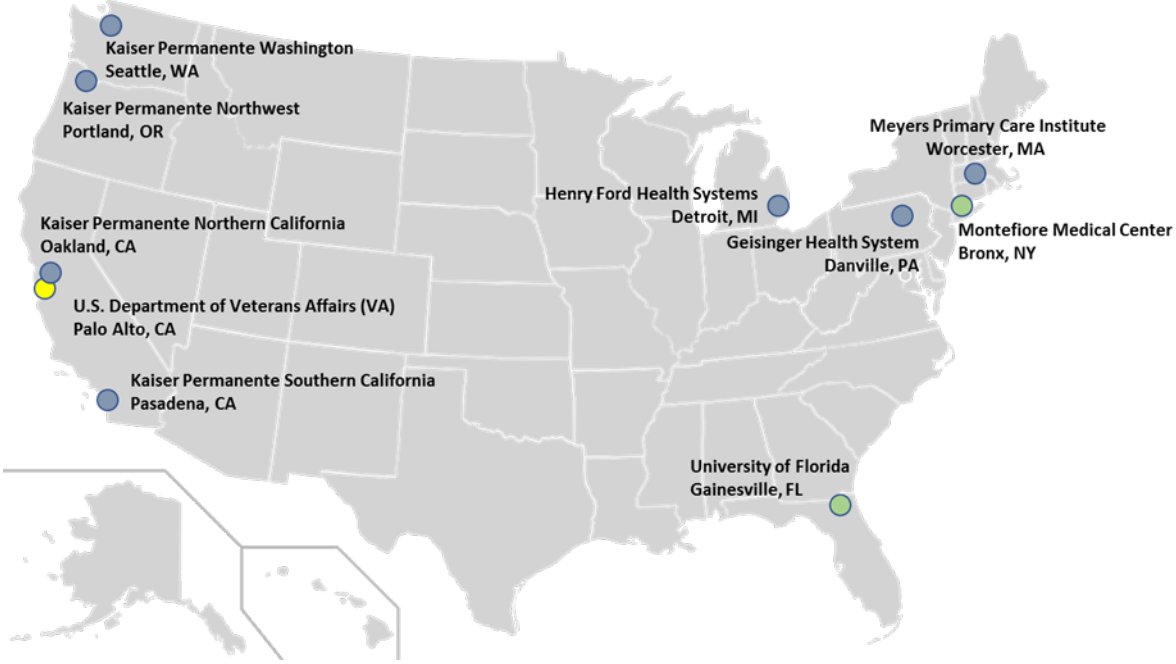
traumatic stress disorder (PTSD), history of parental substance use, adverse childhood experiences (ACEs),[17] poor sleep quality, stress, social support.

- Genetic factors: opioid receptor mu 1 (OPRM1) burden score, cytochrome P450 2D6 burden score, cytochrome P450 3A4 burden score.

3.1.3 3033-1 Prospective Study Design and Methodology

The prospective PMR 3033-1 study was designed to assess the incidence of and risk factors associated with misuse, abuse, and addiction in a population of patients on long-term OA therapy. The study population for PMR 3033-1 comprised adults aged 18 to 79 years old selected from 10 sites in the United States (Figure 3) between August 2017 and October 2021. Data were from EHR and claims data, as well as a battery of patient questionnaires and interviews. Patients were contacted every three months during the 12-month follow-up period, as shown in the flow diagram in Appendix Figure 11.

Figure 3. Study Sites for the Cross-Sectional and Prospective PMR 3033-1 Studies



Legend
Yellow Veterans Administration site
Blue Health Care Systems Research Network site
Green Clinical Directors Network (Primary Care Practice-based Research Network) site

Source: Figure 1, Final Report on the Prospective Study Results

Note: Kaiser Permanente Northern California participated in prospective PMR 3033-1 only.

Abbreviations: CA, California; FL, Florida; MA, Massachusetts; MI, Michigan; NY, New York; OR, Oregon; PA, Pennsylvania; PMR, postmarketing requirement; U.S., United States; WA, Washington

In addition to patients meeting the original eligibility criteria for new long-term ER/LA OA therapy (the ER/LA cohort), a second cohort of patients on long-term Schedule II OA therapy (long-term opioid therapy [LtOT] cohort) was added when it became apparent that recruitment would not be complete

[17] Includes neglect, emotional, physical, or sexual abuse, or domestic violence before age 18.

until 2028 if the study cohort were limited to patients using ER/LA OA therapy.[18] Note that IR/SA opioid therapy was permitted for both cohorts in the study. A propensity score analysis was conducted to determine if the ER/LA and LtOT cohorts could be combined for the statistical analysis as originally intended. If the propensity score distributions for the ER/LA and LtOT cohorts overlapped by 80% or more, then they would be combined. Otherwise, they would be analyzed separately.

Patients were eligible for the study if they met the following conditions:

- ER/LA Cohort: Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.
- LtOT Cohort: Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

Of note, there could be a gap of time between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days.

Additional inclusion criteria for both cohorts were as follows:

- Between 18 and 79 years old
- Enrolled in a health plan or with evidence of receiving healthcare at the study site for at least 12 months prior to being identified as eligible for the study, based on EHR and claims data
- Able to complete interview and self-administered questionnaires in English
- Willing and able to provide informed consent

The exclusion criteria for prospective PMR 3033-1 were:

- Not using an ER/LA OA or schedule II IR/SA OA at the time of recruitment or first interview
- Cognitive impairment that interfered with the ability to consent or participate in study interviews and self-administered questionnaires
- Unavailable for 12 months of follow-up
- Receiving hospice care at the time of study eligibility
- Diagnosis of a terminal illness in the prior 12 months per chart review or self-report
- Existing OUD (using International Classification of Diseases, Ninth Revision (ICD-9) or International Classification of Diseases, Tenth Revision (ICD-10) diagnosis codes)
- Medication-assisted treatment with methadone or buprenorphine (from either EHR/claims or self-report)

[18] Patients that met the criteria for both the ER/LA and LtOT cohorts in the prospective study were prioritized to the ER/LA cohort. The inclusion criteria for the cross-sectional 3033-1 study (required >1 year of opioid therapy) and the prospective 3033-1 study (new to Schedule II opioid therapy in the past 6 months) precluded patients being eligible for both studies.

All demographic, prescription, clinical, and genetic information were collected from EHR data or during the patient's baseline interview. Patients also completed the standardized questionnaires and interviews, including the POMAQ, and PRISM-5-Op. Patients were contacted every 3 months for the next year to update Schedule II OA therapy duration and repeat the questionnaire and interview administration, as appropriate. The POMAQ was readministered at 3, 6, 9, and 12 months after study entry. The PRISM-5-Op was repeated after 12 months.

Patients were included in the analysis for a given outcome (i.e., misuse, abuse, or OUD) if they did not have that outcome at baseline and completed a minimum of two of the 3-, 6-, 9-, and 12-month follow-up assessments for the POMAQ (misuse and abuse analyses) or the 12-month follow-up assessment for the PRISM-5-Op (OUD analysis). As a result, the analyses for misuse, abuse, and OUD did not have the same number of patients.

Statistical Analysis

Incidence was calculated as the percentage of patients ever having an outcome during the study follow-up among patients under observation at the relevant time point (e.g., 3, 6, 9, and 12 months for the misuse and abuse, and only 12 months for OUD).[19] For all outcome measures, 12-month incidence was reported. For the misuse and abuse outcomes, additional 3-, 6-, and 9-month incidence were calculated. Ninety-five percent confidence intervals (95% CIs) of the incidences were calculated assuming a Poisson distribution. Within-site correlation was accounted for by using cluster-robust standard errors.

The associations of potential risk factors (see Section 3.1.2 for a list of risk factors) with each outcome were also assessed using generalized estimating equations (GEE) with logit link and exchangeable covariance (to account for within-site correlation). The three phases of the risk factor analysis were conducted as follows:

1. Unadjusted models: A series of univariate models were used to determine which risk factors were significant at the $p<0.10$ level. These risk factors were included in the fully adjusted analysis. For categorical variables, if one category was significant, all levels were included in the fully adjusted model.
2. Demographically adjusted models: Each risk factor was assessed in a series of minimally adjusted models that included age, sex, race, and ethnicity.
3. Fully adjusted/final models: Limited to risk factors found to be significant in the unadjusted analyses at the $p<0.10$ level, as well as age, sex, race, and ethnicity.

When not used as the outcome, misuse, abuse, and OUD (as measured at baseline) were included in the risk factor models for the other outcomes. Except where otherwise indicated (e.g., categorical and continuous risk factors), patients with the risk factors were compared to those without the risk factor of interest (i.e., risk factors were binary). In the unadjusted and demographically adjusted models, specific nonopioid/non-nicotine SUDs were assessed, as were genotyping variables. In the fully adjusted models, only the overall nonopioid/non-nicotine SUD risk factor variable was modeled; the genotyping factors were not included.

[19] Patients under observation were defined as patients (1) with an evaluable PRISM-5-Op interview at month 12 for the OUD outcome, or (2) with more than two evaluable POMAQ measures over the 12-month follow-up for prescription opioid misuse and abuse outcomes, among those without the outcome of interest at baseline.

Odds ratios (ORs) and p-values were reported from the unadjusted models; ORs and 95% CIs were reported from the demographically adjusted and fully adjusted models. No multiplicity adjustment was performed in the risk factor analyses, primarily due to the nature of safety studies that prioritizes controlling for Type II errors (i.e., failing to detect true adverse effects or risk factors) (ICH 1998; European Medicines Agency 2002; Council for International Organizations of Medical Sciences Working Group 2005).

Sample Size and Statistical Power to Identify Risk Factors

The prospective 3033-1 study targeted enrollment of approximately 2,331 participants, with 58% being ER/LA OA initiators and 42% being LtOT initiators. The sample size calculations assumed that there would be a 75% retention rate at the 12-month follow-up, and approximately 20% of patients would be excluded due to baseline misuse, abuse, or addiction. Finally, for ER/LA initiators, an additional 10% attrition was considered, assuming these patients would not meet the criteria for long-term use status. Based on these assumptions, the final expected sample size was 1,318.

Next, the study examined minimum detectable ORs for risk factors across various estimates of rates of misuse, abuse, and addiction reported in the literature (Adams et al. 2001; Reid et al. 2002; Denisco et al. 2008). As this evaluation considered different distributions of a single binary risk factor and did not account for potential dependence among multiple risk factors, the minimum detectable ORs presented in Table 5 are likely underestimates (Neuhaus 1998; Xing and Xing 2010). A key observation from this analysis is that when the outcome rate is low, (e.g., less than 5% or <0.05), the minimum detectable OR is approximately 2, even when the sample size exceeds 1,000 (see bolded row in Table 5). Therefore, for outcomes with low incidence, the risk factor analysis may be underpowered to detect true risk factors unless the magnitude of the OR is greater than 2.

Table 5. Minimum Detectable Odds Ratio at Estimated Sample Size, 80% Statistical Power, and Alpha=0.05, Under Varying Rates of Outcome and Risk Factor Distribution

Estimated Final Sample Size	Rate of Outcome	Minimum Detectable Odds Ratio by Distribution of Binary Risk Factor		
		10:90	30:70	50:50
ER/LA N=729	0.05	3.15	2.33	2.24
	0.20	2.14	1.69	1.63
	0.40	1.99	1.58	1.52
LtOT N=589	0.05	3.47	2.52	2.42
	0.20	2.31	1.78	1.71
	0.40	2.15	1.66	1.59
Total N=1318[1]	**0.05**	**2.48**	**1.93**	**1.86**
	0.20	1.79	1.49	1.44
	0.40	1.67	1.4	1.37

Source: Table 8, protocol amendment 1 and statistical analysis plan for PMR 3033-1 prospective study, dated May 8, 2020.

[1] This is the minimum detectable OR even when the total sample size exceeds 1,000 patients and the outcome rate is low (e.g., ≤0.05).

Abbreviations: ER/LA, extended-release/long-acting; LtOT, long-term opioid therapy; N, number of subjects; PMR, postmarketing requirement

3.1.4 3033-1 Prospective Study Results

Study Population

A total of 9,601 patients were invited to be screened for participation in the study based on their prescription OA medication use history. Of those, 3,498 were determined to be eligible, and 2,388

completed the baseline evaluation, questionnaires, and interviews and enrolled in the study. After 1 year, 2,222 patients (93%) were able to be included in the analyses. The total numbers of patients included in analyses for each of the primary outcomes were:

- Misuse: N=1,807
- Abuse: N=2,062
- OUD: N=1,952

See Appendix Figure 11 for additional details about the resulting number of patients.

Patients in the ER/LA and LtOT cohorts were compared to determine if they could be combined for the analysis. The propensity for a patient to belong to either cohort was calculated using all the available risk factors collected for the study. The actual overlap between cohorts was 9.2%, well below the predefined threshold of ≥80%. Therefore, the ER/LA and LtOT cohorts were analyzed separately. Of the 2,222 patients included in the analytic cohort, 978 (44%) were in the ER/LA cohort, and 1,244 (56%) were in the LtOT cohort.

Table 6 lists selected baseline characteristics for the ER/LA and LtOT cohorts (for the complete list of characteristics, see Appendix Table 29). While the ER/LA and LtOT cohorts were similar for some risk factors, they differed in the risk factors related to OA use and characteristics, healthcare utilization, and other medication use. About half of patients in each cohort were ≥60 years old; both included more women than men and were majority White. About 20% of each cohort received insurance through Medicaid. When SUD and mental health risk factors were examined, similar and fairly high percentages of patients in each cohort had a history of a nonopioid/non-nicotine SUD or a prior-to-past-year history of OUD. Both cohorts had approximately the same percentage of participants with a history of parental substance abuse and four or more ACEs.

While all patients in the ER/LA cohort were required to have some ER/LA OA use, patients in both the ER/LA and LtOT cohorts could use both IR/SA and ER/LA OAs. The product with the greatest total days' supply (i.e., the predominant OA) was an ER/LA OA in about 40% of the ER/LA cohort, compared to about 2% of the LtOT cohort. Having morphine as the patient's predominant opioid moiety was more common in the ER/LA cohort, as was use of an ADF OA, while the majority of the LtOT cohort primarily used hydrocodone. Notably, about 46% of the ER/LA cohort had a baseline average daily dose of <50 MMEs, while 86% of the LtOT cohort had a baseline average daily dose of <50 MMEs. The ER/LA cohort had more inpatient stays, ED visits, and more pain conditions, although the Elixhauser comorbidity scores were similar. Use of other, nonopioid, CNS-active medications (e.g., antidepressants) was common in both cohorts, but the ER/LA cohort had a higher frequency of use compared to the LtOT cohort for all nonopioid medications examined in this study.

Table 6. Baseline Characteristics of the ER/LA and LtOT Cohorts in the Prospective PMR 3033-1 Study

	ER/LA Cohort[1]	LtOT Cohort[2]
	N=978	N=1,244
Baseline Characteristic	**%**	**%**
Age group, years		
18-39	10.6	10.6
40-49	13.5	17.2
50-59	27.4	27.3
≥60	48.5	44.9
Sex		
Female	56.9	59.4
Male	43.1	40.6
Race		
White	83.4	78.1
Black	9.1	14.8
Other/mixed	7.0	6.4
Missing	0.5	0.8
Hispanic/Latino ethnicity	10.8	9.2
BMI (kg/m^2)		
Underweight/normal	18.4	13.1
Overweight	22.9	22.8
Obese	48.2	49.4
Missing	10.5	14.7
Medicaid insurance	19.7	20.8
Predominant place of care		
Care and insurance in an integrated delivery system	76.2	63.2
Care only in an integrated delivery system	17.7	26.4
Network or fee-for-service providers	6.1	10.4
ED visits (n)		
0	53.0	61.7
1-2	30.9	28.9
≥3	16.2	9.4
Inpatient stays (n)		
0	69.3	75.2
1	19.6	18.5
≥2	11.0	6.3
Predominant OA formulation[3]		
IR/SA	60.2	97.6
ER/LA	39.6	2.2

Baseline Characteristic	ER/LA Cohort[1] N=978 %	LtOT Cohort[2] N=1,244 %
Predominant opioid moiety[3]		
Oxycodone	27.5	34.6
Morphine	26.5	2.0
Hydrocodone	19.4	57.8
Fentanyl	5.8	0.1
Methadone	5.4	0.2
Oxymorphone	0.5	0.0
Hydromorphone	2.5	1.3
Tramadol	8.0	2.3
Buprenorphine[4]	2.6	0.4
Codeine	1.3	0.7
Tapentadol	0.2	0.2
Meperidine	0.0	0.1
Butorphanol	0.1	0.0
Abuse deterrent OA exposure[3]	10.1	1.0
Average daily dose at baseline, MMEs[3]		
<50	46.2	86.1
50-89	32.2	10.3
90-119	10.1	1.9
≥120	11.2	1.4
Other medication use[5]		
Antidepressants	60.9	49.5
Tricyclic antidepressants	13.5	8.9
Nontricyclic antidepressants	54.9	44.9
Antipsychotics	7.7	7.4
Buprenorphine for OUD	1.3	0.2
Gabapentinoids	47.3	39.7
Muscle relaxers	37.8	35.9
Naloxone	20.0	13.6
Sedative hypnotics	32.2	26.5
Benzodiazepines	27.5	21.9
Nonbenzodiazepine sedative hypnotics	7.9	7.6
Stimulants	3.7	3.4

Baseline Characteristic	ER/LA Cohort[1] N=978 %	LtOT Cohort[2] N=1,244 %
Pain conditions from EHR		
Abdominal and bowel	23.1	18.6
Limb/extremity, joint, noninflammatory arthritic disorders	68.4	66.3
Back	64.9	59.2
Musculoskeletal and chest	11.8	8.9
Fractures, contusions, sprains, and strains	18.4	14.4
Fibromyalgia	15.4	8.5
Headache	14.5	12.6
Neck	24.4	22.5
Neuropathy	23.2	16.2
Orofacial, ear, and temporomandibular	1.5	1.0
Other[6]	76.5	60.5
Systemic disorders or diseases causing pain	11.9	5.3
Urogenital, pelvic, and menstrual	3.3	3.1
Number of pain conditions recorded in EHR		
0	2.5	4.7
1-2	27.7	36.7
≥3	69.8	58.6
Elixhauser Comorbidity Index		
0	7.5	10.4
1	11.6	13.6
≥2	80.4	75.8
Missing	0.6	0.2
Annual household income, $		
$25,000 or less	27.5	30.0
$25,001-$50,000	19.7	21.9
$50,001-$75,000	16.9	15.9
$75,001-$100,000	13.0	13.6
$100,001-$150,000	10.1	9.9
Greater than $150,000	7.9	5.2
Prefer not to report	4.9	3.5
Education		
<High school degree	5.3	9.2
High school or General Equivalency Degree	19.7	24.7
Any college	62.4	56.3
Any graduate school	12.6	9.8

Baseline Characteristic	ER/LA Cohort[1] N=978 %	LtOT Cohort[2] N=1,244 %
Substance use disorders from baseline PRISM-5-Op interviews		
Nonopioid and non-nicotine substance use disorder, past year	6.5	8.3
Nonopioid and non-nicotine substance use disorder, prior to past year	29.0	34.1
OUD,[7] past year	3.1	1.6
OUD-H, past year	0.0	0.0
OUD-P, past year	3.1	1.6
OUD,[7] prior to past year	6.7	5.9
OUD-H, prior to past year	1.6	1.9
OUD-P, prior to past year	5.5	4.7
Other measures from baseline PRISM-5-Op		
Major depressive disorder, past year	15.1	12.8
Major depressive disorder, prior to past year	25.6	20.7
History of parental substance use	44.2	46.5
Prescription opioid misuse and prescription opioid abuse from baseline POMAQ questionnaire		
Prescription opioid misuse, past 3 months	16.3	18.1
Prescription opioid abuse, past 3 months	5.2	6.1
Participant-reported questionnaires: categorical or binary measures		
ACE		
0	19.9	21.6
1	16.1	17.0
2	13.7	11.6
3	13.0	12.9
4+	37.0	36.5
Missing	0.3	0.4
ADHD[8]	14.8	13.5
Borderline personality disorder	8.7	8.6
GAD	21.9	23.6
Fibromyalgia from patient-reported symptoms	8.6	7.6
Poor sleep quality	78.8	79.7
PTSD	14.7	12.5

Baseline Characteristic	ER/LA Cohort[1] N=978 %	LtOT Cohort[2] N=1,244 %
Duration of Schedule II opioid therapy during baseline period,[3] mean (SD) days	131.7 (45.4)	107.7 (25.6)
Participant-reported questionnaires: continuous measures, mean (SD)		
Pain severity	5.5 (2.0)	5.6 (2.0)
Pain interference	6.1 (2.3)	5.9 (2.5)
Stress	15.4 (7.9)	14.4 (8.1)
Social support	71.8 (25.6)	71.8 (26.3)
SF-12 physical score	30.7 (8.7)	32.6 (9.0)
SF-12 mental score	47.9 (10.9)	48.9 (11.5)

Source: FDA-generated table adapted from data provided in Final Prospective Tables, Table 7a and Table 7b, FDA IR Response dated July 19, 2023.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] Baseline OA exposure is measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominance was based on greatest total days' supply, or most prescriptions if there was a tie.

[4] Does not include buprenorphine formulations used to treat opioid use disorder.

[5] Other medication use defined as two or more dispensings in the prior year except for buprenorphine and naloxone where use defined as one or more dispensings or one or more procedure codes.

[6]Other pain conditions include: acquired deformities (excluding back), cancer-related, general, postoperative, post-trauma, restless leg syndrome, spinal cord injury, bone infections, infectious arthritic diseases.

[7] OUD-P measures in this table use the pain-adjusted DSM-5-OUD definition.

[8] ADHD was missing for 0.5% of the ER/LA cohort and 0.3% of the LtOT cohort. Percentage with ADHD is based on all participants, including those missing ADHD status.

Abbreviations: ACE, adverse childhood experiences; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; ED, emergency department; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, immediate-release/short-acting; kg/m^2, kilogram/meter$^{2;}$ LtOT, long-term opioid therapy; MME, morphine milligram equivalent; n, number; OA, opioid analgesic; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, post-traumatic stress disorder; SD, standard deviation; SF-12, 12-item Short Form Health Survey

Twelve-Month Incidence

Table 7 shows the 12-month incidence for the misuse and abuse outcomes overall and by age, sex, race, and ethnicity. The overall incidence of misuse was 22.8% in the ER/LA cohort and 21.6% in the LtOT cohort. The overall incidence of abuse was 9.4% in the ER/LA cohort and 8.6% in the LtOT cohort.

Table 7. Twelve-Month Incidence of Misuse and Abuse for the ER/LA and LtOT Cohorts

Characteristic	Misuse[1] (ER/LA Cohort[2]) (N=804)	Misuse[1] (LtOT Cohort[3]) (N=1,003)	Abuse[1] (ER/LA Cohort[2]) (N=911)	Abuse[1] (LtOT Cohort[3]) (N=1,151)
	Incidence, % (95% CI)	Incidence, % (95% CI)	Incidence, % (95% CI)	Incidence, % (95% CI)
Overall	22.8 (21.6, 24.0)	21.6 (18.3, 25.5)	9.4 (7.7, 11.6)	8.6 (7.4, 10.0)
Age group, years				
18-39	15.6 (11.5, 21.1)	19.6 (10.8, 35.7)	12.1 (9.3, 15.7)	12.3 (6.6, 22.9)
40-49	25.0 (19.2, 32.5)	18.9 (13.3, 26.9)	11.7 (9.1, 15.0)	7.7 (5.0, 11.9)
50-59	20.8 (16.9, 25.7)	26.1 (21.4, 31.8)	7.5 (5.0, 11.4)	7.5 (5.9, 9.7)
≥60	24.6 (21.2, 28.6)	20.4 (17.6, 23.6)	9.3 (7.0, 12.4)	8.7 (7.1, 10.8)
Sex				
Female	20.8 (18.3, 23.6)	22.5 (18.3, 27.7)	8.9 (6.6, 12.0)	7.6 (6.3, 9.3)
Male	25.5 (21.8, 29.9)	20.2 (16.7, 24.3)	10.2 (8.6, 12.2)	10.1 (7.5, 13.5)
Race[4]				
White	21.7 (19.7, 23.9)	20.7 (17.6, 24.3)	8.7 (6.7, 11.3)	8.8 (7.4, 10.6)
Black	25.7 (18.3, 36.1)	27.4 (22.5, 33.3)	8.2 (4.9, 13.9)	8.7 (5.9, 12.8)
Other/mixed	31.7 (24.4, 41.2)	20.9 (13.3, 32.9)	18.8 (12.2, 28.9)	6.8 (4.6, 10.3)
Hispanic/Latino ethnicity[5]				
No	23.2 (22.0, 24.5)	21.9 (18.4, 26.0)	9.7 (7.8, 12.1)	8.6 (7.4, 10.1)
Yes	19.0 (14.4, 25.1)	19.6 (13.3, 28.8)	7.1 (4.2, 12.3)	8.3 (5.1, 13.5)

Source: FDA-generated table adapted from data provided in Final Prospective Tables, Table 9a and Table 9b, FDA IR Response dated July 19, 2023.

[1] Opioid misuse and opioid abuse were measured with the POMAQ. The 12-month incidence was calculated using the 3-, 6-, 9-, and 12-month POMAQ measures.

[2] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[3] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[4] Some patients were missing race and were therefore excluded from this incidence calculation. For the ER/LA cohort: n=3 missing, abuse: n=4 missing. For the LtOT cohort: misuse: n=10 missing, abuse: n=10 missing.

[5] For the LtOT cohort, 1 patient was excluded from this incidence calculation due to missing ethnicity.

Abbreviations: CI, confidence interval; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR, information request; IR/SA, immediate-release/short-acting; LtOT, long-term opioid therapy; N, number of patients; OA, opioid analgesic; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire

Table 8 presents 12-month incidence estimates for OUD in the ER/LA and LtOT cohorts, at varying severity thresholds, using the pain-adjusted DSM-5-OUD and DSM-5-OUD definitions. Overall patterns were similar across the two cohorts, although estimates varied between the two OUD definitions. At all severity thresholds, estimates were substantially higher using the DSM-5-OUD definition, compared to estimates based on the pain-adjusted DSM-5-OUD definition. There were zero patients with OUD-H in the ER/LA cohort and three with OUD-H in the LtOT cohort.

Table 8. Twelve-Month Incidence of Pain-Adjusted DSM-5-OUD and DSM-5-OUD in the ER/LA and LtOT Cohorts, by Severity Level

	ER/LA Cohort[1] (N=978)		LtOT Cohort[2] (N=1,244)	
OUD Definition and Severity	**Cases**	**Incidence, % (95% CI)**	**Cases**	**Incidence, % (95% CI)**
Pain-adjusted DSM-5-OUD,[3] any [5]	71	8.4 (6.8, 10.2)	64	5.8 (4.4, 7.7)
Pain-adjusted DSM-5-OUD,[3] moderate-to-severe*,[6]	12	1.4 (0.9, 2.3)	18	1.6 (0.9, 2.9)
Pain-adjusted DSM-5-OUD[3] severe[7]	3	0.4 (0.1, 1.7)	10	0.9 (0.4, 1.9)
DSM-5-OUD[4] any[5]	191	22.5 (19.0, 26.5)	163	14.8 (13.0, 16.8)
DSM-5-OUD[4] moderate-to-severe[6]	49	5.8 (4.5, 7.3)	38	3.4 (2.3, 5.1)
DSM-5-OUD[4] severe[7]	9	1.1 (0.6, 1.7)	17	1.5 (0.8, 3.1)

Source: FDA-generated table adapted from data provided in Supplemental Tables 8a, 9a, 8b, and 9b, Final Report on the Prospective Study Results.

* Primary OUD definition in PMR 3033-1.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated of either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] The pain-adjusted DSM-5 OUD definitions incorporated reason for opioid use (i.e., pain-related or not) when determining whether each DSM-5 symptom of OUD was present.

[4] The DSM-5-OUD definition of OUD did not incorporate reason for opioid use (i.e., pain-related or not) .

[5] In PMR 3033-1, any OUD was defined as having two or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

[6] In PMR 3033-1, moderate-to-severe OUD was defined as having four or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

[7] In PMR 3033-1, severe OUD was defined as having six or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; LtOT, long-term opioid therapy; N, number; OA, opioid analgesic; OUD, opioid use disorder; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version

The 12-month incidence of the composite outcome (i.e., opioid misuse, opioid abuse, or moderate-to-severe pain-adjusted DSM-5 OUD based on the pain-adjusted DSM-5-OUD definition), overall and stratified by demographic characteristics, is shown in Table 9.

Table 9.Twelve-Month Incidence of the Composite Outcome in the ER/LA and LtOT Cohorts

	Composite Outcome[1] (ER/LA Cohort[2])		Composite Outcome[1] (LtOT Cohort[3])	
Characteristic	**Cases (n)**	**Incidence, % (95% CI)**	**Cases (n)**	**Incidence, % (95% CI)**
Overall	190	24.5 (23.3, 25.7)	208	21.4 (18.8, 24.2)
Age group, years				
18-39	14	18.9 (13.2, 27.1)	19	19.0 (9.7, 37.1)
40-49	29	27.4 (22.0, 34.0)	32	18.5 (14.0, 24.5)
50-59	46	21.9 (17.5, 27.4)	68	26.0 (20.2, 33.3)
≥60	101	26.2 (22.8, 30.0)	89	20.3 (17.2, 24.0)
Sex				
Female	103	22.6 (20.1, 25.5)	134	22.4 (18.8, 26.7)
Male	87	27.1 (23.1, 31.8)	74	19.7 (16.6, 23.5)
Race[4]				
White	151	23.5 (21.5, 25.7)	153	20.4 (17.9, 23.3)
Black	19	26.0 (17.6, 38.5)	41	27.7 (23.8, 32.3)
Other/mixed	20	34.5 (26.7, 44.6)	13	20.0 (12.7, 31.4)
Hispanic/Latino ethnicity[5]				
No	173	24.9 (23.5, 26.4)	189	21.6 (18.9, 24.7)
Yes	17	20.7 (16.3, 26.4)	19	19.8 (13.9, 28.3)

Source: FDA-generated table adapted from data provided in Final Prospective Tables, Table 9a and Table 9b, FDA IR Response dated July 19, 2023.

[1] The composite outcome is defined as having misuse (measured with the POMAQ), abuse (measured with the POMAQ), and/or moderate-to-severe pain-adjusted DSM-5-OUD (measured with the PRISM-5-Op) at any time during the 12 months of follow-up.

[2] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[3] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[4] Some patients were excluded from this incidence calculation due to missing race. For the ER/LA cohort: n=3 missing. For the LtOT cohort: n=10 missing.

[5] For the LtOT cohort, one patient was excluded from this incidence calculation due to missing ethnicity.

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR, information request; IR/SA, immediate-release/long-acting; LtOT, long-term opioid therapy; n, number of patients; OA, opioid analgesic; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version

Risk Factor Analyses

As stated in the methods (Section 3.1.3), unadjusted risk factor analyses (results shown in Appendix Table 30) were conducted to identify risk factors to be included in the multivariate model, along with automatic inclusion of age, sex, race, and ethnicity. In the ER/LA cohort, this resulted in 31 variables included in the fully adjusted model for misuse, 30 variables included in the fully adjusted model for abuse, and 9 variables included in the fully adjusted model for OUD. In the LtOT cohort, this resulted in 24 variables included in the fully adjusted model for misuse, 21 variables included in the fully adjusted model for abuse, and 19 variables included in the fully adjusted model for OUD. Demographically adjusted analyses examining individual risk factors with adjustment for age, sex, race, and ethnicity were

also conducted to examine individual associations between risk factors and outcomes, adjusted for demographic factors (results shown in Appendix Table 31).

A summary of selected findings from the fully adjusted risk factor analyses for misuse, abuse, and moderate-to-severe pain-adjusted DSM-5-OUD follows. The full set of results for these outcomes, including all variables assessed in the analysis, can be found in Appendix Table 32. Results for the composite outcome are not reported further, as due to differences in findings across the primary outcomes, the findings for individual outcomes were considered more informative. As there were no patients with OUD-H in the ER/LA cohort, the risk factor assessment for OUD-P was identical to that for the primary OUD outcome. Three patients in the LtOT cohort were diagnosed with OUD-H – too few to conduct the subcategory analysis.

In describing the results, we emphasize that the term "significant" refers to statistical significance at α=0.05 level unless otherwise specified. Statistical significance does not necessarily indicate clinical significance (i.e., clinical importance) because it can be influenced by the effective sample size. For instance, when the number of patients with a given outcomes or with a specific risk factor is small, the absence of statistical significance may not accurately reflect a lack of clinical significance. Conversely, with a large sample size, results may appear statistically significant regardless of their clinical relevance. Note that due to rounding, some significant associations include one in the 95% CI. Statistically significant associations are identified in bold. As described in Section 3.1.3, these results do not reflect formal hypothesis testing, and no multiplicity adjustment was performed; this decision was made to facilitate risk factor identification, prioritizing reducing the chance of failing to detect true adverse effects or risk factors (i.e., Type II errors).

Potential Risk Factors for Misuse, Abuse, and OUD

Table 10 shows selected results of the risk factor analyses for abuse, misuse, and OUD in the ER/LA and LtOT cohorts (full results containing all variables included in the model are provided in Appendix Table 32). Risk factors were selected for inclusion in Table 10 if they were significantly associated with the same outcome in both the ER/LA and LtOT cohorts, were significantly associated with multiple outcomes within a cohort, or were of particular regulatory interest to FDA (e.g., related to OA dose or formulation). There was a great deal of variability in terms of which risk factors were significantly associated with misuse, abuse, and OUD, and differences were observed across the two cohorts (ER/LA and LtOT).

Sociodemographic Factors

Age did not have a consistent direction of association across outcomes or cohorts. In the ER/LA cohort, compared to patients aged 18 to 39 years, patients aged ≥60 years had increased odds of misuse and decreased odds of OUD, but age was not associated with any outcome in the LtOT cohort. ER/LA cohort patients of other/mixed race had increased odds of misuse and abuse compared to White patients. Sex was not associated with any of the primary outcomes.

OA-Related Factors

Hydromorphone was associated with increased odds of abuse in both the ER/LA and LtOT cohorts, compared to oxycodone. A baseline average daily dose of 90 to 119 MMEs and >120 MMEs (compared to <50 MMEs) was associated with increased odds of misuse in the ER/LA cohort, and a baseline average daily dose between 90 and 119 MMEs was associated with increased odds of abuse in the LtOT cohort.

Each additional week of Schedule II OA therapy duration during the baseline period was associated with a small but statistically significant increase in the odds of misuse in both cohorts. ADF OA use and predominant OA formulation either did not meet criteria for inclusion in any of the fully adjusted models or were not statistically significantly related to the primary outcomes if they were included.

SUD History

Having a past-year nonopioid/non-nicotine SUD was associated with increased odds of misuse and abuse in both cohorts; a prior to past year nonopioid/non-nicotine SUD was associated with increased odds of OUD in the LtOT cohort. Baseline misuse was associated with an increased odds of abuse in both cohorts, and baseline abuse was associated with increased odds of misuse and OUD in the LtOT cohort. Past year OUD-P (at baseline) was associated with abuse at follow-up in the LtOT cohort.

Health- and Pain-Related Factors

Having one or more inpatient stays (versus none) was associated with decreased odds of misuse in the ER/LA cohort. Higher Elixhauser comorbidity scores (versus a score of zero) were associated with lower odds of misuse, abuse, and OUD in the ER/LA cohort. Having one or two ED visits (versus none) was associated with decreased odds of misuse in the ER/LA cohort and OUD in the LtOT cohort. Gabapentinoid use (versus no use) was associated with increased odds of misuse and OUD in the ER/LA cohort. Each unit change (for the worse) in pain severity, stress, and physical function was associated with increased odds of misuse in the ER/LA cohort. Each unit change (for the worse) in pain interference was associated with decreased odds of misuse in the ER/LA cohort.

Mental Health Conditions and Social Factors

Borderline personality disorder was associated with increased odds of misuse and abuse in the ER/LA cohort. PTSD was associated with increased odds of OUD in the ER/LA cohort and misuse in the LtOT cohort; however, it was associated with decreased odds of misuse in the ER/LA cohort. Past-year MDD, prior to past year MDD, and anxiety were not associated with any of the primary outcomes in either cohort in the fully adjusted models where they met the criteria for inclusion.

Table 10. Selected ORs and 95% CIs From Fully Adjusted Models for Misuse, Abuse, and Moderate-to-Severe Pain-Adjusted DSM-5-OUD in the ER/LA and LtOT Cohorts of the Prospective PMR 3033-1 Study

Selected Potential Risk Factors[1]	Misuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Misuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)
Selected sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	1.2 (0.5, 2.7)	1.0 (0.3, 2.7)	0.8 (0.5, 1.2)	0.6 (0.1, 2.3)	**0.1 (0.0, 0.4)**	0.9 (0.1, 6.6)
50-59	1.3 (0.7, 2.1)	1.5 (0.5, 4.6)	**0.5 (0.3, 0.7)**	0.5 (0.2, 1.2)	0.3 (0.1, 1.3)	0.8 (0.2, 3.5)
≥60	**1.8 (1.0, 3.0)**	1.3 (0.6, 2.8)	1.0 (0.5, 1.9)	1.0 (0.5, 2.3)	**0.0 (0.0, 0.5)**	0.9 (0.1, 4.9)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.8 (0.7, 4.2)	1.2 (0.7, 1.9)	0.8 (0.3, 1.9)	1.1 (0.7, 1.7)	1.04 (0.1, 8.0)[7]	**3.0 (1.3, 7.0)**
Other/mixed	**1.8 (1.1, 2.9)**	1.0 (0.6, 1.8)	**2.2 (1.5, 3.3)**	0.8 (0.5, 1.3)		0.8 (0.1, 7.9)
OA-related factors						
Predominant OA formulation[8]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	1.3 (0.7, 2.2)	N/I	1.3 (0.7, 2.4)	N/I	N/I	N/I
Average daily dose at baseline, MME[8]						
<50	Ref	Ref	Ref	Ref	Ref	Ref
50-89	1.2 (0.8, 1.7)	N/I	N/I	1.2 (0.6, 2.6)	N/I	N/I
90-119	**1.8 (1.0, 3.2)**	N/I	N/I	**2.7 (1.3, 5.6)**	N/I	N/I
≥120	**2.4 (1.2, 4.5)**	N/I	N/I	1.9 (0.2, 15.5)	N/I	N/I

Selected Potential Risk Factors[1]	Misuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Misuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)
Predominant opioid moiety[8,9]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.8 (0.3, 1.8)	0.8 (0.2, 2.8)	0.9 (0.4, 1.9)	2.3 (0.7, 7.4)	1.1 (0.5, 2.4)	*
Hydrocodone	1.1 (0.7, 1.9)	1.2 (0.9, 1.5)	1.8 (0.9, 3.5)	1.5 (1.0, 2.4)	*	2.4 (0.9, 6.4)
Fentanyl	0.3 (0.1, 1.2)	*	1.2 (0.5, 2.8)	*	*	*
Methadone	0.4 (0.1, 1.8)	*	1.0 (0.3, 3.4)	*	*	*
Oxymorphone	*	*	*	*	*	*
Hydromorphone	1.4 (0.7, 2.5)	*	**6.8 (3.3, 14.0)**	**6.9 (2.7, 17.6)**	*	*
Tramadol	**0.4 (0.2, 0.7)**	0.7 (0.3, 1.7)	0.5 (0.2, 1.0)	*	*	*
Buprenorphine	1.1 (0.6, 2.1)	*	2.1 (0.1, 31.5)	*	*	*
Codeine	1.1 (0.2, 6.7)	**3.2 (1.4, 7.4)**	*	*	*	*
Tapentadol	*	*	*	*	*	*
Meperidine	*	*	*	*	*	*
Butorphanol	*	*	*	*	*	*
Other[10]	4.4 (0.7, 26.7)	0.4 (0.1, 1.6)	**4.1 (1.4, 12.6)**	0.4 (0.1, 3.4)	0.2 (0.0, 1.6)	**0.2 (0.0, 0.7)**
Use of an ADF OA[8]						
None	Ref	Ref	Ref	Ref	Ref	Ref
Any	N/I	N/I	N/I	N/I	N/I	N/I
Duration of Schedule II OA therapy during the baseline period[8]						
Per 7-day increase	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.1)	N/I	N/I	N/I
SUD history						
Past-year nonopioid, non-nicotine SUD (yes vs. no)	**2.7 (1.1, 6.7)**	**3.4 (2.3, 5.0)**	**5.5 (2.0, 15.6)**	**2.3 (1.5, 3.5)**	N/I	2.4 (0.5, 11.2)
Nonopioid, non-nicotine SUD prior to the past year (yes vs. no)	1.6 (1.0, 2.7)	N/I	1.0 (0.5, 1.9)	1.2 (0.7, 2.0)	N/I	**9.8 (3.1, 30.8)**
POMAQ-classified opioid misuse (yes vs. no)	Not applicable	Not applicable	**3 (1.8, 5.1)**	**2.2 (1.2, 3.8)**	3.4 (0.7, 16.8)	1.9 (0.6, 5.8)
POMAQ-classified opioid abuse (yes vs. no)	1.3 (0.7, 2.4)	**3.6 (2.3, 5.6)**	Not applicable	Not applicable	N/I	**5.4 (2.3, 12.9)**
OUD-H, past year (yes vs. no)	N/I	N/I	N/I	N/I	Not applicable	Not applicable
OUD-P,[11] past year (yes vs. no)	N/I	1.1 (0.3, 3.9)	0.6 (0.1, 4.9)	**5.2 (1.9, 14.8)**	Not applicable	Not applicable
Selected health- and pain-related factors						
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.7 (0.6, 1.0)**	0.7 (0.4, 1.1)	0.8 (0.4, 1.4)	N/I	N/I	N/I
≥2	**0.4 (0.2, 0.9)**	1.1 (0.8, 1.6)	0.4 (0.1, 1.4)	N/I	N/I	N/I

Selected Potential Risk Factors[1]	Misuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Misuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Abuse[2] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (ER/LA Cohort[4]) Fully Adjusted[6] OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (LtOT Cohort[5]) Fully Adjusted[6] OR (95% CI)
ED visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	**0.7 (0.6, 0.9)**	N/I	N/I	N/I	N/I	**0.0 (0.0, 0.1)**
≥3	1.0 (0.7, 1.6)	N/I	N/I	N/I	N/I	2.2 (0.5, 9.8)
Other medication use[12] (any vs. none)						
Antidepressants	1.3 (0.9, 1.9)	1.4 (0.9, 2.0)	N/I	N/I	N/I	**2.3 (1.3, 4.1)**
Antipsychotics	1.5 (1.0, 2.3)	0.7 (0.3, 1.6)	N/I	2.4 (0.8, 7.3)	N/I	N/I
Gabapentinoids	**1.3 (1.0, 1.8)**	N/I	N/I	N/I	**5.0 (2.1, 11.9)**	N/I
Muscle relaxers	N/I	N/I	N/I	N/I	1.8 (0.5, 6.1)	N/I
Naloxone	N/I	N/I	N/I	N/I	N/I	**9.0 (2.8, 28.4)**
Sedative hypnotics	N/I	1.3 (1.0, 1.7)	N/I	N/I	N/I	1.1 (0.5, 2.5)
Stimulants	N/I	N/I	Not estimable[13]	N/I	N/I	N/I
ECI score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.2 (0.1, 0.4)**	1.4 (0.6, 3.3)	**0.3 (0.1, 0.7)**	N/I	**0.2 (0.1, 0.3)**	N/I
≥2	**0.4 (0.3, 0.7)**	1.5 (0.7, 3.4)	**0.4 (0.2, 0.8)**	N/I	**0.1 (0.0, 0.6)**	N/I
Selected mental health conditions						
Borderline personality disorder (yes vs. no)	**1.9 (1.1, 3.3)**	1.1 (0.5, 2.7)	**2.5 (1.7, 3.6)**	1.2 (0.7, 2.2)	N/I	0.6 (0.1, 3.3)
PTSD (yes vs. no)	**0.6 (0.4, 0.9)**	**1.6 (1.0, 2.6)**	1.7 (0.7, 4.1)	0.8 (0.4, 2.0)	**1.4 (1.0, 2.0)**	1.4 (0.3, 7.0)
Other patient-reported measures (per 1-unit change worse)						
Pain severity	**1.1 (1.0, 1.2)**	1.1 (1.0, 1.2)	N/I	N/I	1.1 (0.9, 1.3)	N/I
Pain interference	**0.9 (0.8, 1.0)**	N/I	1.0 (0.9, 1.2)	1.1 (1.0, 1.2)	N/I	1.2 (1.0, 1.4)
Stress	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)	N/I	1.1 (1.0, 1.2)
Social support	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	N/I	1.0 (1.0, 1.0)
SF-12 physical score	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	N/I	N/I	N/I
SF-12 mental score	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)	N/I	1.0 (0.9, 1.0)

Source: FDA-generated table adapted from data provided in Appendix 1 Q5 Table F REV and Q5 Table I REV, FDA IR Response dated June 04, 2024.

Notes: For nonreference variables denoted "N/I", the variable did not reach statistical significance at p<0.10 in univariate analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in bold. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Risk factors are included in this table if they were statistically significant for the same outcome in both the ER/LA and LtOT cohorts, were significantly associated with multiple outcomes within a cohort, or were of particular interest to FDA. The full set of risk factor findings from the fully adjusted model can be found in Appendix Table 32.

[2] Opioid misuse and opioid abuse were measured with the POMAQ.

[3] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.
[4] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.
[5] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).
[6] Fully adjusted models were adjusted for all risk factors for which ORs and 95% CIs are presented in Appendix Table 32. The risk factors included in the fully adjusted models were those that were statistically significantly associated with a given outcome in unadjusted analyses, plus age, sex, race, and ethnicity. Not all risk factors included in the model are listed in the present table.
[7] There were no Black participants with moderate-to-severe pain-adjusted OUD. To achieve model convergence, Black race was combined with Other/Mixed race for this outcome.
[8] Baseline OA exposure is measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days.
[9] The following active pharmaceutical ingredients were not prescribed in this study and are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene. Predominance was based on greatest total days' supply, or most prescriptions if there was a tie.
[10] When an opioid moiety contained ≤2 events for a given outcome, it was collapsed into the "other" category for the respective outcome. Opioid moieties included in the "other" category for a given outcome are indicated by *.
[11] OUD-P measures in this table use the pain-adjusted DSM-5-OUD definition.
[12] Other medication use is defined as two or more dispensings in the prior year except naloxone where use defined as one or more dispensings or one or more procedure codes.
[13] For cells denoted "not estimable", odds ratios could not be estimated due to a lack of model convergence arising from the small number of participants with this outcome.
Abbreviations: ADF, abuse-deterrent formulation; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; ED, emergency department; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR, information request; IR/SA, immediate-release/short-acting; LtOT, long-term opioid therapy; MME, morphine milligram equivalent; N/I, not included in model; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; Ref, reference; SF-12, 12-item Short Form Health Survey; SUD, substance use disorder

Comparison of Risk Factor Results Across Pain-Adjusted DSM-5-OUD and DSM-5-OUD Definitions

Table 11 presents selected risk factors comparing the fully adjusted models for two definitions of moderate-to-severe OUD: the pain-adjusted DSM-5-OUD definition (primary outcome, also shown in (Table 10) and the DSM-5-OUD definition (secondary outcome) in the ER/LA and LtOT cohorts. Full results of these analyses, as well as results for any DSM-5-OUD and any pain-adjusted DSM-5-OUD are presented in Appendix Table 33. Selected risk factors included in Table 11 are those included in the models for both the pain-adjusted and standard DSM-5-OUD definitions in either the ER/LA or LtOT cohorts, regardless of statistical significance, or those that were of particular interest to FDA (e.g., related to OA dose or formulation).

As with the misuse and abuse risk factor analyses, many variables did not meet the criteria for inclusion in the fully adjusted cohort based on the results of the unadjusted analyses. Furthermore, many of the CIs for the included risk factors were wide. Again, there was substantial variation in findings across the two cohorts and when using the primary (pain-adjusted DSM-5-OUD) versus the standard DSM-5-OUD definitions.

Sociodemographic Factors

In the ER/LA cohort, compared to the reference group aged 18 to 39 years, age groups 40 to 49 and ≥60 years were associated with lower odds of OUD using the pain-adjusted DSM-5-OUD definition. Age and sex were not associated with OUD using the DSM-5-OUD definition. In the ER/LA cohort, Black (compared to White) race and Hispanic/Latino ethnicity were associated with increased odds of OUD using the DSM-5-OUD definition. In the LtOT cohort, Black (compared to White) race and Latino/Hispanic ethnicity were associated with increased OUD odds using the pain-adjusted DSM-5-OUD definition.

OA-Related Factors

Compared to predominant use of oxycodone (reference), hydrocodone was associated with lower odds of OUD, and fentanyl use was associated with higher odds of OUD using the DSM-5-OUD definition in the ER/LA cohort. Other individual opioid moieties were not associated with increased or decreased OUD incidence relative to oxycodone. Formulation, ADF OA use, baseline average daily dose, and duration of Schedule II OA therapy during the baseline period were either not included in the fully adjusted model or not significantly associated with OUD in either cohort using either the pain-adjusted DSM-5-OUD or DSM-5-OUD definitions.

SUD History

Although not consistently significant across all risk factors, cohorts, and OUD definitions, in general, having a history of a substance use disorder was associated with increased odds of incident OUD (both definitions). Baseline misuse and abuse were also associated with incident OUD, although these were significant only in the LtOT cohort.

Health- and Pain-Related Factors

In the LtOT cohort, one to two ED visits (versus none) were associated with lower odds of OUD, but three or more ED visits (versus none) was associated with higher odds of OUD.

In the LtOT cohort, antidepressant use was associated with increased odds of OUD using the pain-adjusted DSM-5 definition but not the DSM-5 definition. In the ER/LA cohort, gabapentinoid use was associated with increased odds of OUD using both OUD definitions. Results for ACEs were mixed, although most ORs were >1 when comparing ACE scores >1 to ACE score of 0, particularly in the ER/LA

cohort. Most of the other patient-reported measures were not associated with OUD outcomes in these analyses.

Mental Health Conditions and Social Factors

Other mental health conditions, including MDD, ADHD, and GAD, were associated with incident OUD in at least one fully adjusted model. Associations between ACEs and OUD were mixed, and many confidence intervals were wide.

Table 11. Selected ORs and 95% CIs From the Fully Adjusted Models for Moderate-to-Severe Pain-Adjusted DSM-5-OUD and Moderate-to-Severe DSM-5-OUD in the ER/LA and LtOT Cohorts of the Prospective PMR 3033-1 Study

	ER/LA Cohort[2]		LtOT Cohort[3]	
	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]
Selected Potential Risk Factor[1]	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**
Selected sociodemographic factors				
Age group, years				
18-39	Ref	Ref	Ref	Ref
40-49	**0.1 (0.0, 0.4)**	0.7 (0.3, 1.5)	0.9 (0.1, 6.6)	0.7 (0.3, 1.4)
50-59	0.3 (0.1, 1.3)	0.5 (0.2, 1.6)	0.8 (0.2, 3.5)	0.6 (0.3, 1.3)
≥60	**0.0 (0.0, 0.5)**	0.5 (0.2, 1.2)	0.9 (0.1, 4.9)	0.7 (0.3, 1.8)
Sex				
Female	Ref	Ref	Ref	Ref
Male	1.2 (0.4, 3.5)	1.1 (0.4, 3.0)	1.0 (0.3, 3.2)	1.4 (0.7, 2.9)
Race				
White	Ref	Ref	Ref	Ref
Black		**3.4 (1.4, 7.9)**	**3.0 (1.3, 7.0)**	1.4 (0.8, 2.8)
Other/mixed	1.0 (0.1, 8.0)[7]	2.1 (0.5, 9.6)	0.8 (0.1, 7.9)	0.3 (0.0, 1.9)
Hispanic/Latino ethnicity				
No	Ref	Ref	Ref	Ref
Yes	1.4 (0.4, 5.0)	**2.5 (1.1, 5.8)**	**3.6 (1.2, 10.9)**	1.3 (0.6, 3.0)
OA-related factors				
Predominant OA formulation[8]				
IR/SA	Ref	Ref	Ref	Ref
ER/LA	N/I	N/I	N/I	N/I
Average daily dose at baseline, MME[8]				
<50	Ref	Ref	Ref	Ref
50-89	N/I	0.4 (0.1, 1.4)	N/I	N/I
90-119	N/I	1.0 (0.5, 2.0)	N/I	N/I
≥120	N/I	1.2 (0.5, 3.1)	N/I	N/I

	ER/LA Cohort[2]		LtOT Cohort[3]	
	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]
Selected Potential Risk Factor[1]	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**	**Fully Adjusted[6] OR (95% CI)**
Predominant opioid moiety[8,9]				
Oxycodone	Ref	Ref	Ref	Ref
Morphine	1.1 (0.5, 2.4)	0.5 (0.2, 1.4)	*	*
Hydrocodone	*	**0.4 (0.2, 1.0)**	2.4 (0.9, 6.4)	0.9 (0.4, 1.9)
Fentanyl	*	**3.1 (1.8, 5.3)**	*	*
Methadone	*	*	*	*
Oxymorphone	*	*	*	*
Hydromorphone	*	*	*	*
Tramadol	*	*	*	*
Buprenorphine	*	*	*	*
Codeine	*	*	*	*
Tapentadol	*	*	*	*
Meperidine	*	*	*	*
Butorphanol	*	*	*	*
Other[10]	0.2 (0.0, 1.6)	0.4 (0.1, 1.3)	**0.2 (0.0, 0.7)**	0.6 (0.1, 2.9)
Use of an ADF OA[8]				
None	Ref	Ref	Ref	Ref
Any	N/I	N/I	N/I	N/I
Duration of Schedule II OA therapy during the baseline period[8]				
Per 7-day increase	N/I	1.0 (1.0, 1.1)	N/I	N/I
SUD history				
Past-year nonopioid, non-nicotine SUD (yes vs. no)	N/I	**4.0 (1.3, 11.9)**	2.4 (0.5, 11.2)	2.0 (0.5, 7.3)
Nonopioid, non-nicotine SUD prior to the past year (yes vs. no)	N/I	1.5 (0.8, 2.7)	**9.8 (3.1, 30.8)**	**2.4 (1.3, 4.5)**
POMAQ-classified misuse (yes vs. no)	3.4 (0.7, 16.8)	2.3 (1.0, 5.4)	1.9 (0.6, 5.8)	**2.2 (1.1, 4.6)**
POMAQ-classified abuse (yes vs. no)	N/I	N/I	**5.4 (2.3, 12.9)**	1.5 (0.7, 3.4)
OUD-H, past year (yes vs. no)	Not applicable	N/I	Not applicable	N/I
OUD-P,[11] past year (yes vs. no)	Not applicable	N/I	Not applicable	N/I
OUD-P,[11] prior to past year (yes vs. no)	N/I	0.7 (0.2, 2.9)	**9.0 (2.6, 31.0)**	**4.4 (1.7, 11.7)**
Selected health- and pain-related factors				
ED visits				
0	Ref	Ref	Ref	Ref
1-2	N/I	N/I	**0.0 (0.0, 0.1)**	0.5 (0.2, 1.4)
≥3	N/I	N/I	2.2 (0.5, 9.8)	**2.9 (1.6, 5.3)**

Selected Potential Risk Factor[1]	ER/LA Cohort[2]		LtOT Cohort[3]	
	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[4]	Moderate-to-Severe DSM-5-OUD[5]
	Fully Adjusted[6] OR (95% CI)	Fully Adjusted[6] OR (95% CI)	Fully Adjusted[6] OR (95% CI)	Fully Adjusted[6] OR (95% CI)
Other medication use (any vs. none)[12]				
Antidepressants	N/I	1.1 (0.5, 2.1)	**2.3 (1.3, 4.1)**	1.5 (0.5, 3.9)
Antipsychotics	N/I	N/I	N/I	2.1 (0.9, 5.2)
Gabapentinoids	**5.0 (2.1, 11.9)**	**2.8 (1.9, 4.3)**	N/I	1.3 (0.5, 3.5)
Muscle relaxers	1.8 (0.5, 6.1)	N/I	N/I	1.3 (0.7, 2.5)
Naloxone	N/I	N/I	**9.0 (2.8, 28.4)**	N/I
Sedative hypnotics	N/I	N/I	1.1 (0.5, 2.5)	N/I
Stimulants	N/I	N/I	N/I	N/I
Selected mental health conditions and social factors				
ACE				
0	Ref	Ref	Ref	Ref
1	4.8 (1.0, 23.9)	**4.2 (2.4, 7.3)**	N/I	0.8 (0.1, 5.0)
2	1.3 (0.1, 14.6)[13]	2.0 (1.0, 4.2)	N/I	**0.2 (0.1, 0.4)**
3		2.5 (0.5, 12.7)	N/I	1.0 (0.2, 4.8)
4+	1.3 (0.1, 21.2)	2.5 (0.8, 8.5)	N/I	1.2 (0.3, 5.7)
MDD, past year (yes vs. no)	2.6 (1.0, 6.8)	**3.1 (1.4, 6.6)**	N/I	N/I
ADHD (yes vs. no)	N/I	**2.4 (1.1, 5.3)**	1.8 (0.5, 6.4)	0.8 (0.4, 1.8)
Borderline personality disorder (yes vs. no)	N/I	1.5 (0.5, 4.1)	0.6 (0.1, 3.3)	1.3 (0.4, 4.0)
GAD (yes vs. no)	N/I	0.9 (0.5, 1.6)	1.2 (0.3, 5.0)	**2.5 (1.4, 4.6)**
PTSD (yes vs. no)	**1.4 (1.0, 2.0)**	0.9 (0.3, 3.2)	1.4 (0.3, 7.0)	1.0 (0.3, 3.3)
Other patient-reported measures (per 1-unit change worse)				
Pain severity	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	N/I	1.2 (1.0, 1.4)
Pain interference	N/I	**1.3 (1.1, 1.5)**	1.2 (1.0, 1.4)	1.0 (0.8, 1.1)
Stress	N/I	1.0 (0.9, 1.0)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)
Social support	N/I	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
SF-12 mental score	N/I	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)

Source: FDA-generated table adapted from data provided in Appendix 1 Q5 Table F REV and Q5 Table I REV, FDA IR Response dated June 04, 2024.

Notes: For nonreference variables denoted "N/I", the variable did not reach statistical significance at p<0.10 in univariate analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in bold. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Selected risk factors listed in this table are those included in the models for both OUD definitions in at least one cohort, regardless of statistical significance, or those of particular interest to FDA. The full set of risk factor findings can be found in Appendix Table 33.

[2] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[3] Includes patients who initiated of either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[4] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[5] Moderate-to-severe DSM-5-OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.
[6] Fully adjusted models were adjusted for all risk factors for which ORs and 95% CIs are presented in Appendix Table 33. The risk factors included in the fully adjusted models were those that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.10), plus age, sex, race, and ethnicity. Not all risk factors included in the model are listed in this table.
[7] There were no Black participants with moderate-to-severe pain-adjusted OUD in the ER/LA cohort. To achieve model convergence, Black was combined with other/mixed race for this outcome.
[8] Baseline OA exposure was measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days.
[9] The following predominant opioid moieties were not prescribed in the study and are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene. Predominance based on greatest total days' supply, or most prescriptions if there was a tie.
[10] When a predominant opioid moiety contained ≤2 events of a given outcome, it was collapsed into the "other" category for the respective outcome. Opioid moieties included in the "other" category for a given outcome are indicated by *.
[11] OUD-P measures in this table use the pain-adjusted DSM-5-OUD definition.
[12] Other medication use defined as two or more dispensings in the prior year except naloxone where use was defined as one or more dispensings or one or more procedure codes.
[13] There were no participants with three ACEs with moderate-to-severe pain-adjusted OUD in the ER/LA cohort. To achieve model convergence, participants who had two ACEs were combined with those who had three for this outcome.
Abbreviations: ACE, adverse childhood experiences; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ED, emergency department; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, immediate-release/short-acting; LtOT, long-term opioid therapy; MDD, major depressive disorder; MME, morphine milligram equivalent; N/I, not included in model; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription drugs; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, post-traumatic stress disorder; Ref, reference; SF-12, 12-item Short Form Health Survey; SUD, substance use disorder

3.1.5 3033-1 Cross-Sectional Study Design and Methodology

The cross-sectional PMR 3033-1 study aimed to quantify the prevalence of misuse, abuse, and OUD among patients with chronic pain treated with LtOT for at least 1 year, including a prescription for at least one ER/LA OA, and to identify risk factors for these outcomes within this population. Prevalence was calculated as the percent of participants with an outcome among all eligible participants enrolled in the cross-sectional study. As with the prospective PMR 3033-1 study, data were from EHR and claims data, as well as a battery of patient questionnaires and interviews conducted at a single time point. Adults aged 18 to 79 years were recruited from 9 of the 10 study sites[20] included in the prospective PMR 3033-1 study (see Section 3.1.3). Recruitment and data collection occurred from September 2017 through February 2019. Eligible patients were selected based on EHR data, with eligibility criteria as follows:

- Regularly using prescription opioids for analgesia for at least the 12 months prior (defined as at least 275 days covered by OA prescriptions), based on dispensing and orders recorded in EHR/claims data.
  - Including at least one prescription for an ER/LA OA in the past 12 months.
- Aged 18 to 79 years.
- Enrolled in a health plan or with evidence of receiving healthcare at the study site for at least 12 months prior to being identified as eligible for the study, based on EHR/claims data.
- Ability to complete interview and self-administered questionnaires in English (per interviewer assessment).
- Willing and able to provide informed consent.

Exclusion criteria were as follows:

- Not using a prescription OA at the time of selection (as recorded in EHR/claims data) or at the time of the first interview (self-reported).
- Cognitive impairment that interfered with the ability to consent or participate in the interview and self-administered questionnaires (based on ICD-9 and ICD-10 codes recorded in EHR/claims data, as well as interviewer assessment).
- Receiving hospice care (based on EHR/claims data and self-report)
- Undergoing treatment for a life-threatening condition such as metastatic cancer or end stage renal disease (self-reported at the time of the interview).

The prevalence of each primary, secondary, and sensitivity outcome was estimated, along with 95% CIs, which were calculated assuming a Poisson distribution. Cluster-robust standard errors were used to account for clustering within sites. Overall and stratified prevalence (by age, sex, race, and ethnicity) were calculated.

In addition, as in the prospective PMR 3033-1 study, the associations of potential risk factors with each outcome were assessed using GEE with logit link and exchangeable covariance. Unadjusted, demographically adjusted (i.e., adjusted for age, sex, race, and ethnicity), and fully adjusted (i.e.,

[20] Kaiser Permanente Northern California was included in the prospective 3033-1 study but not the cross-sectional 3033-1 study. While most of the study sites overlapped, the inclusion criteria for the cross-sectional 3033-1 study (required >1 year of Schedule II opioid therapy) and the prospective 3033-1 study (new to Schedule II opioid therapy in the past 6 months) precluded patients being eligible for both studies.

adjusted for age, sex, race, ethnicity, and all risk factors[21] associated with the outcome at α=0.10 [p<0.10] in unadjusted analyses) models were assessed, as described in more detail in Section 3.1.3 (prospective PMR 3033-1 methods). As in the prospective study, for categorical analyses, if one category was significant in the unadjusted analysis, all levels of that variable were included in the fully adjusted model. ORs and p-values were reported from the unadjusted models; ORs and 95% CIs were reported from the demographically adjusted and fully adjusted models. The primary analysis was a complete case analysis in which only patients with complete data on all factors of interest contributed data (i.e., patients missing data for one or more variables were excluded). Finally, secondary and sensitivity analyses were conducted to explore how changing the definition of OUD (see Section 3.1.1 for the OUD definitions used in the secondary analyses) affected the findings.

3.1.6 3033-1 Cross-Sectional Study Results

Characteristics of the Study Population

A total of 5,333 patients were invited to be screened for participation in the 3033-1 cross-sectional study; 1,936 patients met all the eligibility criteria and consented to participate, and 1,212 patients completed the required questionnaires and interviews. Selected characteristics of the 1,212 patients in the cross-sectional 3033-1 study population are shown in Table 12. About half of the patients were 60 years of age or older, and about half received insurance from Medicare. Notably, most patients had two or more comorbidities according to the Elixhauser comorbidity score, and most patients had three or more pain conditions recorded in EHR data in the past 12 months. The most common pain diagnoses were back pain, limb/extremity/joint pain or arthritis, neuropathy, neck pain, and "other pain diagnosis." Sixty-two percent of patients were taking antidepressants, and gabapentinoid use was also common. Also of note, 66% of this sample of individuals with at least some ER/LA OA use *predominantly* used ER/LA OAs, while the rest predominantly used IR/SA OAs, and the most common predominant opioid moiety was morphine, followed by oxycodone.

Table 12. Patient Characteristics in the Cross-Sectional PMR 3033-1 Study (N=1,212)

Characteristic	n (%)
Sociodemographic characteristics	
Age group, years	
18-39	93 (7.7)
40-49	153 (12.6)
50-59	373 (30.8)
≥60	593 (48.9)
Sex	
Female	694 (57.3)
Male	518 (42.7)
Race[1]	
White	893 (73.7)
Black	139 (11.5)
Asian	3 (0.2)
Native Hawaiian/Other Pacific Islander	2 (0.2)
American Indian/Alaskan Native	9 (0.7)
Multiracial	20 (1.7)
Other	23 (1.9)
Unknown	123 (10.1)

[21] See Section 3.1.2 for a list of the risk factors considered for the fully adjusted models.

Characteristic	n (%)
Ethnicity[1]	
Not Hispanic/Latino	949 (78.3)
Hispanic/Latino	61 (5.0)
Unknown	202 (16.7)
Insurance status	
Veterans Administration	55 (4.5)
Medicaid	276 (22.8)
Medicare	517 (42.7)
Other	268 (22.1)
None/unknown	96 (7.9)
Predominant place of care	
Care and insurance in an integrated delivery system	648 (53.5)
Care only in an integrated delivery system	403 (33.3)
Network or fee-for-service providers	161 (13.3)
Annual household income	
$25,000 or less	441 (36.4)
$25,001-$50,000	287 (23.7)
$50,001-$75,000	174 (14.4)
$75,001-$100,000	105 (8.7)
$100,001-$150,000	89 (7.3)
Greater than $150,000	35 (2.9)
Prefer not to report	81 (6.7)
Education	
<High school degree	120 (9.9)
High school or General Equivalency Degree	285 (23.5)
Any college	708 (58.4)
Any graduate school	99 (8.2)
OA prescription characteristics	
Predominant OA formulation[2]	
IR/SA	410 (33.8)
ER/LA	802 (66.2)
Predominant opioid moiety[2]	
Oxycodone	335 (27.6)
Morphine	445 (36.7)
Hydrocodone	124 (10.2)
Fentanyl	126 (10.4)
Methadone	127 (10.5)
Tramadol	25 (2.1)
Other (oxymorphone, hydromorphone, buprenorphine, codeine, tapentadol, butorphanol)	28 (2.4)
Multiple ingredients	2 (0.2)
Abuse-deterrent OA exposure	220 (18.2)
Average daily OA dose	
<50 MME	248 (20.5)
50-89 MME	328 (27.1)
90-119 MME	196 (16.2)
≥120 MME	440 (36.3)
Substance use disorder history	
Nonopioid and non-nicotine substance use disorder from PRISM-5-Op, past year	57 (4.7)
Nonopioid and non-nicotine substance use disorder from PRISM-5-Op, prior to past year	361 (29.8)

Characteristic	n (%)
Health- and pain-related characteristics	
Number of pain conditions from EHR (past 12 months)	
0	64 (5.3)
1-2	387 (31.9)
≥3	761 (62.8)
Pain conditions from EHR	
Abdominal and bowel	218 (18.0)
Limb/extremity, joint, noninflammatory arthritic disorders	690 (56.9)
Back	712 (58.7)
Musculoskeletal or chest	131 (10.8)
Fractures, contusions, sprains, and strains	156 (12.9)
Fibromyalgia	183 (15.1)
Headache	173 (14.3)
Neck	261 (21.5)
Neuropathy	273 (22.5)
Orofacial, ear, and temporomandibular	17 (1.4)
Other[3]	850 (70.1)
Systemic disorders or diseases causing pain	118 (9.7)
Urogenital, pelvic, and menstrual	33 (2.7)
Fibromyalgia from patient-reported symptoms[4]	103 (8.5)
Number of emergency department visits	
0	797 (65.8)
1-2	296 (24.4)
≥3	119 (9.8)
Number of inpatient stays	
0	923 (76.2)
1	192 (15.8)
≥2	97 (8.0)
Elixhauser comorbidity score	
0	97 (8.0)
1	166 (13.8)
≥2	942 (78.2)
Missing	7 (0.6)
Other medication use	
Antidepressants	751 (62.0)
Tricyclic antidepressants	165 (13.6)
Nontricyclic antidepressants	683 (56.4)
Antipsychotics	103 (8.5)
Buprenorphine for opioid use disorder	10 (0.8)
Gabapentinoids	533 (44.0)
Muscle relaxers	459 (37.9)
Naloxone	162 (13.4)
Sedative hypnotics	475 (39.2)
Benzodiazepines	412 (34.0)
Nonbenzodiazepine sedative hypnotics	120 (9.9)
Stimulants	47 (3.9)
Body mass index	
Underweight	17 (1.4)
Normal/healthy	161 (13.3)
Overweight	229 (18.9)
Obese	489 (40.3)
Missing	316 (26.1)
SF-12 physical score (mean, SD)[4]	30.9, 8.4

Characteristic	n (%)
SF-12 mental score (mean, SD)[4]	47.9, 11.5
Mental health conditions and social factors as measured by questionnaires/interviews	
MDD, past year	168 (13.9)
MDD, prior to past year	280 (23.1)
ADHD	189 (15.6)
Borderline personality disorder[4]	89 (7.3)
GAD[4]	314 (26.0)
PTSD[4]	187 (15.4)
History of parental substance use[4]	564 (46.5)
ACEs	
0	235 (19.4)
1	224 (18.5)
2	150 (12.4)
3	135 (11.1)
4+	458 (37.8)
Missing	10 (0.8)
Poor sleep quality[4]	974 (80.4)
Stress score (mean, SD)[4]	15.1, 8.2
Social support score (mean, SD)[4]	70.3, 26.7

Source: FDA-adapted table based on 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, Supplemental Table 1: Comparison of patient characteristics between nonresponders and responders, pp. 96-108.

[1] Race and ethnicity, as reported in this table, are from EHR data. Some analyses in the 3033-1 cross-sectional study utilized data from patient-reported questionnaires, which were more complete.

[2] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[3] Other pain conditions include: acquired deformities (excluding back), cancer-related, general, postoperative, post-trauma, restless leg syndrome, spinal cord injury, bone infections, infectious arthritic diseases.

[4] Missing data: Fibromyalgia from patient-reported symptoms missing for n=28 (2.3%). SF-12 scores missing for n=18 (1.5%). Borderline personality disorder missing for n=1 (0.1%). GAD missing for n=3 (0.2%). PTSD missing for n=7 (0.6%). History of parental substance use missing for n=55 (4.5%). Poor sleep quality missing for n=40 (3.3%). Stress score missing for n=4. Social support score missing for n=4.

Abbreviations: ACE, adverse childhood experience; ADHD, attention-deficit/hyperactivity disorder; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; MDD, major depressive disorder; MME, morphine milligram equivalent; N, number; OA, opioid analgesic; PMR, postmarketing requirement; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, post-traumatic stress disorder; SF-12, Short Form Health Survey; SD, standard deviation

Prevalence of Opioid Misuse, Opioid Abuse, and OUD

The overall prevalence of past-3-month opioid misuse was 14.6%, past-3-month opioid abuse was 6.0%, and past-year moderate-to-severe pain-adjusted DSM-5-OUD was 2.7% (Table 13). There were only two patients with both OUD-P and OUD-H and none with OUD-H alone. Because all OUD cases in this study population were also OUD-P cases, the prevalence of OUD-P was equivalent to that for OUD overall.

Table 13. Prevalence of Opioid Misuse,[1] Opioid Abuse,[1] and Moderate-to-Severe Pain-Adjusted DSM-5-OUD[2] (N=1,212)

	Opioid Misuse (Past 3 Months)[1]		Opioid Abuse (Past 3 Months)[1]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD (Past Year)[2]		Composite Outcome[3]	
Characteristic	n	Prevalence, % (95% CI)	n	Prevalence, % (95% CI)	n	Prevalence, % (95% CI)	n	Prevalence, % (95% CI)
Overall	177	14.6 (12.6, 17.0)	73	6.0 (4.8, 7.6)	33	2.7 (1.8, 4.0)	222	18.3 (16.2, 20.7)
Age group								
18-39 years	18	19.4 (13.5, 27.8)	4	4.3 (2.0, 9.2)	5	5.4 (2.3, 12.6)	22	23.7 (17.7, 31.6)
40-49 years	27	17.6 (12.8, 24.3)	6	3.9 (2.3, 6.7)	8	5.2 (2.2, 12.5)	32	20.9 (16.2, 27.0)
50-59 years	55	14.8 (12.3, 17.7)	27	7.3 (5.6, 9.5)	10	2.7 (2.2, 3.3)	71	19.1 (16.7, 21.8)
≥60 years	77	13.0 (10.0, 16.9)	36	6.1 (4.4, 8.3)	10	1.7 (0.8, 3.6)	97	16.3 (13.0, 20.5)
Sex								
Male	94	18.1 (15.6, 21.1)	45	8.7 (6.3, 12.0)	22	4.2 (3.4, 5.2)	122	23.6 (12.0, 26.4)
Female	83	12.0 (9.9, 14.4)	28	4.0 (3.2, 5.1)	11	1.6 (0.7, 3.6)	100	14.4 (12.6, 16.4)
Race								
White	148	14.9 (12.6, 17.5)	63	6.3 (4.9, 8.1)	24	2.4 (1.6, 3.6)	186	18.7 (16.2, 21.6)
Black	16	11.6 (7.1, 18.9)	5	3.6 (1.5, 8.7)	8	5.8 (2.9, 11.6)	21	15.2 (9.9, 23.3)
Other/mixed	13	17.8 (10.3, 30.7)	4	5.5 (2.1, 14.6)	1	1.4 (0.2, 9.7)	14	19.2 (11.4, 32.4)
Unknown[4]	0	N/A	1	N/A	0	N/A	1	N/A
Hispanic ethnicity								
No	163	14.4 (12.3, 16.8)	67	5.9 (4.7, 7.4)	26	2.3 (1.4, 3.8)	202	17.8 (15.7, 20.2)
Yes	14	18.2 (13.5, 24.5)	6	7.8 (4.1, 14.9)	7	9.1 (4.0, 20.7)	20	26.0 (18.7, 36.1)

Source: FDA-adapted table based on 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, Table 9: Unadjusted prevalence of prescription opioid misuse, prescription opioid abuse, opioid use disorder, and the composite outcome, pp. 55-57.

[1] Opioid misuse and opioid abuse were measured with the POMAQ.

[2] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[3] The composite outcome represents any of past-3-month opioid misuse, past-3-month opioid abuse, or past-year moderate-to-severe OUD.

[4] Patients with unknown race were not included in the prevalence calculations.

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; FDA, Food and Drug Administration; N, number; N/A, not applicable; OUD: opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version

In secondary and sensitivity analyses, the prevalence of any OUD (i.e., two or more symptoms) was 8.5% and the prevalence of severe OUD (i.e., six or more symptoms) was 1.0% using the moderate-to-severe pain-adjusted DSM-5-OUD definition (Table 14). Using the standard DSM-5-OUD definition of OUD, the prevalence of any, moderate-to-severe, and severe OUD increased to 27.1%, 6.3%, and 2.1%, respectively (Table 14).

Table 14. Prevalence of OUD at Different Severity Thresholds and Using Different OUD Definitions (N=1,212)

OUD Definition and Severity	n	Prevalence, % (95% CI)
Pain-adjusted DSM-5-OUD,[1] any[3]	103	8.5 (6.5, 11.1)
Pain-adjusted DSM-5-OUD,[1] moderate-to-severe*,[4]	33	2.7 (1.8, 4.0)
Pain-adjusted DSM-5-OUD,[1] severe[5]	12	1.0 (0.5, 1.8)
DSM-5-OUD,[2] any OUD [3]	328	27.1 (23.5, 31.2)
DSM-5-OUD,[2] moderate-to-severe OUD[4]	76	6.3 (4.3, 9.1)
DSM-5-OUD,[2] severe OUD[5]	25	2.1 (1.3, 3.4)

Source: FDA-adapted table based on 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, Supplemental Table 7: pg. 137-138, and Supplemental Table 8: pg. 139-140.

* Primary OUD outcome in PMR 3033-1.

[1] The pain-adjusted DSM-5-OUD definitions incorporated reason for opioid use (i.e., pain-related or not) when determining whether each DSM-5 symptom of OUD was present.

[2] The DSM-5-OUD definition of OUD did not incorporate reason for opioid use (i.e., pain-related or not).

[3] In PMR 3033-1, any OUD was defined as having two or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

[4] In PMR 3033-1, moderate-to-severe OUD was defined as having four or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

[5] In PMR 3033-1, severe OUD was defined as having six or more DSM-5 criteria related to prescription opioid use *or* two more DSM-5 criteria related to heroin use.

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statical Manual of Mental Disorders, Fifth edition; FDA, Food and Drug Administration; N, number; OUD, opioid use disorder; PMR, postmarketing requirement; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version

Potential Risk Factors for Opioid Misuse, Opioid Abuse, and OUD

As stated in the methods section (Section 3.1.5), unadjusted regression analyses were used to identify variables for the fully adjusted model, with only those significantly associated with a given outcome at α=0.10 included in the fully adjusted model for that outcome (along with age, sex, race, and ethnicity). This resulted in 30 risk factors in the fully adjusted model for opioid misuse, 25 in the fully adjusted model for opioid abuse, 29 risk factors in the fully adjusted model for moderate-to-severe pain-adjusted DSM-5-OUD (i.e., the primary OUD measure), and 34 risk factors in the fully adjusted model for moderate-to-severe DSM-5-OUD (i.e., the secondary OUD measure). In the fully adjusted risk factor analyses, sample sizes were N=1,059 for opioid misuse, N=1,078 for opioid abuse, and N=1,133 for the primary OUD measure[22] due to excluding patients with incomplete data on all risk factors in a given model.

Table 15 contains selected results for the analyses of the three primary outcomes (misuse, abuse, and moderate-to-severe pain-adjusted DSM-5-OUD), as well as moderate-to-severe DSM-5-OUD, with a focus on the demographically adjusted and fully adjusted models. Risk factors were selected for this table if they had strong and/or consistent associations with one or more of the listed outcomes, or if they were of particular regulatory interest to FDA. The full set of findings from these analyses, including results from the unadjusted analyses and results for the complete set of risk factors, can be found in Appendix Table 34 (opioid misuse), Appendix Table 35 (opioid abuse), and Appendix Table 36 (primary OUD measure). In addition, the full set of fully adjusted results (but not unadjusted or demographically adjusted results, for simplicity) for DSM-5 moderate-to-severe OUD can be found in Appendix

[22] The sample size for the fully adjusted analysis of moderate-to-severe DSM-5-OUD (secondary OUD measure) was not reported.

Section 6.5. Appendix Section 6.5 also contains the full set of fully adjusted results for any OUD (using the pain-adjusted DSM-5-OUD definition, for which no results are included in Table 15).

Results for the composite outcome are not reported in this section because due to the differences in findings across the primary outcomes, the findings for individual outcomes were considered more informative. Results for OUD-P and OUD-H are also not reported in this section because there were too few cases of OUD-H to be able to assess these outcomes separately. As in prospective PMR 3033-1, in the description of these findings below, the term "significant" refers to statistical significance at the α=0.05 (p=0.05) level and does not necessarily imply clinical significance. Also, as in prospective PMR 3033-1, no multiplicity adjustment was conducted.

Sociodemographic Risk Factors

Sex (male versus female) showed the strongest and most consistent association with increased odds of each outcome in both the demographically and fully adjusted models. There was no clear pattern of association between age group and any of the outcomes.

OA-Related Risk Factors

Predominant use of an ER/LA OA (versus predominant use of an IR/SA OA)[23] was associated with lower odds of opioid misuse in both the demographically and fully adjusted models. Predominant formulation was not included in the fully adjusted models for abuse or the primary OUD measure, and while it was included in the fully adjusted model for DSM-5-OUD, this association was not significant. Patients who used an ADF OA (versus no ADF use) had lower odds of opioid misuse and opioid abuse in both adjusted models than patients who did not use an ADF OA. There was not a significant association between average daily dose of OAs and any of the outcomes of interest.

SUD History

Having a nonopioid/non-nicotine SUD in the past year and having such a disorder prior to the past year were each relatively strongly associated with increased odds of opioid misuse, opioid abuse, and OUD (both moderate-to-severe measures), although some of these associations were not significant and some were significant but attenuated in the fully adjusted model, compared to the demographically adjusted model.

Health- and Pain-Related Factors

There was not a consistent pattern of association between number of ED visits or number of inpatient stays and any of the outcomes. There was some evidence, mostly from demographically adjusted models only, that more visits were associated with greater risk of some outcomes. Antipsychotic use was associated with increased odds of opioid abuse in both adjusted models. While there were no medications significantly associated with the primary OUD measure, gabapentinoid use was associated with increased odds of moderate-to-severe DSM-5-OUD.

Mental Health Conditions and Social Factors

Nearly all mental health conditions assessed (MDD in the past year, MDD prior to the past year, borderline personality disorder, GAD, and PTSD) were associated with increased odds of opioid misuse, opioid abuse, and OUD (both moderate-to-severe measures) in the demographically adjusted models.

[23] All patients in the cross-sectional 3033-1 sample had some ER/LA OA use due to the study's inclusion criteria.

These associations were often attenuated, and often not statistically significant, in the fully adjusted models. Similarly, having four or more adverse childhood experiences (versus zero) was associated with increased odds of opioid misuse, opioid abuse, and OUD (both moderate-to-severe measures) in the demographically adjusted models, but these associations were attenuated and not statistically significant in the fully adjusted models.

Table 15. Selected Odds Ratios and 95% Confidence Intervals From Demographically Adjusted and Fully Adjusted Models for Opioid Misuse, Opioid Abuse, and Moderate-to-Severe Pain-Adjusted DSM-5-OUD in the PMR 3033-1 Cross-Sectional Study

Selected Potential Risk Factor[1]	Opioid Misuse[2] (Past 3 Months) OR (95% CI)	Opioid Abuse[2] (Past 3 Months) OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (Past Year) OR (95% CI)	Moderate-to-Severe DSM-5-OUD[4] (Past Year) OR (95% CI)
Selected sociodemographic factors				
Male (vs. female)				
Demographically adjusted[5]	**1.7 (1.3, 2.1)**	**2.3 (1.4, 3.7)**	**2.7 (1.2, 6.0)**	**2.1 (1.1, 3.8)**
Fully adjusted[6,7,8,9]	**1.5 (1.0, 2.3)**	**2.2 (1.1, 4.5)**	**4.1 (1.6, 10.9)**	**3.9 (1.7, 9.0)**
Age group				
Demographically adjusted[5]				
18-39 years	Ref	Ref	Ref	Ref
40-49 years	0.9 (0.5, 1.8)	0.7 (0.3, 1.8)	0.9 (0.2, 3.3)	1.0 (0.4, 2.4)
50-59 years	0.7 (0.4, 1.2)	1.7 (0.8, 3.6)	0.5 (0.1, 1.7)	0.6 (0.3, 1.0)
≥60 years	**0.6 (0.4, 0.9)**	1.4 (0.6, 3.1)	0.3 (0.1, 1.1)	0.5 (0.2, 1.0)
Fully adjusted[6,7,8,9]				
18-39 years	Ref	Ref	Ref	Ref
40-49 years	1.0 (0.5, 2.3)	0.9 (0.3, 2.4)	0.7 (0.2, 3.0)	0.6 (0.2, 2.0)
50-59 years	0.8 (0.3, 1.7)	1.9 (0.5, 6.4)	**0.4 (0.2, 0.8)**	**0.4 (0.2, 0.9)**
≥60 years	1.0 (0.5, 1.9)	2.0 (0.6, 6.8)	0.6 (0.2, 2.3)	**0.5 (0.3, 1.0)**
Selected OA-related factors				
Predominant OA formulation (ER/LA vs. IR/SA)[10]				
Demographically adjusted[5]	**0.6 (0.4, 0.7)**	0.8 (0.6, 1.0)	0.7 (0.3, 1.5)	0.7 (0.5, 0.9)
Fully adjusted[6,7,8,9]	**0.5 (0.4, 0.7)**	N/I	N/I	0.7 (0.3, 1.5)
Average daily dose of OAs				
Demographically adjusted[5]				
<50 MME	Ref	Ref	Ref	Ref
50-89 MME	0.8 (0.6, 1.1)	1.0 (0.5, 1.8)	0.6 (0.2, 1.5)	1.3 (0.8, 2.2)
90-119 MME	0.9 (0.7, 1.2)	0.7 (0.4, 1.3)	1.0 (0.4, 2.2)	1.4 (0.9, 2.3)
≥120 MME	0.7 (0.5, 1.1)	1.1 (0.6, 2.0)	1.9 (0.8, 4.2)	1.4 (0.9, 1.9)
Fully adjusted[6,7,8,9]				
<50 MME	Ref	Ref	Ref	Ref
50-89 MME	N/I	N/I	0.6 (0.2, 1.5)	1.8 (0.8, 4.0)
90-119 MME	N/I	N/I	0.5 (0.2, 1.6)	1.1 (0.4, 2.9)
≥120 MME	N/I	N/I	1.2 (0.4, 3.6)	1.2 (0.6, 2.3)

Selected Potential Risk Factor[1]	Opioid Misuse[2] (Past 3 Months) OR (95% CI)	Opioid Abuse[2] (Past 3 Months) OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (Past Year) OR (95% CI)	Moderate-to-Severe DSM-5-OUD[4] (Past Year) OR (95% CI)
Predominant opioid moiety[10]				
Demographically adjusted[5]				
Oxycodone	Ref	Ref	Ref	Ref
Morphine	0.7 (0.5, 1.1)	1.0 (0.6, 1.9)	**0.4 (0.2, 0.7)**	**0.6 (0.5, 0.6)**
Hydrocodone	0.8 (0.6, 1.1)	**2.1 (1.4, 3.2)**	N/A (in "other")	0.6 (0.2, 2.2)
Fentanyl	0.5 (0.2, 1.2)	1.8 (1.0, 3.2)	N/A (in "other")	1.2 (0.6, 2.6)
Methadone	0.8 (0.5, 1.2)	0.9 (0.5, 1.8)	**0.3 (0.1, 1.0)**	**0.5 (0.3, 0.8)**
Other[11]	1.1 (0.7, 1.7)	1.3 (0.5, 3.2)	**0.3 (0.1, 0.9)**	1.0 (0.6, 1.9)
Fully adjusted[6,7,8,9]				
Oxycodone	Ref	Ref	Ref	Ref
Morphine	0.8 (0.4, 1.5)	0.7 (0.3, 1.9)	0.3 (0.1, 1.0)	0.7 (0.4, 1.1)
Hydrocodone	0.6 (0.3, 1.2)	1.5 (0.7, 3.4)	N/A (in "other")	0.6 (0.1, 3.0)
Fentanyl	0.5 (0.1, 1.5)	0.9 (0.5, 1.6)	N/A (in "other")	1.4 (0.4, 5.0)
Methadone	1.1 (0.4, 2.7)	0.6 (0.3, 1.2)	0.1 (0.0, 1.0)	**0.4 (0.2, 0.9)**
Other[11]	0.9 (0.4, 2.2)	1.0 (0.3, 3.4)	**0.3 (0.1, 1.0)**	1.9 (0.6, 5.8)
Use of ADF OA (any vs. none)				
Demographically adjusted[5]	**0.7 (0.5, 0.9)**	**0.5 (0.2, 1.0)**	1.2 (0.4, 3.4)	1.2 (0.8, 1.8)
Fully adjusted[6,7,8,9]	**0.5 (0.3, 0.8)**	**0.4 (0.3, 0.6)**	N/I	N/I
History of substance use disorders				
Past-year nonopioid, non-nicotine SUD (yes vs. no)				
Demographically adjusted[5]	**4.7 (3.3, 6.8)**	**8.5 (5.0, 14.5)**	**4.4 (2.3, 8.6)**	**3.1 (1.4, 7.0)**
Fully adjusted[6,7,8,9]	**4.3 (2.4, 7.6)**	**5.9 (2.9, 11.9)**	2.7 (0.9, 7.6)	1.2 (0.3, 4.4)
Nonopioid, non-nicotine SUD prior to the past year (yes vs. no)				
Demographically adjusted[5]	**2.2 (1.3, 3.5)**	**3.6 (2.6, 4.9)**	**3.8 (1.9, 7.6)**	**3.7 (2.4, 5.6)**
Fully adjusted[6,7,8,9]	1.4 (0.8, 2.5)	**2.1 (1.3, 3.4)**	2.3 (1.0, 5.4)	**3.8 (1.8, 8.2)**
Selected health- and pain-related factors				
Number of emergency department visits				
Demographically adjusted[5]				
0	Ref	Ref	Ref	Ref
1-2	0.8 (0.6, 1.1)	1.4 (0.8, 2.5)	1.3 (0.8, 2.4)	**1.6 (1.1, 2.5)**
≥3	**1.4 (1.0, 2.0)**	1.4 (0.7, 2.9)	**2.4 (1.3, 4.3)**	**2.5 (2.0, 3.3)**
Fully adjusted[6,7,8,9]				
0	Ref	Ref	Ref	Ref
1-2	**0.6 (0.4, 0.9)**	N/I	1.3 (0.7, 2.5)	**1.8 (1.3, 2.4)**
≥3	1.0 (0.6, 1.7)	N/I	1.1 (0.4, 3.0)	2.2 (0.9, 5.2)

Selected Potential Risk Factor[1]	Opioid Misuse[2] (Past 3 Months) OR (95% CI)	Opioid Abuse[2] (Past 3 Months) OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (Past Year) OR (95% CI)	Moderate-to-Severe DSM-5-OUD[4] (Past Year) OR (95% CI)
Number of inpatient stays				
Demographically adjusted[5]				
0	Ref	Ref	Ref	Ref
1	1.1 (0.8, 1.4)	1.2 (0.7, 2.0)	2.0 (1.0, 3.9)	**1.8 (1.1, 2.9)**
≥2	1.0 (0.7, 1.4)	0.7 (0.3, 1.9)	2.2 (0.9, 5.4)	**1.8 (1.2, 2.8)**
Fully adjusted[6,7,8,9]				
0	Ref	Ref	Ref	Ref
1	N/I	N/I	1.7 (0.8, 3.6)	1.4 (0.6, 3.3)
≥2	N/I	N/I	**2.6 (1.0, 6.5)**	1.4 (0.7, 2.8)
Use of antidepressants (yes vs. no)				
Demographically adjusted[5]	1.0 (0.7, 1.5)	0.8 (0.6, 1.2)	**2.2 (1.4, 3.5)**	**2.1 (1.3, 3.4)**
Fully adjusted[6,7,8,9]	N/I	N/I	N/I	0.9 (0.5, 1.6)
Use of antipsychotics (yes vs. no)				
Demographically adjusted[5]	1.6 (0.9, 2.8)	**2.9 (1.4, 5.8)**	0.6 (0.1, 2.8)	0.9 (0.4, 1.8)
Fully adjusted[6,7,8,9]	N/I	**2.5 (1.1, 5.3)**	N/I	N/I
Use of gabapentinoids (yes vs. no)				
Demographically adjusted[5]	**1.2 (1.0, 1.5)**	0.8 (0.6, 1.2)	1.5 (0.7, 3.0)	**1.8 (1.3, 2.6)**
Fully adjusted[6,7,8,9]	1.2 (0.9, 1.6)	N/I	N/I	**2.2 (1.2, 3.7)**
Selected mental health conditions and social factors				
MDD in past year (yes vs. no)				
Demographically adjusted[5]	**2.0 (1.3, 3.1)**	**2.7 (1.9, 3.8)**	**4.1 (1.8, 9.2)**	**3.4 (2.5, 4.7)**
Fully adjusted[6,7,8,9]	**1.6 (1.1, 2.4)**	1.6 (0.7, 3.6)	1.5 (0.5, 4.1)	0.8 (0.4, 1.9)
MDD prior to past year (yes vs. no)				
Demographically adjusted[5]	1.5 (1.0, 2.2)	1.4 (1.0, 2.1)	**3.3 (1.9, 5.9)**	**3.5 (3.0, 4.1)**
Fully adjusted[6,7,8,9]	0.9 (0.6, 1.2)	N/I	**3.2 (1.2, 9.1)**	**3.4 (1.7, 6.8)**
Borderline personality disorder (yes vs. no)				
Demographically adjusted[5]	**1.8 (1.2, 2.7)**	**2.7 (1.6, 4.4)**	**2.9 (1.8, 4.6)**	**1.9 (1.2, 2.9)**
Fully adjusted[6,7,8,9]	1.0 (0.7, 1.5)	0.8 (0.4, 1.5)	1.1 (0.4, 3.0)	0.7 (0.3, 1.5)
GAD (yes vs. no)				
Demographically adjusted[5]	**2.2 (1.4, 3.4)**	**3.1 (1.8, 5.1)**	**3.8 (2.0, 7.4)**	**2.5 (1.6, 4.1)**
Fully adjusted[6,7,8,9]	**1.4 (1.1, 1.9)**	1.8 (0.7, 4.5)	0.6 (0.2, 2.0)	0.5 (0.2, 1.2)
PTSD (yes vs. no)				
Demographically adjusted[5]	**1.6 (1.0, 2.6)**	**2.7 (1.4, 5.2)**	**3.5 (2.3, 5.1)**	**2.6 (2.3, 3.0)**
Fully adjusted[6,7,8,9]	0.8 (0.5, 1.2)	1.1 (0.4, 3.2)	1.3 (0.5, 3.7)	1.1 (0.5, 2.4)

Selected Potential Risk Factor[1]	Opioid Misuse[2] (Past 3 Months) OR (95% CI)	Opioid Abuse[2] (Past 3 Months) OR (95% CI)	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] (Past Year) OR (95% CI)	Moderate-to-Severe DSM-5-OUD[4] (Past Year) OR (95% CI)
ACE score				
Demographically adjusted[5]				
0	Ref	Ref	Ref	Ref
1	1.1 (0.6, 2.1)	1.8 (0.8, 4.0)	0.5 (0.2, 1.8)	0.5 (0.2, 1.1)
2	1.6 (0.9, 2.9)	**2.2 (1.1, 4.5)**	0.8 (0.2, 3.2)	1.1 (0.5, 2.5)
3	1.1 (0.6, 2.0)	**2.3 (1.1, 4.8)**	1.6 (0.4, 5.9)	1.8 (0.8, 4.2)
≥4	**2.1 (1.5, 2.9)**	**3.7 (1.8, 7.4)**	**2.8 (1.1, 7.1)**	**2.5 (1.9, 3.3)**
Fully adjusted[6,7,8,9]				
0	Ref	Ref	Ref	Ref
1	1.0 (0.5, 1.9)	1.1 (0.4, 2.8)	1.2 (0.3, 6.0)	0.8 (0.3, 2.2)
2	1.2 (0.6, 2.2)	1.4 (0.6, 3.2)	0.6 (0.1, 4.8)	1.5 (0.4, 5.9)
3	0.6 (0.3, 1.3)	1.0 (0.4, 2.6)	1.6 (0.1, 18.1)	3.9 (0.7, 23.4)
≥4	1.5 (0.9, 2.3)	1.5 (0.6, 3.7)	2.5 (0.4, 16.6)	**3.4 (1.8, 6.3)**
History of parental substance use (yes vs. no)				
Demographically adjusted[5]	**1.7 (1.4, 2.1)**	**2.5 (1.8, 3.4)**	1.9 (0.9, 4.1)	**1.7 (1.2, 2.4)**
Fully adjusted[6,7,8,9]	1.4 (1.0, 2.0)	**1.7 (1.1, 2.6)**	N/I	0.9 (0.6, 1.3)

Source: FDA-adapted table based on information provided in PMR 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, as well as final data submitted by the OPC on June 4, 2024, in "Response to Clarifying Questions for the PMR 3033-1 Cross-Sectional and Prospective Studies, May 3, 2024," Appendix 1, Q5 Table B and Q5 Table C REV.

Notes: For nonreference variables denoted "N/I", the variable was not statistically significantly associated with the outcome at p<0.10 in unadjusted analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Risk factor analysis findings that showed the strongest and/or most consistent associations with the primary outcomes, as well as those of particular regulatory interest are presented in this table. The full set of risk factor findings can be found in Appendix Table 34 (opioid misuse), Appendix Table 35 (opioid abuse), and Appendix Table 36 (OUD).

[2] Opioid misuse and opioid abuse were measured with the POMAQ.

[3] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] Moderate-to-severe DSM-5-OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[5] For all outcomes, the demographically adjusted model included age, sex, race, and ethnicity.

[6] The fully adjusted model for opioid misuse included: age group, sex, race, ethnicity, annual household income, Medicaid (yes vs. no), predominant place of care (type of system), predominant OA formulation, predominant opioid moiety, use of ADF OA, number of emergency department visits, gabapentinoids, muscle relaxers, naloxone, any nonopioid/non-nicotine SUD in the past year, any nonopioid/non-nicotine SUD prior to the past year, MDD in the past year, MDD prior to the past year, ADHD, borderline personality disorder, GAD, PTSD, history of parental substance use, ACE score (0, 1, 2, 3, ⩾4), poor sleep quality, fibromyalgia from patient-reported symptoms, pain interference score, stress score, social support score, SF-12 physical score, SF-12 mental score

[7] The fully adjusted model for opioid abuse included: POMAQ modality, age group, sex, race, ethnicity, annual household income, education level, predominant opioid moiety, use of ADF OA, antipsychotics, muscle relaxers, any nonopioid/non-nicotine SUD in the past year, any nonopioid/non-nicotine SUD prior to the past year, MDD in the past year, ADHD, borderline personality disorder, GAD, PTSD, history of parental substance use, ACE score (0, 1, 2, 3, ⩾4), poor sleep quality, pain interference score, stress score, social support score, and SF-12 mental score.

[8] The fully adjusted model for moderate-to-severe pain-adjusted DSM-5-OUD included: PRISM-5-Op modality, age group, sex, race, ethnicity, Medicaid (yes vs. no), predominant place of care (type of system), predominant opioid moiety, average daily dose of OAs, number of emergency department visits, number of inpatient stays, naloxone, sedative hypnotics, body mass index, any nonopioid/non-nicotine SUD in the past year, any nonopioid/non-nicotine SUD prior to the past year, MDD in the past year, MDD prior to the past year, ADHD, borderline personality disorder, GAD, PTSD, ACE score (0, 1, 2, 3, ⩾4), fibromyalgia from patient-reported symptoms, pain severity score, pain interference score, stress score, SF-12 physical score, and SF-12 mental score.

[9] The fully adjusted model for moderate-to-severe DSM-5-OUD (secondary OUD measure) included: PRISM-5-Op modality, age, sex, race, ethnicity, annual household income, Medicaid coverage, predominant OA formulation, predominant opioid moiety, average daily dose of opioids, nonopioid/non-nicotine SUD in the past year, nonopioid/non-nicotine SUD prior to the past year, number of emergency department visits, number of inpatient stays, antidepressants, gabapentinoids, muscle relaxers, sedative hypnotics, BMI, fibromyalgia from patient-reported symptoms, MDD in the past year, MDD prior to the past year, ADHD, borderline personality disorder, GAD, PTSD, history of parental substance use, ACE score, poor sleep quality, pain severity score, pain interference score, stress score, social support score, and SF-12 mental score.

[10] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[11] When an opioid moiety category contained ≤2 events of a given outcome, it was collapsed into the "other" category for the analysis of that outcome. For all analyses in this table, the "other" category contained oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, and butorphanol. Additionally, in the analysis of moderate-to-severe pain-adjusted DSM-5-OUD (primary OUD measure), hydrocodone and fentanyl were included in the "other" category.

Abbreviations: ACE, adverse childhood experience; ADF, abuse deterrent formulation; ADHD: attention-deficit/hyperactivity disorder; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; MDD, major depressive disorder; MME, morphine milligram equivalent; N.A, not applicable; N/I: not included; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; PMR, postmarketing requirement; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; Ref, reference; SF-12, 12-Item Short Form Health Survey; SUD, substance use disorder

3.2 3033-2 Retrospective Cohort Study of Opioid-Involved Overdose or Opioid Overdose-Related Death

3.2.1 3033-2 Study Design and Methodology

PMR 3033-2 was a retrospective cohort study with the primary objective of quantifying the incidence of and risk factors for OOD in patients with long-term prescription OA use for the management of chronic pain.

The study identified adult patients with new long-term use of Schedule II OAs (including hydrocodone-containing products)[24] from pharmacy dispensing data (i.e., insurance claims) in four large health care delivery or insurance systems (referred to as *study sites*) from July 2006 to December 2016. The participating study sites were:

- Vanderbilt University Medical Center (VUMC): The Tennessee State Medicaid program.
- Kaiser Permanente Northwest (KPNW): A not-for-profit managed care system in Washington and Oregon.
- HealthCore: Affiliated with Anthem Blue Cross/WellPoint insurance.
- Optum: Affiliated with United Health Group insurance.

Patients were eligible for the study if they had at least nine months of medical and pharmacy healthcare benefits and had sufficient information to link to the National Death Index between January 1, 2006, and December 31, 2016. Patients were included in the study if:

1. They were 18 to 79 years old at their cohort start date.
2. They had no record of Schedule II OA use during the 6-month baseline period immediately prior to the qualification period.
3. They had been dispensed at least 70 days' supply of Schedule II OAs in the 3 months immediately prior to their cohort start date (i.e., the qualification period).

If a patient qualified for the cohort multiple times, the earliest episode was chosen.

Patients were excluded from the study if:

1. They had a record of an opioid overdose during the baseline or qualification periods.
2. They were dispensed a Schedule II OA during the baseline period.
3. They had a nonhospital, institutional stay (e.g., a nursing home) during the baseline or qualification periods.

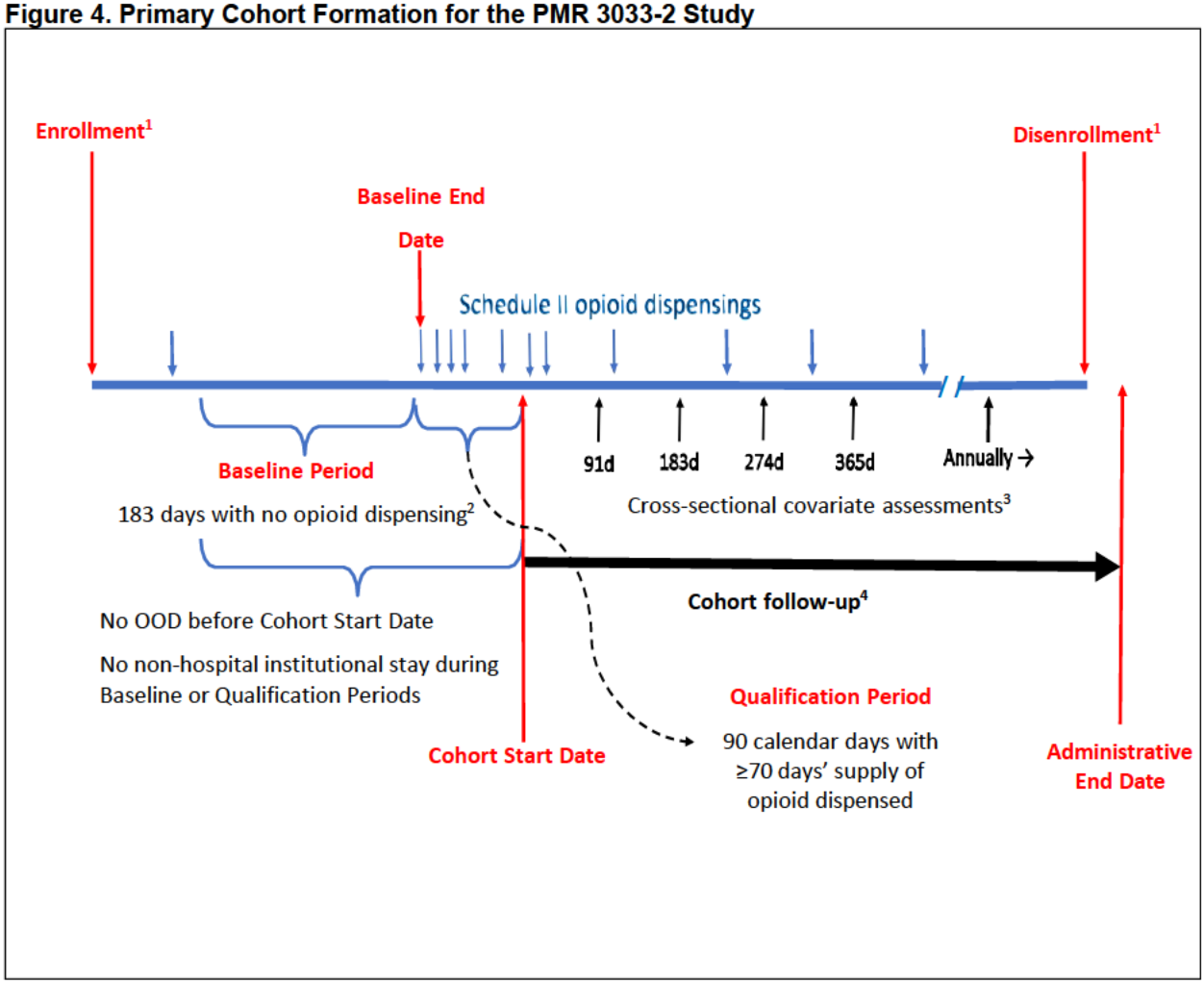
Note that patients with past or current use of Schedule III, IV, or V OAs could still be eligible for the study.

Figure 4 illustrates the key time points and periods for the primary cohort in PMR 3033-2. Patients were eligible for the study if they had been enrolled in the healthcare plan for at least 9 months prior to the baseline period. The inclusion and exclusion criteria applied during the baseline and qualification periods determined final eligibility. Follow-up started at the end of the qualification period, which is referred to as *the cohort start date*. Follow-up continued through the *cohort end date*, defined as the earliest of the following dates: the administrative end date (the earlier date of: the end of the study period (i.e.,

[24] See the baseline characteristics table (Table 16) for the full list of opioid moieties.

December 31, 2017, or the end of the site-specific grace period following the date of disenrollment from the site-specific health care system); the start date of a nonhospital institutional stay (other than for substance use treatment); the day preceding the 80th birthday; the date of death; or the date of the first (incident) OOD.

Figure 4. Primary Cohort Formation for the PMR 3033-2 Study



Source: Whiscon Summary Report, Figure 6-1

[1] Enrollment and Disenrollment refer to the patient's healthcare plan coverage.

[2] No schedule II opioid dispensing was allowed during the 183-day Baseline Period.

[3] Covariate assessments continued annually through cohort follow-up.

[4] Events that terminated cohort follow-up included: OOD, disenrollment, death, a non-hospital institutional stay (other than for treatment of substance abuse), the day preceding the patient's 80th birthday, or the end of the study (December 31, 2017).

Abbreviation: d, days; PMR, postmarketing requirement; OOD, opioid-involved overdose or opioid overdose-related death

The following risk factors were examined:[25]

- Demographic factors: Age, sex, calendar era (patient cohort entry year), and U.S. Census region.
- OA-related factors: Predominant opioid moiety[26] and formulation (ER/LA or IR/SA), total OA dose in the 3 months immediately prior to the patient's cohort start date (quarterly/qualifying cumulative MMEs [QMMEs]),[27] baseline use of Schedule III OAs (other than hydrocodone).
- SUD history: Alcohol use disorder, OUD, other.[28]
- Health- and pain-related risk factors: Concomitant medication use (antidepressants, antipsychotics, benzodiazepines, gabapentinoids, muscle relaxers, naloxone, sedative hypnotics, OUD medications, ADHD medications), and pain conditions.[29]
- Mental health risk factors: Depression, anxiety, psychosis, other.[30]

Demographic risk factors were assessed at the patient's cohort start date. OA-related and concomitant medication use-related risk factors were assessed during the qualification period, except for Schedule III OA use. The information on Schedule III OA use and all other risk factors were assessed using the patient's entire available history prior to their cohort start date.

This study reassessed the OA-related factors during the study follow-up, specifically at the end of months 3, 6, 9, and 12, and at the end of each subsequent year over the 5-year study period; however, this information was not included in the risk factor analyses.

Exploratory Switch/Add Cohort

This cohort consisted of patients in the primary cohort who were dispensed a Schedule II IR/SA OA during the qualification period (Figure 4) and were exclusively on a Schedule II IR/SA OA regimen prior to switching to or adding (switch/add) a new IR/SA or ER/LA OA to their treatment regimen during the follow-up period. Patients who switched to different doses of their baseline IR/SA OA or had an ER/LA OA prior to the switch/add event were not included in this analysis. If a patient qualified for the switch/add cohort more than once during follow-up, the first qualifying dispensing date for the switch/add opioid was chosen for the switch/add cohort entry date. Two end dates were considered – (1) the end of the switch/add opioid therapy episode[31] and (2) the study end date.

To conduct the risk factor analysis, sex, age, and census region were carried forward from the primary cohort start date; the other risk factors were reassessed within the 90-day period preceding the

[25] See Table 16 for full demographic profiles.
[26] The Schedule II OA with the highest total MMEs dispensed during the patient's qualification period.
[27] This risk factor is defined as both the "quarterly" and "qualifying" MME. MMEs were calculated by multiplying prescribed dose, quantity, and conversion factor (published by the CDC) for each Schedule II OA.
[28] Other SUDs include any ICD-diagnosis for an SUD other than alcohol use disorder or OUD.
[29] Pain condition categories: Abdominal and bowel; limb/extremity, joint, noninflammatory arthritic disorders; back; musculoskeletal and chest; fractures, contusions, sprains and strains; fibromyalgia; headache; neck; neuropathy; orofacial, ear, and temporomandibular; other (acquired deformities (excluding back), cancer-related, general, postoperative, post-trauma, restless leg syndrome, spinal cord injury, bone infections, infectious arthritic diseases).
[30] Other mental health conditions include any ICD-diagnosis for a mental health condition that is not depression, anxiety, or psychosis-related.
[31] The switch/add therapy discontinuation date occurred 30 days following the completion of the dispensing date plus days' supply minus one, for any opioid that qualified as the switch/add start opioid.

switch/add event. The daily morphine milligram equivalents (DMMEs) for the quarters immediately before and after the switch/add event were calculated.[32]

Outcome

The primary outcome was incident OOD, which consisted of:

- Nonfatal opioid overdose events identified in insurance claims data, and
- Deaths with a principal or contributing cause of death indicated as opioid-involved overdose, confirmed by a linkage to the National Death Index (NDI).[33]

An additional, exploratory outcome was incident OOD that resulted from intentional self-harm, referred to as intentional OOD.

The algorithm to ascertain OOD, using coded medical terminology (ICD-9 codes for nonfatal overdoses and ICD-10 codes for fatal overdose cases (Green et al. 2017; Green et al. 2019b); see Appendix Table 38 for OOD algorithm ICD codes), was developed and validated in PMR 3033-6 using data from KPNW. In PMR 3033-6, patients who had an elevated risk of an overdose (see Appendix Table 39 and Appendix Table 40)[34] between the years 2008 and 2014 were used to develop and validate the algorithm. The algorithm's performance was evaluated using manual medical records review as the gold standard. Performance of the OOD algorithm in the validation sample was as follows: sensitivity 97.2%, specificity 84.6%, positive predictive value (PPV) 97.4%, and negative predictive value (NPV) 96.5%. Alternative algorithms, including one to determine overdose intentionality, were also developed and evaluated; however, the intentionality algorithm in PMR 3033-6 was not able to distinguish well between intentional and unintentional overdose. Of note, these algorithms were further validated using data from three other healthcare data systems (Kaiser Permanente Washington, Optum, and VUMC).

While ICD-10 codes for mortality have been in use since 1999, the transition from using ICD-9 clinical codes to ICD-10 clinical codes in insurance claims data occurred in October 2015. To ensure that the algorithm performed adequately in data resources beyond the one in which it was developed, and that it remained accurate for capturing nonfatal overdoses after the ICD-9 to ICD-10 code transition, the OOD algorithm was partially revalidated in PMR 3033-2 at HealthCore, KPNW, and VUMC.[35] In PMR 3033-2, the PPV of the updated algorithm was over 80% (Appendix Table 38), which satisfied the prespecified performance criteria.

The ability to distinguish overdose intentionality was revalidated using new ICD-10 codes for opioid overdose intentionality. Sensitivity, specificity, PPV, and NPV were calculated for the updated intentionality evaluation using ICD-10 clinical codes, although no performance criteria were prespecified as it was for exploratory purposes only. The validation of the ICD-10 OOD intentionality codes suggested that the codes were unreliable to determine the intentionality of OOD in this population due to low sensitivity and PPV (Appendix Table 42). However, high NPV values suggested that the absence of the

[32] DMME was calculated as the sum of the patient's Schedule II OA MMEs divided by the days during the 90 days prior to the switch/add event and during the 90 days after the switch/add event.
[33] All patients who disenrolled prior to December 31, 2017, were submitted to NDI for potential matches.
[34] Patients with suspected OOD events or at risk for OOD, screened and selected based on ICD-9 diagnosis and ICD-10 cause of death codes. A complete list of ICD-9 and -10 codes to select suspected OOD or at-risk samples are available in Appendix Table 39 and Table 40.
[35] See Appendix Table 38 for the ICD-9 and ICD-10 codes used for the initial OOD algorithm (PMR 3033-6), as well as the ICD-10 codes used in the updated algorithm (PMR 3033-2).

ICD-10 OOD intentionality codes may reliably reflect no indication of self-harm. Due to these results, neither the incidence estimates nor the risk-factor evaluations for OOD were stratified by intentionality.

Statistical Analysis

Two metrics were used to examine the incidence of OOD over time, at each site and overall – (1) the cumulative incidence, defined as the complement of the Kaplan-Meier OOD-free survival through the end of each time interval, and (2) the incidence rate, defined as the total number of OOD events per 1,000 person-years at the end of each time interval. The cumulative incidence and incidence rate were calculated every 3 months for the first year, then annually for a minimum of 5 years or until less than 10% of the site patient population remained. The calculation of overall cumulative incidence and incidence rate incorporated the varying sizes of the study populations at each site.

Three Cox proportional hazards models (henceforth, Cox models) were used to identify risk factors associated with OOD at each site:

1. Unadjusted analysis: Each individual risk factor was modeled separately.
2. Demographically adjusted analysis: Each individual risk factor was modeled separately along with age group, sex, calendar era, and U.S. Census region.
3. Fully adjusted analysis: All potential risk factors were included simultaneously. A stepwise selection was done to construct the final model if there were too few outcomes to simultaneously estimate regression coefficients, while retaining age and sex in the model. Following this rule, all sites except VUMC used stepwise selection. The p-value for retention of covariates was <0.10. The formulation variable (ER/LA versus IR/SA OA) was forced into the model. For variables retained in the final model, proportionality assumptions were assessed for each covariate by assessing an interaction term between each covariate and the days of follow-up.

Site-specific hazard ratio (HR) estimates from the fully adjusted analyses were then summarized via meta-analysis accounting for variance of the effect estimate in each site. The heterogeneity index, I^2, which ranges from 0 (no variation) to 1 (greatest variation), was calculated as a measure of site variation in effect estimates. An I^2 >0.50 was considered an indication of substantial across-site differences. Note that comparing risks across sites while adjusting for patient characteristics was not part of the study objectives and was therefore not examined.

To examine the HR for the association between switching to or adding an ER/LA OA versus switching to or adding a different IR/SA OA (reference group) and the risk of OOD in the exploratory switch/add cohort, an inverse probability-weighted (IPW) Cox model was used to account for baseline covariate imbalances between the two groups. Instead of QMME, the average daily dose in the 90 days before the switch/add event was included in this model. Changes in dose that occurred with the switch/add event were not included in the model.

3.2.2 3033-2 Retrospective Study Results

Study Population

The study population characteristics for each site and overall can be found in Table 16. At the cohort start date, overall, the largest age group was 45 to 54 years, with a fairly even sex split. Back pain and limb/extremity/joint pain were the most common pain diagnoses. Most patients used IR/SA hydrocodone or IR/SA oxycodone as their predominant OA. A small minority of patients had diagnosis codes indicating alcohol-use disorder (5.0%), OUD (3.6%), or other SUDs (6.0%) at baseline. About one-

fourth of patients had diagnosis codes indicating depression (26.5%) or anxiety (25.4%); about one-third were taking antidepressants (34.1%), benzodiazepines (31.5%), or muscle relaxants (31.7%); and about one-fifth were taking gabapentinoids (20.6%). HealthCore, KPNW, and Optum had similar demographic profiles and risk factor profiles. Although formal comparisons across sites were not conducted, patients at VUMC were somewhat younger and had a nominally higher prevalence of back pain (63.8%), musculoskeletal/chest pain (26.8%), headache (21.7%), OUD (6.1%), other SUD (12.0%), psychosis (17.9%), and dispensing for antipsychotic (10.7%) and gabapentinoid (25.4%) medications compared to the other study sites.

Table 16. Baseline Characteristics of the Study Population for PMR 3033-2

Characteristic	HealthCore (N=81,782)	KPNW (N=12,202)	Optum (N=54,515)	VUMC (N=71,932)	Overall[1] (N=220,249)
Sex					
Female	47.0%	51.6%	45.2%	60.4%	51.1%
Male	53.0%	48.4%	54.8%	39.6%	48.9%
Age, years					
18-24	2.4%	2.8%	2.8%	5.2%	3.4%
25-34	9.1%	7.5%	12.7%	16.5%	12.3%
35-44	15.1%	13.4%	21.2%	22.4%	18.9%
45-54	25.3%	22.0%	31.8%	26.3%	27.0%
55-64	26.4%	27.7%	26.7%	19.5%	24.3%
65-79	21.7%	26.6%	4.9%	10.2%	14.1%
U.S. Census Region					
Northeast	13.0%	0.0%	5.2%	0.0%	6.1%
Midwest	28.9%	0.0%	23.0%	0.0%	16.4%
South	31.8%	0.0%	56.5%	100.0%	58.5%
West	26.1%	100.0%	15.2%	0.0%	18.9%
Other/unknown	0.1%	0.0%	0.1%	0.0%	0.1%
Year of cohort entry					
2006[2]	2.7%	3.3%	2.9%	2.7%	2.8%
2007	11.4%	11.5%	10.9%	10.7%	11.0%
2008	12.0%	11.8%	11.1%	11.0%	11.4%
2009	11.8%	11.4%	10.3%	15.6%	12.6%
2010	11.0%	10.7%	10.2%	9.9%	10.4%
2011	12.1%	11.0%	10.3%	10.7%	11.1%
2012	10.5%	9.7%	9.9%	8.7%	9.7%
2013	9.0%	10.1%	8.7%	7.7%	8.6%
2014	7.6%	7.5%	8.0%	7.9%	7.8%
2015	6.6%	7.2%	7.4%	7.7%	7.2%
2016	5.3%	5.8%	10.2%	7.5%	7.3%

Characteristic	HealthCore (N=81,782)	KPNW (N=12,202)	Optum (N=54,515)	VUMC (N=71,932)	Overall[1] (N=220,249)
Pain diagnosis cluster					
Limb/extremity/joint	59.7%	69.9%	48.9%	58.8%	57.3%
Back	54.8%	56.1%	50.9%	63.8%	56.9%
Abdominal/bowel	27.4%	29.0%	17.8%	33.7%	27.2%
Fractures/contusions/ sprains/strains	25.4%	35.1%	17.3%	32.1%	26.1%
Neck	22.1%	22.7%	20.4%	23.2%	22.1%
Musculoskeletal/ chest	21.9%	21.9%	11.6%	26.8%	21.0%
Other	20.8%	31.4%	13.4%	24.6%	20.8%
Headache	13.7%	16.4%	11.4%	21.7%	15.9%
Neuropathy	10.2%	15.0%	7.5%	10.3%	9.8%
Fibromyalgia	9.8%	11.9%	9.0%	9.0%	9.4%
Urogenital/pelvic/ menstrual	5.5%	7.3%	3.7%	9.8%	6.6%
Systemic disorders	5.3%	4.1%	4.2%	5.7%	5.1%
Orofacial/ear/TMJ	1.3%	2.6%	0.9%	2.0%	1.5%
Substance use disorder					
OUD	2.3%	3.0%	2.2%	6.1%	3.6%
Alcohol	3.8%	9.0%	2.3%	7.7%	5.0%
Other SUD	3.2%	6.1%	2.1%	12.0%	6.0%
Mental health disorder					
Depression	21.5%	34.7%	17.5%	37.7%	26.5%
Anxiety	30.8%	22.1%	15.1%	27.6%	25.4%
Psychosis	3.7%	4.2%	2.8%	17.9%	8.1%
Other	2.2%	3.1%	2.7%	2.2%	2.4%
Predominant[3] opioid moiety and formulation at cohort start date					
Hydrocodone IR/SA	55.5%	39.8%	55.9%	68.1%	58.9%
Oxycodone IR/SA	22.4%	32.9%	24.4%	19.0%	22.4%
Fentanyl ER/LA	7.5%	4.1%	5.6%	2.1%	5.1%
Morphine ER/LA	3.3%	11.8%	3.2%	5.3%	4.4%
Oxycodone ER/LA	5.8%	2.7%	5.1%	1.6%	4.1%
Methadone ER/LA	1.7%	1.9%	1.5%	1.0%	1.4%
Hydromorphone IR/SA	1.5%	2.9%	1.3%	0.2%	1.1%
Morphine IR/SA	0.7%	2.9%	0.6%	0.3%	0.7%
Oxymorphone ER/LA	0.4%	0.3%	0.6%	1.4%	0.7%
Tapentadol IR/SA	0.7%	0.0%	0.9%	0.1%	0.5%
Multiple ER/LA	0.0%	0.0%	0.1%	0.7%	0.3%
Codeine IR/SA	0.1%	0.4%	0.1%	0.0%	0.1%
Meperidine IR/SA	0.1%	0.0%	0.1%	0.1%	0.1%
Multiple IR/SA	0.0%	0.2%	0.2%	0.0%	0.1%
Oxymorphone IR/SA	0.1%	0.0%	0.1%	0.0%	0.1%
Tapentadol ER/LA	0.1%	0.0%	0.2%	0.0%	0.1%
Fentanyl IR/SA	0.1%	0.0%	0.0%	0.0%	0.0%
Hydromorphone ER/LA	0.0%	0.0%	0.1%	0.0%	0.0%

Characteristic	HealthCore (N=81,782)	KPNW (N=12,202)	Optum (N=54,515)	VUMC (N=71,932)	Overall[1] (N=220,249)
QMME (in MMEs)					
<1,500	19.5%	33.3%	16.6%	26.3%	21.8%
1,500 to <2,500	21.1%	18.0%	21.5%	26.5%	22.8%
2,500 to <3,500	16.0%	14.1%	16.7%	15.1%	15.8%
3,500 to <6,000	22.0%	18.1%	22.9%	17.8%	20.6%
≥6,000	21.4%	16.4%	22.3%	14.3%	19.0%
Median QMME (in MMEs)	3,000	2,400	3,150	2,400	2,738
Nonopioid medications and Schedule III opioids					
Antipsychotics	3.6%	4.2%	3.4%	10.7%	5.9%
Antidepressants	32.4%	39.4%	26.9%	40.6%	34.1%
Benzodiazepines	39.2%	27.5%	33.0%	22.4%	31.5%
Sedative hypnotics	16.3%	9.3%	15.4%	10.3%	13.7%
Muscle relaxants	27.3%	23.0%	33.8%	36.7%	31.7%
Gabapentinoids	18.5%	12.9%	19.2%	25.4%	20.6%
Medications for OUD	0.6%	0.5%	0.6%	0.5%	0.6%
Medications for ADHD	4.4%	4.1%	4.9%	5.5%	4.9%
Schedule III OAs	2.5%	2.2%	2.6%	1.3%	2.1%

Source: FDA-generated table adapted from data provided in Whiscon Final Summary Report, Tables 7-11, 7-12, 7-13, and 7-14; Table 1, FDA IR Response dated February 12, 2021; and in Interim Communication, Pooled Table 1 and Appendix Tables 1 through 4, FDA IR Response dated June 23, 2023.

[1] Overall percentages were derived after adding numerators and denominators across all sites.

[2] The year 2006 had relatively few cohort entrants overall and at each site, as the six-month Baseline Period and the 90-day Qualification Period combined to make only the last three months of 2006 eligible for Cohort Start.

[3] Based on predominant OA, defined as the Schedule II OA contributing the most MMEs to the patients' opioid therapy during the Qualification Period.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR, information request; IR/SA, immediate-release/short-acting; KPNW, Kaiser Permanente Northwest; MME, morphine milligram equivalent; N, number; OA, opioid analgesic; OUD, opioid use disorder; QMME, quarterly/qualifying cumulative MMEs; SUD, substance use disorder; TMJ, temporomandibular joint; U.S., United States; VUMC, Vanderbilt University Medical Center

Table 17 outlines the population and OOD frequency for all study sites and overall. There were 220,249 patients included in the study, with HealthCore contributing the largest number of patients and VUMC contributing the greatest number of person-years. The average follow-up was longest in KPNW (4 years) and shortest in Optum (1.6 years). A total of 2,599 OOD events were captured during the 5-year follow-up period, ranging from a low of 115 events at KPNW to 1,635 events at VUMC.

Table 17. Number of Cohort Members, OOD Events, and Person-Years by Site and Overall

Variable	HealthCore	KPNW	Optum	VUMC	Overall
Total cohort members (N)	81,782	12,020	54,515	71,932	220,249
Total OOD events	629	140	287	1,978	3,034
OOD events, fatal (n)	107	15	57	330	509
Proportion fatal (%)	17.0	10.7	19.9	16.7	16.8
Total person-years	197,661	47,599	87,783	244,191	577,234
Average person-years per patient	2.4	4.0	1.6	3.4	2.9[1]
Cumulative OOD events at 5 years (n)	570	115	279	1,635	2,599[1]
Person-years at 5 years	175,529	39,926	83,524	196,801	492,780

Source: FDA-generated table adapted from data provided in Whiscon Final Summary Report, Tables 7-1 and 7-3 and Site Tables 8.1 and 8.2.

[1]This is an FDA-generated value.

Abbreviations: FDA, Food and Drug Administration; KPNW, Kaiser Permanente Northwest; N, number; OOD, opioid-involved overdose or opioid overdose-related death; VUMC, Vanderbilt University Medical Center

Table 18 displays the number of patients under observation in the cohort during each year of the study, and among those, the percentage dispensed IR/SA and ER/LA OAs, and mean daily MMEs, at 91 days, 1 year, and annually through the 5-year follow-up period. There was substantial attrition from the original cohort over the 5-year follow-up period, with approximately 17% of patients remaining at the end of 5 years. Among those remaining in the cohort, both IR/SA and ER/LA OA use was highest during the first year of follow-up, dropping off slightly at year 2. Between years 2 and 5, the percentage of the cohort still under observation who were dispensed an IR/SA OA declined slightly from 77% to 70%, while the percentage of the cohort being dispensed an ER/LA OA remained steady at about 15%. The mean daily morphine milligram equivalents (MMEs) for the last 30 days of the interval increased slightly, from 50 MMEs in the first 91 days to 58 MMEs at the 5-year mark.

When selected non-opioid treatments (antidepressants, antipsychotics, benzodiazepines, and gabapentinoids) were examined over the 5-year follow-up period, the percentage of patients with continued use over time was fairly stable.

Table 18. Cohort Attrition and Opioid and Selected Non-Opioid Medication Treatment During Follow-Up

Time From Cohort Start Date	91 Days	Year 1	Year 2	Year 3	Year 4	Year 5
Cohort members at end of interval (N)	**201,006**	**148,137**	**100,808**	**70,833**	**50,876**	**37,051**
Opioid treatment during follow-up						
Schedule II IR/SA OA	81%	90%	77%	73%	71%	70%
Schedule II ER/LA OA	16%	20%	16%	15%	15%	15%
Daily MME for dispensings in the last 30 days of the follow-up interval (mean)[1]	50	54	56	57	58	58
Selected non-opioid treatment during follow-up						
Antidepressants	33.6%	45.7%	44.5%	44.0%	44.0%	44.4%
Antipsychotics	5.9%	9.0%	9.2%	9.3%	9.5%	9.9%
Benzodiazepines	27.3%	39.5%	35.8%	34.2%	34.7%	35.4%
Gabapentinoids	19.0%	28.8%	26.4%	26.3%	26.8%	28.1%

Source: Adapted from Site Final Reports Tables 5 and 7 and Whiscon Report Tables 7-16 and 7-17.

Means are weighted across the sites according to the site-specific numbers of cohort members at the end of each interval as noted in the column.

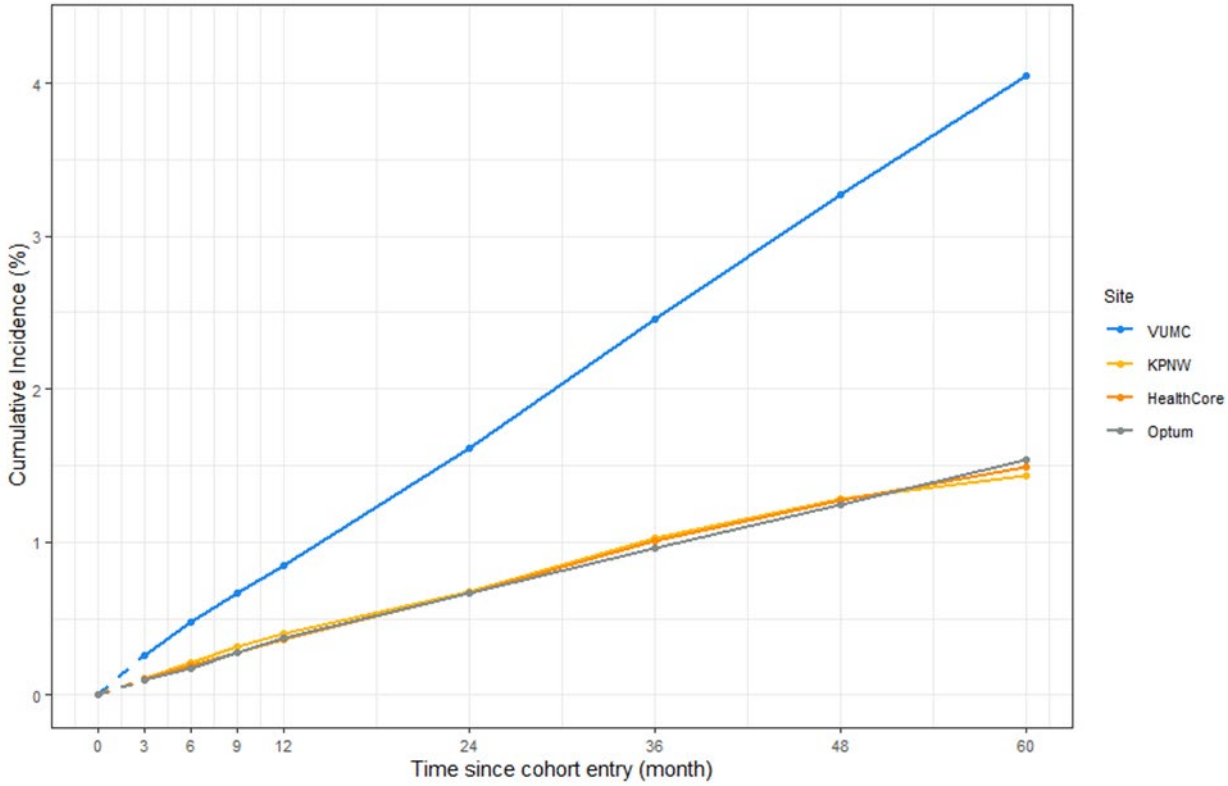
[1] For the 30 days up to and including each end-of-interval point (3, 6, 9, 12 months, and annually thereafter), the mean dispensed daily doses over all Schedule II opioid dispensings were calculated as the total MMEs dispensed divided by total dispensed days. The numbers shown are the unweighted means across the four sites.

Abbreviations: ER/LA, extended-release/long-acting; IR/SA, immediate-release/short-acting; MME, morphine milligram equivalent; OA, opioid analgesic

Cumulative Incidence and Incidence Rates of OOD

Figure 5 and Figure 6 show the cumulative incidence and incidence rates of OOD by site during the 5-year follow-up period (also see Appendix Table 43). The cumulative incidence and incidence rates for VUMC were more than double those for the other study sites, all of which were similar. At each site, the incidence rate was highest at 3 months, declining for each time interval through 2 years, and then stabilizing for the remainder of the 5-year follow-up period. Due to the substantial difference between the VUMC estimate and those for the other sites, overall estimates were not provided.

Figure 5. Five-Year Cumulative Incidence[1] (Percentage) of OOD by Study Site

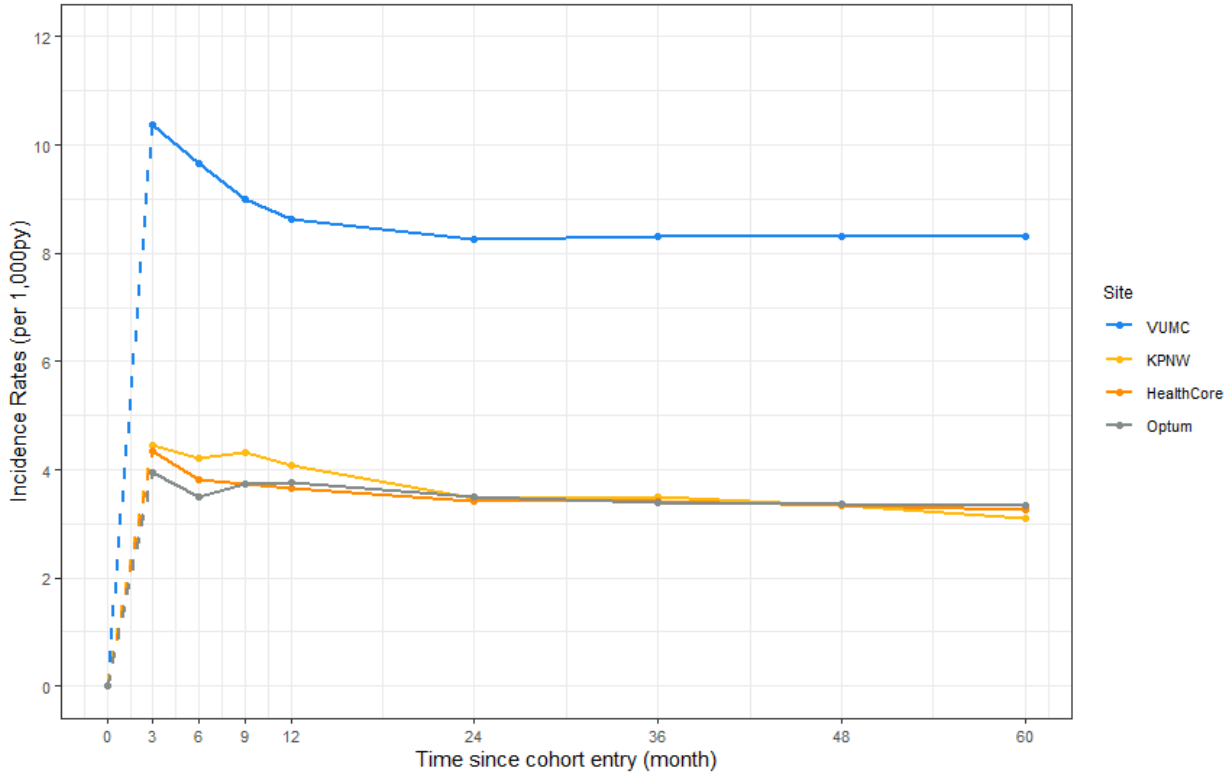


Source: FDA-generated figure adapted from Site Table 8-2, Whiscon Summary Report.

[1] The cumulative incidence at month X (%) is the complement of the Kaplan-Meier OOD-free survival preceding month X or on month X measured in percent (%) scale.

Abbreviations: FDA, Food and Drug Administration; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; VUMC, Vanderbilt University Medical Center

Figure 6. Five-Year Incidence Rates[1] (per 1,000 PY) of OOD by Study Site



Source: FDA-generated figure adapted from Table 7-2 (Site Table 8-2), Whiscon Summary Report.
[1] The incidence rate at month X is the number of total OOD events through month X divided by total person-years through month X multiplied by 1,000.
Abbreviations: FDA, Food and Drug Administration; KPNW, Kaiser Permanente Northwest; OOD, opioid-involved overdose or opioid overdose-related death; PY, person-years; VUMC, Vanderbilt University Medical Center

Risk Factors for OOD

Table 19 lists the fully adjusted risk factor analysis results for OOD by study site and from the meta-analysis. Risk factors that were significantly associated with OOD in the meta-analysis or at two or more study sites are described below (fully adjusted model). Risk factors that met a statistical threshold of $p<0.05$ (referred to as significant) are indicated in bold. Risk factors with substantial heterogeneity ($I^2>0.5$) in the meta-analysis are indicated by bolded lettering in the I^2 column. As a reminder, the term "significant" in the description of these findings below refers to statistical significance at the $\alpha=0.05$ ($p<0.05$) level and does not necessarily imply clinical significance. No multiplicity adjustment was conducted.

Demographic Risk Factors

Younger ages were generally associated with a higher risk of OOD and older ages with lower risks. The exception to this pattern was VUMC where risks were more similar across age groups.

OA-Related Risk Factors

Compared to the reference category of <1,500 QMMEs, higher cumulative OA dose during the qualification period was associated with increased risk of OOD at all sites and in the meta-analysis. Predominant ER/LA OA use (vs. predominant IR/SA OA use) was not associated with increased or

decreased OOD risk at any site or in the meta-analysis. Compared to predominant hydrocodone use,[36] predominant morphine and oxycodone use during the qualification period was associated with an increased risk of OOD in the meta-analysis. Predominant methadone use was also associated with increased risk at two sites and was borderline significant in the meta-analysis.

Health and Pain-Related Risk Factors

OUD, alcohol use disorder, and other SUD diagnoses were all associated with an increased risk of OOD at all sites and in the meta-analysis (except KPNW, which did not include OUD diagnosis in the model and Optum which did not include other SUD diagnoses in the model). Psychosis and depression were both associated with an increased risk of OOD at multiple sites and in the meta-analysis.

Antidepressant, antipsychotic, and benzodiazepine use during the qualification period were significantly associated with an increased risk of OOD at multiple sites and in the meta-analysis. (Note that antipsychotic use was not included in the model for Optum, and benzodiazepine use was not included in the model at KPNW.)

A diagnosis of limb/extremity/joint pain (yes versus no) was associated with a decreased risk of OOD at HealthCore and VUMC, and in the meta-analysis. A diagnosis in the 'other' pain category was associated with an increased OOD risk at all sites (except Optum where it was not included) and in the meta-analysis.

[36] At HealthCore, KPNW, and Optum, predominant moieties that were not modeled separately in the final models were combined with hydrocodone in the reference category.

Table 19. Fully Adjusted Risk Factor Analyses From Site-Level and Meta-Analysis

Risk Factor	HealthCore HR (95% CI)	KPNW HR (95% CI)	Optum HR (95% CI)	VUMC HR (95% CI)	Meta-Analysis HR (95% CI)	I^2
Demographic risk factors						
Age group, years						
18-24	**2.91 (2.11, 4.02)**	1.90 (0.82, 4.38)	**2.94 (1.83, 4.73)**	0.88 (0.68, 1.14)	**1.92 (1.07, 3.44)**	**0.93**
25-34	**1.57 (1.21, 2.05)**	1.76 (0.94, 3.27)	**1.46 (1.01, 2.12)**	0.88 (0.76, 1.01)	1.30 (0.95, 1.78)	**0.86**
35-44	1.23 (0.96, 1.57)	1.10 (0.63, 1.92)	1.36 (0.99, 1.88)	0.90 (0.80, 1.01)	1.09 (0.90, 1.32)	**0.68**
45-54	Ref	Ref	Ref	Ref	Ref	-
55-64	0.97 (0.77, 1.22)	0.79 (0.48, 1.28)	0.95 (0.68, 1.33)	0.91 (0.80, 1.04)	0.92 (0.83, 1.02)	0.00
65-79	1.00 (0.76, 1.30)	1.01 (0.61, 1.66)	1.12 (0.58, 2.16)	**0.70 (0.57, 0.87)**	0.87 (0.71, 1.07)	0.45
Sex						
Female	Ref	Ref	Ref	Ref	Ref	-
Male	1.15 (0.97, 1.35)	0.93 (0.65, 1.31)	1.02 (0.80, 1.31)	1.00 (0.91, 1.11)	1.03 (0.95, 1.12)	0.00
Calendar era						
October 2006-June 2012	-	Ref	-	Ref	Ref	-
July 2012-June 2013	-	1.21 (0.71, 2.05)	-	**0.84 (0.71, 0.99)**	0.92 (0.67, 1.26)	0.40
July 2013-September 2015	-	**0.46 (0.24, 0.91)**	-	**0.64 (0.56, 0.74)**	**0.63 (0.55, 0.73)**	0.00
October 2015-December 2016	-	1.10 (0.46, 2.60)	-	**0.72 (0.58, 0.89)**	**0.73 (0.60, 0.90)**	0.00
OA-related risk factors						
Predominant opioid moiety[1]						
Hydrocodone and others[2]	Ref	Ref	Ref	Ref	Ref	
Codeine	*	*	5.32 (0.74, 38.39)	-	-	-
Fentanyl	*	*	*	0.79 (0.53, 1.18)	-	-
Hydromorphone	*	*	*	1.74 (0.90, 3.39)	-	-
Meperidine	*	*	*	1.13 (0.28, 4.52)	-	-
Methadone	**1.78 (1.20, 2.64)**	1.91 (0.92, 3.96)	**2.63 (1.43, 4.85)**	1.06 (0.69, 1.63)	1.65 (1.00, 2.74)	**0.69**
Morphine	**1.70 (1.21, 2.41)**	*	*	1.29 (0.97, 1.71)	**1.46 (1.11, 1.91)**	0.33
Oxycodone	1.18 (0.98, 1.41)	*	**1.37 (1.05, 1.77)**	**1.15 (1.01, 1.31)**	**1.19 (1.08 1.31)**	0.00
Oxymorphone	*	*	*	1.17 (0.80, 1.71)	-	-
Tapentadol	*	*	*	0.74 (0.18, 2.99)	-	-
Multiple[3]	*	*	*	1.06 (0.44, 2.58)	-	-
Predominant OA formulation[1]						
IR/SA	Ref	Ref	Ref	Ref	Ref	
ER/LA	1.00 (0.80, 1.25)	1.09 (0.71, 1.69)	0.89 (0.63, 1.26)	1.05 (0.81, 1.35)	1.00 (0.87, 1.16)	0.00
QMME category during qualification period						
<1,500 MMEs	Ref	Ref	Ref	Ref	Ref	
1,500 to <2,500 MMEs	**1.46 (1.05, 2.04)**	**3.09 (1.72, 5.56)**	1.52 (0.94, 2.46)	**1.34 (1.15, 1.55)**	**1.59 (1.21, 2.09)**	**0.60**
2,500 to <3,500 MMEs	**1.86 (1.34, 2.60)**	**2.08 (1.07, 4.04)**	1.58 (0.96, 2.59)	**1.52 (1.29, 1.79)**	**1.60 (1.39, 1.84)**	0.00
3,500 to <6,000 MMEs	**1.63 (1.17, 2.26)**	**2.96 (1.62, 5.38)**	1.48 (0.92, 2.40)	**1.89 (1.61, 2.22)**	**1.84 (1.49, 2.27)**	0.22
≥6,000 MMEs	**2.88 (2.06, 4.01)**	**3.40 (1.80, 6.44)**	**2.53 (1.56, 4.12)**	**2.60 (2.14, 3.14)**	**2.69 (2.31, 3.13)**	0.00

Risk Factor	HealthCore HR (95% CI)	KPNW HR (95% CI)	Optum HR (95% CI)	VUMC HR (95% CI)	Meta-Analysis HR (95% CI)	I^2
Health and pain related factors[4]						
Concomitant medication use						
Antipsychotics	**1.56 (1.19, 2.04)**	**1.99 (1.14, 3.46)**	-	**1.29 (1.14, 1.47)**	**1.43 (1.18, 1.73)**	0.40
Antidepressants	**1.36 (1.14, 1.62)**	**1.80 (1.22, 2.63)**	**1.51 (1.16, 1.95)**	**1.21 (1.10, 1.33)**	**1.36 (1.18, 1.57)**	**0.52**
Benzodiazepines	**1.74 (1.45, 2.10)**	-	**1.74 (1.36, 2.23)**	**1.38 (1.24, 1.55)**	**1.57 (1.34, 1.84)**	**0.66**
Sedative Hypnotics	**1.31 (1.08, 1.58)**	-	1.32 (1.00, 1.75)	0.91 (0.79, 1.06)	1.14 (0.90, 1.46)	**0.82**
Muscle relaxants	-	-	-	**1.19 (1.09, 1.30)**	-	-
Gabapentinoids	-	-	-	**1.30 (1.18, 1.44)**	-	-
MOUD	-	-	-	0.91 (0.59, 1.42)	-	-
ADHD medications	-	-	**1.67 (1.16, 2.40)**	1.06 (0.89, 1.27)	1.29 (0.83, 2.00)	**0.79**
Pain conditions from EHR						
Back pain	-	-	-	**1.28 (1.14, 1.43)**	-	-
Neck pain	1.18 (0.99, 1.41)	-	-	1.00 (0.90, 1.11)	1.07 (0.91, 1.25)	**0.59**
Limb, extremity, or joint pain	0.85 (0.71, 1.01)	-	-	**0.86 (0.78, 0.96)**	**0.86 (0.78, 0.94)**	0.00
Fibromyalgia	**1.33 (1.06, 1.66)**	-	-	1.04 (0.91, 1.20)	1.16 (0.91, 1.47)	**0.70**
Headache	-	-	**1.40 (1.04, 1.91)**	0.93 (0.83, 1.05)	1.12 (0.75, 1.67)	**0.84**
Orofacial, ear, or TMJ pain	-	-	-	0.94 (0.71, 1.25)	-	-
Abdominal or bowel pain	-	-	-	1.03 (0.93, 1.15)	-	-
Urogenital, pelvic, or menstrual pain	-	-	-	**0.83 (0.71, 0.97)**	-	-
Musculoskeletal or chest pain	-	-	**1.71 (1.27, 2.31)**	1.03 (0.93, 1.14)	1.30 (0.79, 2.15)	**0.90**
Neuropathy	-	-	-	1.12 (0.98, 1.29)	-	-
Systemic disorders	-	-	-	1.05 (0.88, 1.25)	-	-
Other pain[5]	**1.21 (1.01, 1.46)**	**1.54 (1.08, 2.21)**	-	**1.45 (1.29, 1.62)**	**1.38 (1.22, 1.56)**	0.31
Fractures, contusions, sprains, or strains	-	-	-	**1.11 (1.01, 1.23)**	-	-
SUDs						
OUD	**1.47 (1.08, 2.01)**	-	**1.66 (1.06, 2.60)**	**1.60 (1.39, 1.84)**	**1.58 (1.40, 1.79)**	0.00
Alcohol use disorder	**1.55 (1.17, 2.05)**	1.56 (0.97, 2.51)	**2.74 (1.78, 4.21)**	**1.33 (1.16, 1.53)**	**1.66 (1.23, 2.23)**	**0.70**
Other SUD[6]	**1.68 (1.25, 2.25)**	**1.70 (1.04, 2.77)**	-	**1.79 (1.58, 2.03)**	**1.77 (1.58, 1.98)**	0.00

Risk Factor	HealthCore HR (95% CI)	KPNW HR (95% CI)	Optum HR (95% CI)	VUMC HR (95% CI)	Meta-Analysis HR (95% CI)	I^2
Mental health conditions						
Psychosis	**1.76 (1.35, 2.29)**	**1.92 (1.10, 3.33)**	**1.66 (1.10, 2.53)**	1.09 (0.97, 1.22)	**1.48 (1.13, 1.93)**	**0.81**
Depression	**1.38 (1.14, 1.67)**	**1.51 (1.03, 2.21)**	1.32 (1.00, 1.75)	**1.16 (1.04, 1.29)**	**1.25 (1.13, 1.39)**	0.23
Anxiety	-	-	-	**1.34 (1.20, 1.49)**	-	-
Other mental health[7]	-	-	-	0.99 (0.76, 1.30)	-	-

Source: Adapted from September 22, 2023, IR Response, IR Response and Site Table 1.

Note: Fully adjusted models were determined via stepwise selection in HealthCore, KPNW, Optum - Covariates with p≤0.10 to retain. Age, and sex, and OA formulation (ER/LA vs. IR/SA) were forced into the final fully adjusted models; VUMC had sufficient sample size and no stepwise selection was conducted. In the meta-analysis, only the covariates that appeared in the final model with p≤0.10 for at least two sites are shown. HR >1 implies that the hazard (risk) of experiencing OOD is higher among patients in that risk factor category compared to the hazard among those in the reference level. An I^2>0.50 (bold) indicates substantial heterogeneity between sites.

"-" indicates that the covariate association was not examined due to the following reasons: (1) the covariate information was absent in the site, or (2) the covariate was dropped from the stepwise model selection process, or (3) number of patients was insufficient to estimate the association.

"*" In the stepwise selection process, these predominant opioid moieties were collapsed into the reference category (i.e., combined with hydrocodone).

[1] Predominant OA formulation and predominant opioid moiety were based on predominant OA, defined as the Schedule II OA contributing the most MMEs to the patients' opioid therapy during the 90-day Qualification Period.

[2] The "*others*" includes opioid moieties that were not selected into the final model through the stepwise selection process. As the stepwise selection was performed separately at each site, opioid moieties included in the reference category varied across sites. In HealthCore, the "others" includes codeine, hydrocodone, hydromorphone, levorphanol, meperidine, opium, oxymorphone, and tapentadol. In KPNW, the "others" includes codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, oxycodone, oxymorphone, and multiple long-acting and short-acting opioids. In Optum, the "others" includes codeine, fentanyl, hydrocodone, hydromorphone, levorphanol, meperidine, morphine, opium, oxymorphone, and multiple long-acting and short-acting opioids. As no stepwise selection was conducted at VUMC, no opioid moiety other than hydrocodone was included in the reference category.

[3] The "*multiple"* category was used when a patient had two Schedule II OA products that contributed equally to their QMME calculation.

[4] Except where otherwise indicated, each covariate under this category has been modeled as a binary variable (yes vs. no) where "no" (not shown) is the reference level – e.g., diagnosis of back pain (yes vs. no [reference]); substance use disorder diagnosis of alcohol (yes vs. no [reference]); diagnosis of psychosis (yes vs. no [reference]); concomitant antipsychotics use (yes vs. no [reference]).

[5] Other pain conditions include: acquired deformities (excluding back), cancer-related, general, postoperative, post-trauma, restless leg syndrome, spinal cord injury, bone infections, infectious arthritic diseases.

[6] Other SUDs include any ICD-diagnosis for an SUD other than alcohol use disorder or OUD.

[7] Other mental health conditions include any ICD-diagnosis for a condition that is not depression, anxiety, or psychosis-related.

Abbreviations: ADHD, attention deficit/hyperactivity disorder; CI, confidence interval; EHR, electronic health records; ER/LA, extended-release/long-acting; HR, hazard ratio; I^2, heterogeneity index; IR, information request; IR/SA, immediate release/short-acting; MME, morphine milligram equivalent; MOUD, medications for opioid use disorder; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; QMME, qualifying/quarterly MME; Ref, reference; SUD, substance use disorder

Switch/Add Cohort Analysis

Overall, 53,257 patients who were on a stable IR/SA OA only regimen[37] were included in the switch/add cohort. During the study period, 11,572 of these patients (21.7%) were switched to or had an ER/LA OA added to their treatment regimen, while 41,685 patients (78.3%) were switched to or had a new (i.e., different opioid moiety) IR/SA OA added to their treatment regimen.

Table 20 shows the median DMME in the 90 days prior to the switch/add event, the median DMME in the 90 days after the switch/add event, and the change in DMME following the switch/add event. IR/SA OA to new IR/SA OA switches/adds generally resulted in a *decrease* of approximately five DMMEs overall (median decrease across sites: −4.1 to -7.0 DMMEs). IR/SA OA to ER/LA OA add/switches resulted in an *increase* of approximately 12.8 DMMEs overall (median increase across sites: 6.4 to 20 DMMEs).

Table 20. Median DMME Changes for Switching to/Adding an IR/SA OA or ER/LA OA

	Daily MME Prior to Switch/Add		Daily MME After Switch/Add		Change in Median Daily MME	
Variable	IR/SA to IR/SA	IR/SA to ER/LA	IR/SA to IR/SA	IR/SA to ER/LA	IR/SA to IR/SA	IR/SA to ER/LA
Total (all sites combined)						
n	41,685	11,572	41,685	11,572	41,685	11,572
Median DMME	13.2	24.1	7.8	36.9	-5.4	+12.8
HealthCore						
n	13,433	3,860	13,433	3,860	13,433	3,860
Median DMME	13.3	25.0	8.0	45.0	-5.3	+20.0
KPNW						
n	2,253	758	2,253	758	2,253	758
Median DMME	9.4	17.8	5.3	32.7	-4.1	+14.9
Optum						
n	7,070	1,816	7,070	1,816	7,070	1,816
Median DMME	15.0	30.0	8.0	40.0	-7.0	+10.0
VUMC						
n	18,929	5,138	18,929	5,138	18,929	5,138
Median DMME	15.0	23.6	10.0	30.0	-5.0	+6.4

Source: FDA-generated table adapted from IR Response Table 1, FDA IR Response dated August 15, 2024.
Abbreviations: DMME, daily morphine milligram equivalent; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; IR, information request; IR/SA, immediate-release/short-acting; KPNW, Kaiser Permanente Northwest; N, number; OA, opioid analgesic; VUMC, Vanderbilt University Medical Center

Table 21 presents incidence rates and fully adjusted HRs from the IPW Cox analyses for OOD in the switch/add cohort. Both site-level and meta-analysis estimates, under the two censoring events (the end of the switch/add OA therapy episode[38] and the cohort end date), are provided. All risk factors (i.e., potential confounders) considered in the switch/add analysis were balanced between the ER/LA OA and IR/SA OA switch/add groups after weighting (i.e., standardized mean difference <0.2).

[37] Patients meeting study inclusion criteria with IR/SA OA use during the qualification period and at least one IR/SA OA prescription during a time period of ≥90 days after the cohort start date but before the switch/add date.
[38] The end or discontinuation date of switch/add OA therapy was defined as 30 days following the completion of the dispensing date, plus days' supply, minus one.

Meta-analytic HRs from IPW Cox analyses showed higher risk of OOD among patients who switched to or added an ER/LA OA compared to those switching to or adding a new IR/SA OA when censoring at the end of the switch/add treatment episode (HR=1.59, 95% CI [1.10, 2.30]) and when censoring at study end date (HR=1.35, 95% CI [1.02, 1.77]). However, the meta-analytic HR was subject to substantial heterogeneity across sites (I^2=0.53) when follow-up was censored at the study end date. Although most HR point estimates at the individual sites were >1, the estimates were only statistically significant at the HealthCore site.

As described in Section 4.2.1, these analyses did not account for changes in dose associated with switch/add of a new OA. Only dose in the 90 days prior to the switch/add event was included in the model.

Table 21. Fully Adjusted OOD Incidence Rates Among Patients Who Switched to or Added an ER/LA Compared to an IR/SA OA

		End of Switch/Add Treatment Episode				Study End Date			
Study Site	OA Switch/Add Group	OOD (n)	PY (1,000s)	Incidence Rate* (95% CI)	HR** (95% CI)	OOD (n)	PY (1,000s)	Incidence Rate* (95% CI)	HR** (95% CI)
VUMC	ER/LA	23	1.15	20.0 (13.3, 30.1)	1.50 (0.82, 2.74)	225	16.56	13.6 (11.9, 15.5)	1.17 (0.99, 1.39)
	IR/SA (Ref)	36	2.86	12.6 (9.1, 17.5)		607	61.08	9.9 (9.2, 10.8)	
KPNW	ER/LA	6	0.73	8.2 (3.0, 17.8)	1.35 (0.38, 4.82)	17	2.83	6.0 (3.5, 9.6)	0.91 (0.47, 1.76)
	IR/SA (Ref)	5	0.65	7.7 (2.5, 17.9)		33	7.29	4.5 (3.1, 6.4)	
HealthCore	ER/LA	23	1.99	11.6 (7.3, 16.2)	2.03 (1.09, 3.78)	66	8.07	8.2 (6.3, 10.1)	1.74 (1.26, 2.41)
	IR/SA (Ref)	21	5.01	4.2 (2.6, 5.9)		112	31.09	3.6 (3.0, 4.3)	
Optum	ER/LA	11	0.82	13.5 (6.7, 24.1)	1.21 (0.52, 2.84)	26	2.82	9.2 (6.0, 13.5)	1.60 (0.99, 2.59)
	IR/SA (Ref)	16	1.83	8.7 (5.0, 14.2)		60	11.53	5.2 (4.0, 6.7)	
Meta-analysis	ER/LA	63	4.7	13.4 (10.5, 17.2)	1.59 (1.10, 2.30) I^2=0.00	334	30.3	11.0 (9.9, 12.3)	1.35 (1.02, 1.77) I^2=0.53
	IR/SA (Ref)	78	10.4	7.5 (6.0, 9.4)		812	111.0	7.3 (6.8, 7.8)	

Source: Adapted from IR Response Table 2 and Site Tables 5, FDA IR response dated August 15, 2024.

* Rate per 1,000 PY.

** Obtained from IPW Cox analysis.

Abbreviations: CI, confidence interval; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; HR, hazard ratio; I^2, heterogeneity index; IPW, inverse probability-weighted; IR, information request; IR/SA, immediate-release/short-acting; KPNW, Kaiser Permanente Northwest; N, number; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; PY, person-years; Ref, reference; VUMC, Vanderbilt University Medical Center

4 Key Discussion Points and Considerations for the AC

4.1 Overarching Considerations

The ER/LA OA PMR studies were issued to quantify the serious risks of misuse, abuse, addiction (OUD), and fatal and nonfatal overdose in patients using long-term OAs and to better understand risk factors for these outcomes. As these were known risks at the time the PMRs were issued, the goal was not to assess *whether* long-term use of OAs was associated with the outcomes relative to an unexposed comparator group, or to quantify the causal contribution of OA use to these risks, but rather to examine how common these serious adverse outcomes were in this patient population, and to study a large number of potential risk factors, including both possible etiologic factors and markers of increased risk. The information from these studies was intended to inform regulatory, clinical, and policy decisions related to the safety of long-term use of prescription OAs and to contribute to scientific knowledge and methodology in this area.

During the development of the PMR studies, there were several competing priorities that impacted the designs and methods of the studies. For example, in PMR 3033-1, there was a need to ensure sufficient sample sizes for acceptable precision of estimates and meaningful analyses of risk factors; however, this needed to be balanced against the need for population variability with respect to geography, payor source, and demographics; and the time required to complete recruitment. The use of validated outcome measures was a strength of these studies, though the development and validation of new instruments and algorithms prolonged the time to complete the full PMR study program.

As discussed in Section 2.1, the landscape of OA prescribing is different today from when these PMRs were issued and even from the time periods covered in the studies. Myriad efforts to reduce unnecessary or inappropriate opioid use have resulted in more selective use of OAs (particularly for chronic noncancer pain), and a substantial decline in the use of OAs overall. Important concerns have also emerged about risks associated with tapering and discontinuation of OAs in patients with chronic pain. Furthermore, the contribution of prescription OAs to the overdose crisis has become more complex, with widespread availability of counterfeit opioids and a predominance of illicitly manufactured fentanyl in overdose deaths. The findings from these PMR studies must be interpreted in the context of these changes.

Overarching Strengths

This suite of studies, and PMRs 3033-1 and 3033-2 in particular, have several important strengths. The studies were conducted in accordance with prespecified protocols and statistical analysis plans and were subject to FDA review and approval at multiple time points. Study design considerations were discussed in a public scientific workshop and incorporated input from multiple external experts not affiliated with the products' manufacturers. The main PMR studies, 3033-1 and 3033-2, were large, multisite investigations that together included patients who were commercially insured, in managed care, on Medicaid, using safety net clinics, and veterans, and covered a range of geographic areas in the United States. In addition, PMRs 3033-1 and 3033-2 used measures of opioid misuse and abuse, OUD, and OOD that were developed and validated as part of the suite of ER/LA OA PMR studies, specifically for use in these study populations. While developed for use in these studies, these instruments and measures may also be useful for other studies assessing risks in patients using OAs. The prospective collection of detailed, standardized information on opioid use, risk factors, misuse, abuse, and OUD in PMR 3033-1 adds meaningfully to the body of research in this area. For example, assessment of patient-reported

information on important risk factors such as history of SUDs, ACEs, mental health conditions, pain severity, and pain interference in large observational studies is rare in the published literature, as these variables are absent or incompletely captured in commonly used insurance claims databases. In addition, the use of standardized instruments administered at standardized time points to measure misuse, abuse, and OUD reduces concerns about detection bias (i.e., that providers concerned about patients' high risk for certain outcomes may be more likely to assess for those outcomes), which is a common concern in published literature that has relied on EHR and claims data for outcome assessment. Linkage to the NDI data to capture fatal overdoses was an important strength of PMR 3033-2, as this is often cost-prohibitive and infrequently done in insurance claims-based studies. Finally, the studies included both valuable descriptive and prevalence data as well as longitudinal analyses restricted to patients free of the outcome under investigation at baseline, allowing for robust estimation of incidence and temporal ordering of risk factors in relation to the outcomes of interest.

Other Contributions of ER/LA OA PMR Studies to Scientific Knowledge

In addition to the findings from PMRs 3033-1 and 3033-2, the foundational studies to support these main studies also contributed some useful information to the scientific field more generally.[39] The development of the PRISM-5-Op, and validation of its various measures (Hasin et al. 2020) offers a new option for evaluating OUD in patients prescribed OAs chronically for pain—and provides additional information about the complexity of diagnosing OUD in this population—and the POMAQ (Coyne et al. 2021a; Coyne et al. 2021b; Coyne et al. 2021c; Coyne et al. 2022; Coyne et al. 2023) offers a validated tool for researchers studying opioid misuse and abuse. In PMRs 3033-6 (Green et al. 2019a; Green et al. 2019b; Hazlehurst et al. 2019) and 3033-7 (Carrell et al. 2020), we learned that medical code-based algorithms perform poorly in capturing abuse, OUD, and overdose intentionality; but nonfatal opioid overdose for any reason can be reasonably well captured using an insurance-claims-based algorithm. PMRs 3033-8, 3033-9, and 3033-10 found that although higher levels of doctor/pharmacy shopping, based on pharmacy dispensing data algorithms, is associated with misuse, abuse, and OUD, these measures are not good proxies for these outcomes, because they are likely to misclassify a high proportion of patients as engaging in misuse or abuse or having OUD when that is not true, or conversely, do not identify these outcomes when they actually occur. It was clear that prospectively collecting data using validated tools was the best approach for ascertaining opioid misuse, abuse, and OUD, ideally with repeated assessments over time. These findings were incorporated into the design of PMRs 3033-1 and 3033-2 and may also be useful for other research.

Overarching Limitations

Despite these strengths, PMRs 3033-1 and 3033-2 also had limitations, including the prolonged time required to complete the studies. Because of the multiple sites involved, responses to FDA information requests and corrections of errors and omissions in study reports often took many months, further extending these timelines. Although the study populations were large and drew from multiple sites that

[39] FDA's reviews of the FSRs for PMR studies 3033-3 through 3033-5 and PMR studies 3033-7 through 3033-10 are available online at: https://www.fda.gov/drugs/information-drug-class/new-safety-measures-announced-extended-release-and-long-acting-opioids. PMR study 3033-6 cannot be fulfilled until the review of PMR study 3033-2 has been finalized, as the OOD algorithm in PMR study 3033-6 underwent further testing as part of PMR study 3033-2. The final study report for PMR study 3033-6 (OOD algorithm) was reviewed by FDA, but the review is not available publicly and the PMR has not yet been fulfilled because of additional OOD algorithm validation conducted as part of PMR study 3033-2.

varied in terms of geography, setting of care, and payor source, the overall study population for PMR 3033-1 was predominated by integrated or managed care health systems. In PMR 3033-2, the use of insurance-based data resources precluded gathering information on patients without insurance.

As is common in pharmacoepidemiologic investigations using claims data, PMR 3033-2 could not account for medications that were paid for with cash or obtained outside of the healthcare system providing data for the study. In addition, some conditions (e.g., SUDs, mental health conditions) are poorly captured in claims databases, and this has implications when considering the impact of misclassification of these factors when analyzed as risk factors and covariates. Next, risk factor analyses used OA exposure characteristics and covariates measured at baseline rather than using time-updated exposure or covariate measurements. This choice may be particularly important in interpreting results of incidence estimates and risk factor analyses related to OA dose, formulation, and opioid moiety, which may change substantially over the follow-up period.

Another consideration relevant to both 3033-1 studies as well as PMR 3033-2 pertains to the risk factor models. These models were exploratory and hypothesis-generating, and they were not designed to evaluate prespecified causal associations between specific risk factors and misuse, abuse, OUD, or OOD. A data-driven method was used to determine which risk factors to include in the fully adjusted models, resulting in a single mutually adjusted model assessing the independent associations between each risk factor and a given outcome; however, this could have resulted in lack of inclusion of important confounders as well as the potential for overadjustment (i.e., adjustment for a mediator). In addition, because a large number of analyses were conducted for the purpose of risk factor exploration, and thus without correction for multiplicity, it is possible that some statistically significant results were due to chance. However, for some outcomes with low prevalence or incidence, such as OUD, it is also possible that statistically insignificant results were due to insufficient statistical power to detect true risk factors. Future research could consider assessment of individual risk factor-outcome associations by building models with confounders and effect measure modifiers selected with respect to individual associations of interest *a priori*, and studies could be powered appropriately to test prespecified hypotheses about those associations. The results of PMR studies 3033-1 and 3033-2 offer preliminary insights that could be helpful in designing such studies. Finally, the complex interplay among various OA-related factors and between OA-related factors, pain, and health conditions was not fully explored in these studies. For example, OA dose and duration of OA therapy are likely correlated such that dose changes as duration increases, and it can be difficult to separate the unique effect of each of these factors, especially when only one of these risk factors is included in a given model. These limitations and considerations are further discussed in Section 4.2.

4.2 Key Study Findings and Interpretation of Studies 3033-1 and 3033-2

4.2.1 Risk of Opioid Misuse, Abuse, OUD, and OOD: Summary and Interpretation

In both the prospective and cross-sectional PMR 3033-1 studies, opioid misuse[40] was the most frequently identified of the outcomes measured (Table 22). Opioid abuse[41] was approximately half as common as opioid misuse. Incidence and prevalence of moderate-to-severe OUD were lower, but these estimates depended substantially on the OUD definition used. Using the pain-adjusted DSM-5-OUD definition—in which most DSM-5 symptoms were counted only when the patient indicated a nonpain reason for opioid use associated with that symptom, and multiple attempts to quit or cut down were required in order to count the "quit or cut down" criterion—past-year prevalence of moderate-to-severe OUD was 2.7% in the cross-sectional study, and the one-year incidence was 1 to 2% in the two cohorts in the prospective study. Estimates for moderate-to-severe OUD were substantially higher using the DSM-5-OUD definition of OUD—which counted criteria regardless of the reported reason for opioid use associated with that symptom. The treatment of tolerance and withdrawal was consistent between the two definitions, with these symptoms not counted if OAs were only used as prescribed. Nearly all observed OUD cases involved prescription opioids. The incidence and prevalence of OUD involving heroin were very low in both the prospective and cross-sectional PMR 3033-1 studies.

The 5-year cumulative incidence of OOD in patients with long-term OA use ranged from approximately 1.5% in the two commercially insured sites and one managed-care site to approximately 4% in the fourth study site, comprised of patients enrolled in Medicaid. Incidence rates at the end of the 5-year follow-up ranged from approximately three events per 1,000 person-years in the commercially insured and managed care sites to more than eight events per 1,000 person-years at the Medicaid site. Approximately one in six of the overdose events observed in this study was fatal. As shown in Figure 6 in Section 3.2.2, results from PMR 3033-2 suggested that the OOD incidence rate was highest during the first 3 months of follow-up, which began after the qualification period for long-term opioid use.

[40] Misuse is defined as intentional use of a drug for a therapeutic purpose (i.e., to reduce an aversive symptom or state) inappropriately outside label directions or in a way other than prescribed or directed by a health care practitioner (e.g., using a drug for a condition different from that for which the drug was prescribed, taking more of a drug than prescribed, using a drug at different dosing intervals than what was prescribed).

[41] Abuse is defined as the intentional use of a drug for a nontherapeutic purpose, repeatedly or sporadically, for the purpose of achieving a positive psychological or physical effect.

Table 22. Summary of Prevalence and Incidence Estimates of Misuse, Abuse, and OUD and Cumulative Incidence and Incidence Rates of OOD

			Moderate-to-Severe OUD		
Estimate (%, 95% CI)	Misuse	Abuse	Pain-Adjusted DSM-5-OUD[1]	DSM-5-OUD[2]	OOD
Prospective 3033-1: ER/LA cohort[3] 12-month incidence (%)	22.8 (21.6, 24.0)	9.4 (7.7, 11.6)	1.4 (0.9, 2.3)	5.8 (4.5, 7.3)	
Prospective 3033-1: LtOT cohort[4] 12-month incidence (%)	21.6 (18.3, 25.5)	8.6 (7.4, 10.0)	1.6 (0.9, 2.9)	3.4 (2.5, 3.1)	
Cross-sectional 3033-1: prevalence (%)	14.6 (12.6, 17.0)	6.0 (4.8, 7.6)	2.7 (1.8, 4.0)	6.3 (4.3, 9.1)	
3033-2: 5-year cumulative incidence (%)[5]					
HealthCore					1.49 (1.35, 1.63)
KPNW					1.43 (1.19, 1.73)
Optum					1.54 (1.27, 1.80)
VUMC					4.05 (3.85, 4.27)
3033-2: 5-year incidence rate (N per 1000 person-years)[6]					
HealthCore					3.25 (2.99, 3.51)
KPNW					3.11 (2.59, 3.74)
Optum					3.34 (2.96, 3.76)
VUMC					8.31 (7.91, 8.71)

Source: Adapted from Final Report on Cross-Sectional Study Results, Figure 4 (prevalence); Tables 9a and 9b, Final Report on the Prospective Study Results (incidence); Whiscon Summary Report Site Table 8.2 (OOD)

[1] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[2] Moderate-to-severe DSM-5 OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[3] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[4] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[5] Five-year cumulative incidence is the complement of the Kaplan-Meier OOD-free survival preceding 5 years measured in percent (%) scale

[6] 5-year incidence rate=total number of OOD events at 5 years of follow-up ÷ 1,000 person-years at 5 years of follow-up.

Abbreviations: CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER/LA, extended-release/long-acting; KPNW, Kaiser Permanente Northwest; LtOT, long-term opioid therapy; OA, opioid analgesic; OOD, opioid-involved overdose or opioid overdose-related death; OUD, opioid use disorder; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DMS-5, Opioid Version; VUMC, Vanderbilt University Medical Center

Considerations for Interpreting Misuse, Abuse, and OUD Estimates

Prior to completion of this study, published studies in similar populations of individuals with chronic pain and/or receiving LtOT had found a very wide range of prevalence and incidence estimates. For example, one systematic review (Vowles et al. 2015) assessed literature published between 2000 and 2013[42] focusing on individuals with chronic noncancer pain using oral OAs and found that among studies rated by the authors as high quality (13 studies), the prevalence of opioid misuse ranged from 2.0% to 56.3%, with an unweighted mean of approximately 24%. In 10 studies rated by the authors as high quality, addiction prevalence ranged from 0.7% to 23.0%, with an unweighted mean of approximately 9%. The prevalence of opioid abuse was reported as 8% in the single study rated as high quality. Notably, few of these studies were explicitly designed to assess prevalence or incidence of the outcomes, with some being validation studies in highly specific clinical populations and some being interventional studies in

[42] The years of data collection were not reported in all studies included in the systematic review, but among those that did include this information, patient recruitment took place between 1996 and 2009.

which at least one study arm received an intervention aimed at reducing adverse opioid-related events. Other explanations for the high degree of variation in reported prevalence include variation in study populations, variation in outcome measurements and definitions (Voon et al. 2017), different referent time-periods for assessing the outcomes, and/or variation in the amount of time patients had been on opioid therapy (not specified in many studies; approximately 3 months to 1 year in several studies in which it was specified).

PMR 3033-1 adds to the existing body of evidence by using clearly defined outcome definitions based on validated instruments and prospectively collected data, rather than relying on EHR- or claims-based outcome measurement, as has commonly been done in other research studies. The prospective 3033-1 study also provided some insight into how ascertainment of OUD based on EHR or claims data may differ from that based on a standardized interview. Patients were excluded if they had an ICD diagnosis of OUD at baseline; however, 63 patients included in the study were actually classified by the PRISM-5-Op as having baseline OUD (these patients were excluded from analyses using OUD as the outcome), highlighting that claims-based measures likely have limited sensitivity to detect OUD cases, compared to a validated interview measure. This finding is consistent with the findings of PMR 3033-7, which found that claims-based algorithms for abuse and addiction have poor sensitivity and should not be used in PMR 3033-2 to estimate the incidence of addiction in patients with long-term use of OAs.

As noted above, the estimated prevalence and incidence of OUD were substantially lower using the pain-adjusted DSM-5-OUD definition than the standard DSM-5-OUD definition of OUD. This is unsurprising, given that the pain-adjusted DSM-5-OUD definition requires a nonpain reason for opioid use for most symptoms to count towards a designation of OUD. The pain-adjusted DSM-5-OUD measure was developed and validated in PMR 3033-5 because the DSM-5-OUD definition typically used to identify OUD was not originally designed for or tested in a population of patients prescribed OAs chronically. Furthermore, some aspects of the validation study suggested that the PRISM-5-Op pain-adjusted criteria may more accurately identify OUD compared to the standard DSM-5-OUD criteria in populations receiving opioids for pain—for example, the pain-adjusted definition had stronger associations with external validators than the nonpain-adjusted version. However, both versions were associated with external validators to some degree, suggesting that both OUD definitions may be valid in this population. A concern with the DSM-5-OUD definition is that it might misclassify patients as having OUD if, for example, they meet criteria by reporting that they spend a great deal of time in activities to obtain opioids, but they are referring to time spent to obtain or fill an opioid prescription for management of pain; or if efforts to taper or discontinue opioids have been unsuccessful because of physiologic dependence or uncontrolled pain rather than due to uncontrolled opioid use associated with a use disorder. However, the pain-adjusted DSM-5-OUD definition could miss true cases of OUD if, for example, opioids were used to manage opioid withdrawal in the setting of a use disorder. The difference in observed OUD risk based on these two definitions highlights the complexity of diagnosing and generating population-based risk estimates of OUD in patients using OAs chronically under medical supervision, and the findings raise important questions about the clinical and public health implications of the findings from PMR 3033-1 that a substantial proportion of patients who endorse DSM-5 symptoms of OUD do not report misusing opioids for nonpain reasons. A recent publication raised a similar question about changes to the definition of OUD used in the National Survey on Drug Use and Health, which previously included only respondents who endorsed past-year misuse of prescription pain relievers when assessing for OUD symptoms but recently changed the survey methods to include all

respondents endorsing past-year use of prescription pain relievers in the OUD symptom assessment. This change resulted in a substantial increase in the number of individuals in the United States estimated to have OUD (Kolodny and Bohler 2024).

Misuse, abuse, and OUD are often described as a continuum, with gradations of severity and each one following the next. The associations observed in the PMR 3033-1 prospective study to some extent support this concept but suggest that these relationships may be quite complex and variable. In the fully adjusted models, baseline misuse was strongly associated with abuse at 1 year in both the ER/LA and LtOT cohorts, whereas baseline abuse was associated with later misuse only in the LtOT cohort. Baseline abuse was strongly associated with pain-adjusted DSM-5-OUD at 1 year, and the inverse was also noted (i.e., baseline OUD was associated with abuse at follow-up assessment) in the LtOT cohort, although the confidence intervals were wide for both point estimates. In contrast, baseline misuse was not associated with pain-adjusted DSM-5-OUD in either cohort in fully adjusted models (which include baseline abuse). Interestingly, in the LtOT cohort, baseline misuse was associated with DSM-5-OUD at one year, but the association between baseline abuse and later DSM-5-OUD was not as strong. These findings suggest that while misuse and abuse are clearly associated, they are also independent concepts and have complicated longitudinal relationships with one another and with OUD; and these relationships may further depend on how OUD is measured and defined.

Finally, it is important to keep in mind that the original study inclusion criteria were designed to focus on patients on long-term ER/LA OA therapy, resulting in study populations in which ER/LA OA use was common, despite observations from previous FDA analyses which have found that long-term OA use primarily involves IR/SA opioids (Hwang et al. 2018). Both the PMR 3033-1 cross-sectional study and the ER/LA cohort in the prospective study required some ER/LA OA use, and as a result, two-thirds of the cross-sectional study population had an ER/LA OA as their predominant OA, and 40% of patients in the ER/LA cohort in the prospective study had an ER/LA OA as their predominant OA. These studies were also, by design, restricted to the relatively small proportion of patients receiving OAs who go on to use them long-term (Appendix Table 26) and therefore do not inform questions of risk related to shorter-term use of OAs; patients could misuse or abuse their opioids, suffer a fatal overdose, or transition to illicit opioids before meeting eligibility criteria for long-term use in these studies. As described in Section 2.1, only 17% of patients initiating OA therapy in 2021 or 2022 had presumed long-term therapy, and among those with presumed long-term therapy, only 0.7% received predominantly ER/LA OA prescriptions while approximately 97% received predominantly IR/SA OAs and 2.5% received both. In summary, results from the PMR studies may apply to only a minority of patients using OAs.

Considerations for Interpretation of OOD Estimates

As with misuse, abuse, and OUD, the *Boxed Warning* in OA labels includes a warning about the potential for overdose and death ("risks of addiction, abuse, and misuse, which can lead to overdose and death") without quantifying this risk. Again, the range of estimates from PMR 3033-2 for incidence of OOD provide some insight into this question, but only among a very specific population of patients using OAs (i.e., those newly initiating long-term therapy). OOD estimates in PMR 3033-2 were generally within the range of estimates from previous, published studies in similar populations (Greene et al. 2023), although direct comparison is challenging due to differences in cohort eligibility, study period and length of follow-up, outcome definition, and other study parameters. As shown in Table 18 in Section 3.2.2, there was substantial attrition of the overall study 3033-2 cohort over the 5-year follow-up period, with only about 17% of the original cohort still under observation at the end of the 5 years. While this loss to

follow-up was accounted for in the calculation of the incidence estimates, if those who left the cohort (e.g., due to disenrollment or change of insurance coverage due to job loss or change) were systematically at higher or lower risk of OOD than those remaining under observation in the study, then incidence estimates could be biased. It is also important to keep in mind that patients with a documented opioid-involved overdose in the baseline or qualification periods were excluded, limiting generalizability of findings to a population of new long-term opioid users at inherently lower risk of OOD during follow-up.

PMR study 3033-2 found that, although the cumulative incidence of OOD (the complement of the Kaplan-Meier OOD-free survival through the end of five years) increased throughout the 5-year study period, the incidence rate of OOD (total number of events by the end of each time interval divided by the person-years accumulated till the end of the time interval) was highest at the first timepoint during follow-up (3 months after cohort entry) and then decreased before stabilizing through the end of the 5-year follow-up period. The interpretation of this finding is not entirely clear. It is possible that this initial 3-month period reflected the most intensive period of opioid use within the cohort, with decreasing use over time contributing to gradual reductions in observed OOD incidence. Alternatively, the declining OOD incidence could be due to "depletion of susceptibles," where patients who are at highest risk of the outcome experience it earlier and therefore are censored and not included in the population at risk for subsequent time periods. Finally, it cannot be ruled out that the early period of long-term OA therapy may be a period of increased OOD risk for some patients, perhaps because doses are being adjusted more often or patients may not have developed tolerance to their current dose.

The algorithm developed for assessing OOD in PMR study 3033-2 builds on, and its validation had results generally consistent with, other studies evaluating ICD-9 and electronic health record-based overdose algorithms (Reardon et al. 2016; Rowe et al. 2017; Vivolo-Kantor et al. 2021). The initial OOD algorithm developed from PMR 3033-6 was shown to have high sensitivity, specificity, PPV, and NPV (Section 3.2.2). The OOD algorithm was further refined and revalidated in PMR 3033-2 to incorporate ICD-10 codes beginning in 2015, and the revalidation found high PPV in the population of individuals on long-term OA therapy. As only the PPV was examined in the revalidation study, FDA conducted additional analyses to determine to what extent the updated OOD algorithm in PMR 3033-2 might over- or underestimate the true OOD risk. Crude incidence, defined as the total number of OOD events divided by the total number of patients available at baseline, was used for illustration. We estimated the (true) crude incidence[43] across different levels of sensitivity, under plausible ranges of PPV estimates using PMR 3033-2 results as a basis (Appendix Table 41). Based on these analyses, Appendix Table 44 shows that the true crude incidence of OOD could be between 1.04% and 1.55%, compared to the observed crude incidence, 1.38%,[44] in PMR 3033-2. These findings lend further support to the acceptability of the overall OOD algorithm performance.

PMR 3033-2 was able to capture both nonfatal and fatal overdose events through linkage with the NDI, even if the fatal overdose did not generate an insurance claim. It remains possible, however, that some opioid-involved overdose deaths were not recorded as such by the death certifier. Additionally,

[43] Estimated crude incidence = (observed crude incidence × PPV) ÷ sensitivity.

[44] Can be obtained from the numbers reported in Table 18. Total number of OOD events ÷ total number of patients × 100=3034 ÷ 220249 × 100 = 1.37 (%).

overdoses were not stratified based on intentionality in the main analysis[45] because of inadequate performance of the code-based intentionality algorithm in the validation study. The specific opioid(s) and other substances potentially co-involved in the overdose were also not analyzed as part of the OOD outcome. This study was also subject to the inherent limitations of using medical codes for outcome ascertainment, including that events must come to the attention of a healthcare professional to be identified. Therefore, opioid overdoses that were reversed by a bystander or that otherwise did not result in either a medical claim or death were not captured. Additionally, since the outcome for this study includes only the first OOD event, a patient could have experienced subsequent events, including fatal overdose, that would not be included in the OOD incidence estimates.

Another consideration when interpreting the OOD estimates is the notable difference between VUMC (Medicaid) versus the two commercially insured populations (HealthCore and Optum) and the managed-care site (KPNW). The VUMC population was younger and had a nominally higher prevalence of many pain conditions, OUD, other SUDs, and psychosis compared to the populations at the other study sites. The increased OOD risk in Medicaid populations has been reported previously (Hasegawa et al. 2014; Martin et al. 2024) and highlights that both individual and societal factors likely contribute to OOD risk. However, there were no pre-planned analyses to adjust for the population characteristics differences between study sites. The inclusion of varied populations with regard to socioeconomic status, payor, and care delivery models is a strength of this study, although it complicates interpretation of the meta-analytic results. The substantial variation in OOD risk estimates across study sites appears to preclude establishing a single best risk estimate, and instead supports the concept of a range of risk estimates that depend on many individual and population-level factors.

Current FDA labeling clearly warns about the known serious risks of misuse, abuse, addiction, and overdose, including in the *Boxed Warning* and in multiple other sections of the label; however, there is no quantification of these risks. The results of these PMR studies do provide new quantitative estimates of these risks, but only in specific subgroups of patients meeting eligibility criteria for long-term OA use; adverse outcomes occurring during the early months of use were not assessed, and patients with a recent history of nonfatal overdose were excluded from the cohorts. The varying eligibility criteria across the study cohorts (with a requirement for ER/LA OA use in some) and the differing results based on insurance coverage further complicate attempts to generalize findings to the broader population of patients prescribed OAs. Finally, the studies also included data from earlier time periods, raising questions about relevance to the current opioid landscape.

4.2.2 Risk Factor Analyses: Summary and Interpretation

Overarching Considerations for Interpreting Risk Factor Analysis Findings[46]

When the PMR 3033-1 and 3033-2 studies were designed, there was limited information about the risk factors for misuse, abuse, OUD, and OOD in patients using OAs long-term. Therefore, the risk factor analyses in these studies were exploratory rather than designed to evaluate prespecified causal

[45] These were conducted as exploratory analyses only.

[46] In this section, we use the term *risk* as a general term that is not meant to specify the type of model used. For example, we discuss increased risk of an outcome within categories of a risk factor even though logistic models were used to calculate ORs and Cox models were used to calculate HRs. We acknowledge that the OR and HR approximate a risk ratio only if the outcome is relatively rare.

relationships between specific risk factors and the outcomes of interest. Given that these studies do not use a causal inference framework, results are most appropriately interpreted as identifying factors possibly associated with increased or decreased risk of misuse, abuse, OUD, and OOD, and not necessarily etiological factors. In addition, statistical power for some risk factor analyses may have been insufficient to detect true associations, particularly for less common outcomes such as OUD, whereas some observed associations may also have been due to chance, as no multiplicity adjustment was considered.

PMRs 3033-1 and 3033-2 analyzed associations of potential risk factors with each opioid-related outcome using three types of models: unadjusted (i.e., crude, or univariate), demographically adjusted, and fully adjusted. Each type of analysis provides different information that might be important in different contexts. Although unadjusted analyses (results included in Appendices 6.5 and 6.6 for prospective and cross-sectional PMR 3033-1, respectively) may provide useful information on groups who may be at heightened risk of misuse, abuse, OUD, or OOD, we primarily focused on the fully adjusted results, which identify factors that are still associated with the outcomes after controlling for a large number of other potential risk factors. There are some important considerations in interpreting results from the fully adjusted models, however. Some analyses may have adjusted for factors in the underlying causal pathway between the exposure and outcome of interest, which could lead to an attenuated, or even null, observed association between the risk factor and outcome when a true association may exist. For example, in the cross-sectional PMR 3033-1 study, the number of reported ACEs (four or more versus zero) was associated with misuse, abuse, and OUD in the unadjusted analyses but not in the fully adjusted analyses; this does not necessarily imply that ACEs are not associated with these outcomes. Rather, the potential effect of these experiences may be mediated by other factors (e.g., adult mental health and substance use problems) also included in the models. In addition, for PMR 3033-1, most potential risk factors were not included in the fully adjusted models if unadjusted associations were not statistically significant. However, it is possible that some associations were not significant due to low power to detect the association, even for some true risk factors. This could have occurred due to low prevalence of the risk factor or low prevalence of the outcome (especially in the OUD models), leading to reduced precision of estimates. Although some strategies were considered to reduce the number of variables and improve power and precision in the fully adjusted models, the number of variables in the fully adjusted models was still quite high, likely reducing power and precision despite this effort. Again, this could have led to some clinically important associations not being statistically significant, as for some factors, 95% confidence intervals were quite wide.

Contextualizing the Findings of the Risk Factor Analyses

In the sections that follow, we summarize key risk factor findings from the PMR 3033-1 and 3033-2 studies, starting with the strongest and most consistent findings, and present findings in the context of both published literature and current OA labels where possible. FDA has previously conducted focused literature reviews on several specific potential opioid-related risk factors (i.e., dose, formulation, and duration of opioid use), as described below in the relevant sections. It is also useful to consider the findings of PMRs 3033-1 and 3033-2 in the context of published literature that considered multiple risk factors simultaneously, similar to what was done in the PMRs. For example, one published meta-analysis (Cragg et al. 2019) assessed factors associated with adverse opioid-related outcomes (e.g., any aberrant

drug behavior, opioid abuse, opioid addiction or dependence)[47] among people whose first exposure to opioids was through a prescription (whether for chronic or acute pain). Observational and experimental studies (e.g., randomized controlled trials and cross-sectional, prospective, or retrospective cohort or case-control studies) were included. This meta-analysis found that after mutual adjustment for all other risk factors of interest, risk factors associated with increased risk of adverse opioid-related outcomes included age <40 years, male sex, predominant use of an IR/SA OA (versus an ER/LA OA), increasing opioid dose, previous substance use, and any mental health diagnosis; use of an ADF opioid was associated with decreased risk of an adverse opioid-related outcome. Finally, we comment on relevant aspects of current OA labels to highlight the extent to which findings from the PMR 3033-1 and 3033-2 support what is already in labeling.

Health- and Pain-Related Risk Factors

Substance Use Disorder History

Studies 3033-1 and 3033-2 suggest that a notable proportion of patients starting long-term OA therapy have a personal history of SUD, whether in the past year (5% to 8% in the PMR 3033-1 studies, 3.6% to 6% overall in PMR 3033-2) or prior to the past year (approximately 30% in PMR 3033-1 studies). These markers of a personal history of previous SUD were consistently associated with an increased risk of opioid misuse, opioid abuse, OUD, and OOD. A history of parental substance use was also common (almost half of patients in both cohorts of prospective PMR 3033-1 and in cross-sectional PMR 3033-1 had a history of parental substance use) and was associated with opioid misuse and abuse in some analyses.

The *Warnings and Precautions* section of the current OA labeling recommends that clinicians consider a patient's "personal or family history of substance abuse (including drug or alcohol abuse or addiction)" but also clarifies that the potential for addiction, abuse, and misuse should not "prevent the proper management of pain in any given patient."

Mental Health Conditions

Baseline or history of mental health conditions—including major depression, PTSD, generalized anxiety disorder, and psychosis—were quite common in all the study populations. Depression and psychosis were significantly associated with OOD at multiple sites and in the meta-analysis in PMR 3033-2. Major depression was strongly associated with misuse and OUD in both the demographically and fully adjusted models in the cross-sectional PMR 3033-1 study. Other associations between mental health conditions and misuse, abuse, and OUD were also observed in PMR 3033-1, although more frequently in the demographically adjusted than in the fully adjusted models. As described in the beginning of this section, the lack of significant associations in fully adjusted models may have been due to the models' inclusion of factors (e.g., substance use) in the underlying causal pathway between mental health conditions and the outcomes. Again, limited power for certain analyses, particularly for OUD outcomes, also may have been a factor.

[47] While the meta-analysis refers to this composite outcome as misuse, we have revised the terminology here for clarity.

Current OA labeling notes that, with regard to addiction, abuse, and misuse, "risks are increased in patients with a personal or family history of mental illness (e.g., major depression)" but that potential for these risks should not "prevent the proper management of pain in any given patient."

Nonopioid CNS-Active Medication Use

In PMR 3033-2, baseline use of CNS-active medications such as antidepressants, benzodiazepines, and gabapentinoids was common at baseline and remained high throughout the 5-year follow-up period. Baseline antidepressant use was associated with an increased risk of OOD at all sites as well as in the meta-analysis, and baseline antipsychotic use and benzodiazepine use were both associated with an increased risk of OOD in at least two study sites and in the meta-analysis (fully adjusted models). Gabapentinoid use at baseline was significantly associated with OOD at one site in the fully adjusted model.

In both the prospective and cross-sectional PMR 3033-1 studies, antidepressants were the most used nonopioid CNS active medications, with use at baseline by half or more of patients,[48] and gabapentinoids were used by approximately 40% of patients. In the PMR 3033-1 prospective study, gabapentinoid use was associated with an increased risk of misuse and OUD in the ER/LA cohort, while antidepressants had a strong association with OUD risk in the LtOT cohort (fully adjusted models). In cross-sectional PMR 3033-1, use of antipsychotics was associated with increased prevalence of abuse in the fully adjusted model.

Current OA labeling includes the following language in the *Boxed Warning*: "Concomitant use of opioids with benzodiazepines or other CNS depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in patients for whom alternative treatment options are inadequate; limit dosages and durations to the minimum required; and follow patients for signs and symptoms of respiratory depression and sedation." Additional information in the *Clinically Significant Drug Interactions* section specifies additional examples of CNS depressants, including anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, and other opioids. In 2019, FDA required new warnings about the risk of respiratory depression with gabapentinoids and issued PMRs to the NDA holders to conduct clinical studies further evaluate their abuse potential, particularly in combination with opioids (FDA 2024b). FDA has engaged in research to study possible drug interactions between selective serotonin reuptake inhibitors (SSRIs) and opioids (Florian et al. 2022) and continues to explore this as a potential safety signal.

Nonpsychiatric Comorbidities and Healthcare Utilization

Nonpsychiatric comorbidities and hospital use were assessed as potential risk factors in the PMR 3033-1 studies but not PMR 3033-2. These factors were not consistently associated with misuse, abuse, or OUD; however, when there was an association, increased comorbidities and healthcare utilization were often associated with lower risk of an outcome (with some exceptions). There are several potential explanations for these observed inverse associations: for example, perhaps patients who are seriously ill may be truly less likely to misuse or abuse their opioids; or increased engagement with healthcare providers could have a protective effect, for example, through screening and treatment of mental health

[48] In prospective study 3033-1, 60% of ER/LA cohort patients and 50% of LtOT cohort patients. In cross-sectional study 3033-1, 62% of patients.

disorders, opportunities for proactive adjustment of pain medicine regimens, or referral for needed social support services.

Current OA labeling warns of increased risk of respiratory depression associated with specific nonpsychiatric comorbidities (e.g., chronic obstructive pulmonary disease) but does not otherwise comment on higher or lower risk patient populations based on general comorbidity burden or healthcare utilization.

OA-Related Risk Factors

Overarching Considerations Regarding OA-Related Risk Factors

When interpreting associations between OA-related risk factors and misuse, abuse, OUD, and OOD, potential interrelationships among OA formulation, dose, duration of therapy, and opioid moiety must be considered. The multiple analyses conducted across the various outcomes within the cross-sectional and prospective PMR 3033-1 studies and PMR 3033-2 varied in terms of the OA-related factors assessed and which risk factors were included in the fully adjusted models. Again, these studies did not aim to control for confounding to assess specific, causal associations, and the OA-related factors included in each model affect the interpretation of the other risk factor associations. For example, including OA dose in the fully adjusted model for PMR 3033-2 would be expected to affect the estimate for the correlated factor, formulation (i.e., ER/LA versus IR/SA OA). In models that included either OA dose or formulation (but not both), it was difficult to completely separate the unique associations of each factor with the outcomes of interest. It is also important to consider that these factors could also have been effect measure modifiers; however, these analyses did not assess effect modification or interactions between variables.

Baseline OA Dose and Duration

Increasing dose category (QMME) during the 90-day qualifying period was strongly and consistently associated with OOD in PMR 3033-2. In PMR 3033-2, each category of qualifying dose higher than the reference category of <1,500 MMEs (an average of 16.7 MMEs/day, or the equivalent of two to three 5 mg oxycodone tablets) was associated with increased risk of OOD at all four study sites and in the meta-analysis (fully adjusted models). In contrast, findings in the PMR 3033-1 studies were mixed on the associations between baseline dose and misuse and abuse. In the prospective PMR 3033-1 study, higher average daily dose at baseline was associated with misuse in the ER/LA cohort and with abuse in the LtOT cohort (fully adjusted models). Average daily dose was not associated with misuse or abuse in PMR 3033-1 cross-sectional study and was not associated with OUD in either the prospective or cross-sectional 3033-1 studies; however, there may have been insufficient power to detect associations. This includes limited power to detect an association in unadjusted analyses, which could have led to dose not being included in the fully adjusted model in some analyses.

The clear association between increasing dose category and OOD in PMR 3033-2 is consistent with FDA reviews of published literature (Coyle et al. 2018; Radin et al. 2019; Janiszewski et al. 2023), which have found that among adults, higher dispensed OA doses are associated with higher risks of fatal and nonfatal overdose in a dose-dependent manner, even after controlling for confounding. In contrast to the findings from the cross-sectional and prospective PMR 3033-1 studies, some published studies have found an association between higher prescribed opioid doses and increased risk of OUD; however, these studies had important limitations, including incomplete capture of OUD in electronic healthcare data

and inability to establish a clear temporal relationship. Some published studies also found an association between higher prescribed opioid doses and an increased risk of various composite opioid-related adverse outcomes, some of which included misuse or abuse measured in variable ways.

Duration of Schedule II OA therapy during the 6-month baseline period did not have a consistent association with misuse, abuse, or OUD in the one study in which this risk factor was assessed (prospective PMR 3033-1). In fully adjusted analyses, the only notable association with duration of Schedule II OA therapy (during the baseline period) was an increased risk of misuse with increasing duration of use in the ER/LA and LtOT cohorts. It is important to keep in mind, however, that changes in duration of use during the one-year follow-up period were not assessed in relation to the outcomes of interest, given that the study design did not allow for any covariates to be updated over time. FDA's review of the published literature (Greene et al. 2023) found that the relationship between duration of OA therapy and adverse outcomes may change throughout a patient's therapy episode. Some published studies showed that the risk of adverse outcomes was highest in the first few months of OA therapy, a period in which outcomes were not assessed in these PMRs. Other published studies found that the risk of adverse outcomes increased as the duration of therapy increased. Since the risk factor analysis in the prospective PMR 3033-1 study only examined duration of opioid use prior to entry into the cohort (i.e., during the baseline period), it was not able to assess changes in risk associated with differing durations of use during follow-up.

The *Dosage and Administration* section of current OA labeling for both IR/SA and ER/LA OAs advises that prescribers "Use the lowest effective dosage for the shortest duration of time consistent with individual patient treatment goals." In 2023, the labeling was updated to emphasize the relationship between increased dose and increased risk of OOD. All current OA labeling advises, "Because the risk of overdose increases as OA doses increase, reserve titration to higher doses of [DRUG] for patients in whom lower doses are insufficiently effective and in whom the expected benefits of using a higher dose OA clearly outweigh the substantial risks."

Tapering or discontinuing opioid therapy is another consideration related to dose and duration of long-term OA therapy; however, neither PMR 3033-1 nor 3033-2 was designed to assess the associations between changes in OA dose or discontinuation of opioids and overdose or other adverse outcomes. In 2019, FDA required new language in OA labeling to provide information on safer tapering of OAs after becoming aware of serious signs and symptoms of withdrawal, uncontrolled pain, psychological distress, and suicide occurring among patients whose OA dose was rapidly decreased, or the medications suddenly discontinued. Some published observational studies have also found associations between prescription opioid discontinuation and increased heroin use (Binswanger et al. 2020) or increased nonprescribed opioid pain reliever use (Coffin et al. 2020). With or without tapering or discontinuation of OAs, use of nonprescribed opioids is a serious public health concern, even more so since heroin, and then illicitly manufactured synthetic opioids and falsified (i.e., counterfeit) pills became widespread. PMR 3033-1 identified very few cases of heroin use disorder one year after initiation of long-term OA therapy; however, none of the OUD definitions in this study were specifically designed to assess OUD involving illicitly made fentanyl or counterfeit opioids, and the OOD definition used in PMR 3033-2 did not specify which opioids were involved in the overdose.

OA Formulation (ER/LA Versus IR/SA)

We are not able to draw firm conclusions from these studies regarding associations between OA formulation and risks of misuse, abuse, OUD, or OOD. No associations were observed between predominant OA formulation and any of the outcomes in the fully adjusted models in the prospective PMR 3033-1 study or in the main cohort of PMR 3033-2. In the PMR 3033-1 cross-sectional study, predominant ER/LA OA use (versus predominant IR/SA OA use) was associated with lower odds of misuse in both demographically and fully adjusted models; formulation did not meet criteria for inclusion in the fully adjusted models for abuse or OUD. Inferences about formulation are limited by the analytic approach focusing on *predominant* ER/LA OA use, rather than *only* ER/LA OA use during the qualifying period among individuals who all had *at least some* ER/LA OA use. In the cross-sectional 3033-1 study, this resulted in all patients in the predominant IR/SA category having both ER/LA and IR/SA OA prescriptions.

The exploratory switch/add analysis in PMR 3033-2 adds some information on OA formulation. This subgroup analysis found that compared to patients on a stable IR/SA OA who switched to or added a different IR/SA OA, OA patients who switched to or added an ER/LA OA had a moderately increased risk of OOD by the end of the follow-up period, after adjusting for average daily dose in the 90 days before the switch/add event. There was an increase in median daily dose after the switch/add of an ER/LA OA (+ 12.8 daily MMEs), in contrast to a decrease after the switch/add of a different IR/SA OA (-5.4 daily MMEs), and these changes in dose were not adjusted for in the analysis. These findings suggest that an increase in dose in patients who switched to or added an ER/LA OA may have been the primary driver of the observed association between switching to or adding an ER/LA OA and increased risk of OOD, although the analysis could not tell us whether the change in formulation may have also been a contributing factor.

A focused FDA review of published epidemiologic literature found little information on associations between ER/LA versus IR/SA OA formulation and misuse, abuse, or OUD; however, there was some evidence that individuals who were prescribed and/or used any ER/LA OA (alone or in addition to an IR/SA OA, depending on the study, versus only IR/SA OAs) had an increased risk of overdose during the course of an opioid prescription (e.g., on a day with an active opioid prescription) and shortly after an initial opioid prescription (e.g., within 2 weeks to 1 month of beginning opioid therapy) (Miller et al. 2015; Mudumbai et al. 2019; Chua et al. 2020), but not during later time periods. The finding of no association between predominant OA formulation and overdose risk over a 5-year follow-up period aligns with evidence from the literature of no increased risk of overdose during periods farther from an initial OA prescription or OA use. Because patients in PMR 3033-2 were required to be on LTOT for at least 70 of the 90 days before entering the study, OOD risks shortly after initiating OA therapy were not assessed.

The ER/LA OA labeling *Limitations of Use* section currently contains the following language: “Because of greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve [DRUG] for use in patients for whom alternative treatment options (e.g., non-OAs or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.”

Predominant Opioid Moiety

In the PMR 3033-2 fully adjusted model, compared to predominant use of hydrocodone during the baseline period, predominant use of methadone, morphine, and oxycodone during the baseline period were associated with significantly increased OOD risk in at least one of the individual sites or the meta-analysis. In the prospective 3033-1 study, compared to predominant use of oxycodone, predominant use of hydromorphone was associated with a substantially increased risk of abuse in both the ER/LA and LtOT cohorts. Again, the prospective 3033-1 study did not assess changes in opioid moiety over time, and only baseline dose (which may be correlated with moiety) was considered for inclusion in the models. In addition, the results only show comparisons of each opioid moiety with oxycodone, but comparisons between other pairs of opioid moieties were not assessed. In the fully adjusted models for the cross-sectional 3033-1 study, compared to predominant use of oxycodone, there were no individual opioid moieties associated with a significantly higher or lower odds of misuse, abuse, or OUD. Across studies, there was limited power to assess less commonly used OAs.

Because risks of misuse, abuse, OUD, and overdose apply to all OAs, distinctions are not made in OA labeling with regard to differences in risk across opioid moieties.

Abuse-Deterrent Formulation (ADF) Use

Use of an ADF OA was examined in PMR 3033-1 but not PMR 3033-2. Findings from the cross-sectional and prospective PMR 3033-1 studies were mixed. In the cross-sectional PMR 3033-1 demographically and fully adjusted models, patients who used an ADF OA had lower odds of misuse and abuse than patients who did not use an ADF OA. In contrast, ADF use did not meet criteria for inclusion in any fully adjusted models in the prospective PMR 3033-1 study. These PMR studies were not specifically designed to assess whether these formulations meaningfully reduce the risks of misuse, abuse, OUD, or overdose, and OAs with approved ADF labeling were issued individual PMRs to examine this question (for example, see the September 2020 joint DSaRM/AADPAC AC (FDA 2020b) meeting discussion of the findings of the PMRs on the effects of OxyContin's reformulation). A discussion of ADF labeling based on postmarketing studies is beyond the scope of this document and is not the focus of this AC meeting.

Sociodemographic and Genetic Factors

Sociodemographic Risk Factors

Results of sociodemographic risk factor analyses were mixed. Male (versus female) sex was strongly and consistently associated with misuse, abuse, and OUD in the PMR 3033-1 cross-sectional study, but sex was not associated with any outcome in prospective PMR 3033-1 or with OOD in PMR 3033-2. In the prospective PMR 3033-1 study, age did not have a consistent association with the primary outcomes; compared to patients <40 years of age, patients ≥60 years had increased odds of misuse in the ER/LA cohort but no association with any outcome in the LtOT cohort. Age was not a significant risk factor in any of the cross-sectional PMR 3033-1 analyses. In PMR 3033-2, the risk of OOD generally decreased with increasing age at three of the four study sites, with some differences by site. In prospective PMR 3033-1, other or mixed (versus white) race was associated with increased risks of misuse and abuse in the ER/LA cohort. Race was not included as a risk factor in PMR 3033-2.

Current OA labeling does not comment on most sociodemographic risk factors for misuse, abuse, OUD, or overdose, other than noting, "Life-threatening respiratory depression is more likely to occur in elderly

patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients."

Genetic Risk Factors

Overall, the findings of the PMR 3033-1 cross-sectional and prospective studies found that the interrogated single nucleotide polymorphisms (SNPs) do not appear to be associated with opioid misuse, abuse, or OUD; however, the interrogated SNPs within the selected genes were limited in their ability to capture the effects of genetic variabilities on opioid treatment outcomes, and the rationale for selecting these SNPs lacked robustness. Furthermore, the analysis conducted was exploratory in nature and included only limited variants within these genes (see Appendix Section 6.8 for more information). A more thorough assessment would be needed to make conclusive statements about the role of genetics in opioid misuse or abuse.

There is no information in current OA labeling regarding genetic risk factors (other than noting that risks of addiction, misuse, and abuse are increased in patients with a family history of substance abuse) or regarding genetic testing. In December 2023, FDA (Center for Devices and Radiologic Health) approved AvertD, the first test that uses DNA to assess whether certain individuals may have an elevated risk of developing OUD. This approval occurred after the end of the PMR 3033-1 and 3033-2 study periods, and a discussion of the role of this or other potential genetic tests in clinical management is beyond the scope of this briefing document and will not be a point of discussion for this AC meeting.

4.3 Summary

Together, the PMR 3033-1 and 3033-2 studies provide ranges of quantitative estimates of the known serious risks of misuse, abuse, OUD, and overdose in various patient populations with long-term OA use. All these risks are currently described in the *Boxed Warning* and other sections of OA labeling, although labeling does not provide any quantification of these adverse outcomes. Mitigation of these risks is also an overarching goal of the current OA REMS and of many other actions FDA has taken since these PMRs were issued (FDA 2024c).

Estimates generated by these studies are generally within the range of those reported in previous published studies in similar populations; however, robustness of the PMR study results is enhanced by the inclusion of prospectively collected longitudinal data, use of instruments and algorithms specifically validated for use in these study populations, the multisite study population including both publicly and privately insured patients, and the use of prespecified protocols and external review processes. Still, interpretation of these findings must consider the study limitations, as well as the limited patient populations to which inferences can be made. Foremost, the studies included only those with long-term use and therefore provided no information on risks associated with Schedule II OA use of less than 3 months' duration. The different study cohorts also had varying eligibility criteria, with a requirement of ER/LA OA use in some cohorts, and especially in PMR 3033-2 much of the study period predated more recent changes in opioid prescribing practices and in the nature of the opioid crisis.

Furthermore, estimates for OUD depended substantially on the outcome definitions used (i.e., pain-adjusted or standard DSM-5-OUD), highlighting uncertainties and challenges in identifying OUD in patients using OAs long-term for pain.

Eligibility criteria for the PMR 3033-2 cohort required that patients did not have a documented overdose during the baseline or qualification periods, likely selecting for patients at lower risk of OOD during the

follow-up period. PMR 3033-2 also had substantial loss to follow-up, raising the possibility of biased estimates (if patients who remained in the cohort differed systematically from those who were lost to follow-up in their risk of experiencing the outcome). In addition, because follow-up was censored at the first OOD event, a fatal overdose that followed a nonfatal overdose event during follow-up would not be captured in the OOD estimates. Finally, OOD estimates were more than twice as high in populations receiving Medicaid as in those with commercial insurance coverage or under managed care, precluding the determination of a single risk estimate and serving as a reminder of the individual- and system-level factors that may converge to increase OA-related harms.

The analyses of potential risk factors in these studies were exploratory and were not designed to evaluate prespecified causal relationships. Statistical power for some analyses may have been insufficient to detect true associations, particularly with less common outcomes such as OUD, whereas some statistically significant associations may also have been due to chance, as no multiplicity adjustment was considered. Additionally, both overadjustment and underadjustment was possible in the fully adjusted models, as each association was adjusted for all other risk factors in the model, selected based on meeting a statistical threshold in univariate models, regardless of whether those other factors were confounders, mediators, or effect measure modifiers of the particular risk factor of interest.

Main findings from the risk factor analyses from PMR studies 3033-1 and 3033-2 are generally consistent with existing knowledge and with current OA labeling. Both studies identified some factors that were significantly associated with multiple outcomes across multiple cohorts, when adjusted for the other risk factors in the model—most notably, having a personal history of SUD, which was associated with all primary outcomes in both PMR studies. Depression and psychosis were significantly associated with higher risk of OOD in PMR 3033-2, as were several classes of CNS-active medications used to treat these disorders. Multiple mental health disorders were also associated with misuse, abuse, and OUD in PMR 3033-1, primarily in the demographically adjusted models, but less commonly in the fully adjusted models. Higher opioid dose (during the 90-day qualification period) was strongly and significantly associated with an increased risk of OOD in PMR 3033-2. In PMR 3033-1, baseline opioid dose was associated with risk of misuse and abuse in some analyses, but not with OUD. These and other findings from the risk factor analyses contribute to our understanding of misuse, abuse, OUD, and OOD, but the study limitations described previously should be taken into account when interpreting them.

After controlling for differences in dose during the qualification period, formulation was not associated with risk of OOD, but an exploratory analysis in Study 3033-2 found that adding or switching from an IR/SA OA to an ER/LA OA (compared to adding or switching to another IR/SA OA) was associated with a modestly increased risk of OOD even after adjusting for differences in daily dose just before the add/switch event. Adding or switching to an ER/LA OA also led to an increase in dose (compared to adding or switching to an IR/SA OA, which resulted in a decrease in dose), however, suggesting that the dose increase—as opposed to change in formulation—may be the primary driver of the increased OOD risk observed after the addition of or switch to an ER/LA OA. Baseline use of some opioid moieties had greater risk of certain outcomes relative to other moieties (e.g., predominant use of hydromorphone was associated with a greater risk of abuse than did predominant use of oxycodone, and predominant methadone, morphine, and oxycodone use each were associated with a greater risk of OOD than predominant hydrocodone use), but these associations were not consistent across cohorts or outcomes.

Other factors (e.g., age, sex, parental substance use) showed strong associations in some analyses but not in others.

In addition to the main findings, these studies provide other descriptive information about patient populations using OAs long term. For example, some of the strongest risk factors for OUD and/or overdose, such as having a personal history of SUD or a mental health condition, were quite common at baseline. The relationships between misuse, abuse, and OUD were explored in depth but were not entirely straightforward; because OUD and overdose were studied separately, it was not possible to examine the relationships between them directly. Finally, some important aspects of OA prescribing and risk have become more salient as the opioid landscape has evolved, for example, relationships between changes in dose or discontinuation of OAs and risk of overdose, suicide, or use of illicit opioids. These were not examined in these studies but are important considerations for interpreting the study findings.

5 References

Guidances for Industry

Draft guidance for industry *Drug Abuse and Dependence Section of Labeling for Human Prescription Drug and Biological Products — Content and Format* (July 2019)

Guidance for industry *Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework* (June 2019)

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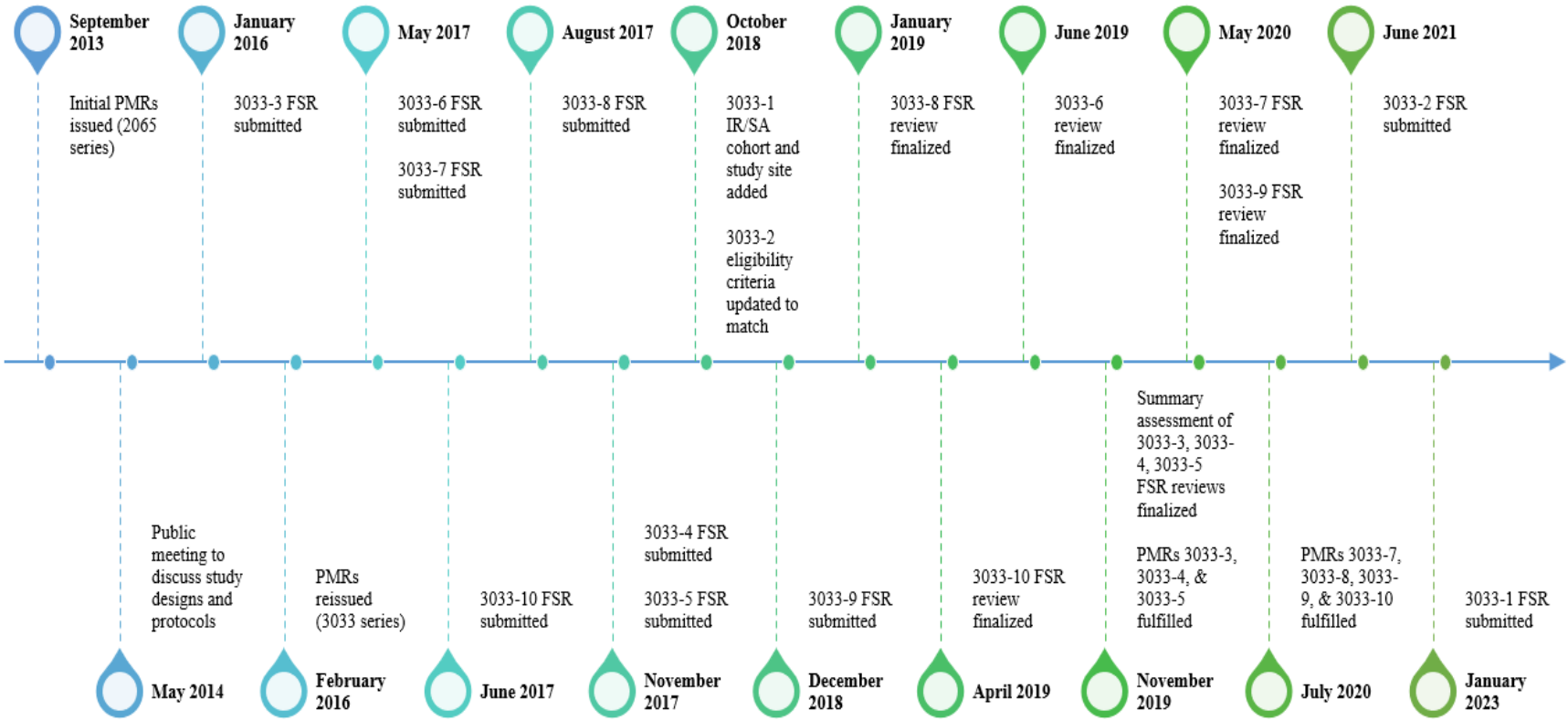
6 Appendix

6.1 Timeline of Significant Events for the Observational ER/LA OA PMRs

Figure 7. Timeline of Significant Events for the Observational ER/LA OA PMRs[1]



Source: FDA-generated figure.

[1] Many of the study reports, including the FSRs for the main studies, PMRs 3033-1 and 3033-2, were followed by information requests from FDA and submissions of additional or corrected results and study reports.

Abbreviations: ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; FSR, final study report; IR/SA, immediate-release/short-acting; OA, opioid analgesic; PMR, postmarketing requirement

6.2 Drug Utilization Analyses

6.2.1 Drug Utilization Methods

DEPI II used proprietary drug utilization databases available to FDA to conduct the drug utilization analyses. The drug products selected, and the database descriptions are available in Appendix Section 6.2.4. We used the IQVIA National Prescription Audit™ (NPA) database to obtain the estimated annual number of OA prescriptions dispensed from U.S. outpatient retail and mail-order pharmacies from 1992 to 2023. Annual population-adjusted prescription data were provided using U.S. Census data to calculate the estimated number of OA prescriptions dispensed per year adjusted for 100 U.S. residents. We also used NPA to obtain the estimated annual number of ER/LA OA prescriptions, stratified by prescriber specialty, dispensed from U.S. outpatient retail and mail-order pharmacies from 2019 to 2023 as well as the estimated annual number of units of OAs (e.g., tablets, milliliters, patches) dispensed from 1992 to 2023. We used these data and publicly available MME conversion factors (McPherson 2018; CDC 2019; GlobalRPh 2019; Medscape 2022) to calculate estimated annual dispensed MMEs using the formula: units dispensed multiplied by MME conversion factor multiplied by product strength. We used these data to calculate the aggregate, average MMEs per prescription, by formulation, dispensed from U.S. retail and mail-order pharmacies from 1992 to 2023 using the formula: total MMEs divided by total prescription volume.

Additionally, we used Syneos Health Research and Insights LLC., Treatment Answers™ with Pain Panel to obtain diagnosis data associated with drug use mentions[49] of OA products during office visits, by formulation, from 2019 to 2023, aggregated. The diagnoses are based on the ICD-10[50] codes.

For age-stratified data, we used the Symphony Health Metys™ database to obtain the nationally estimated number of prescriptions dispensed for ER/LA and IR[51] OA products from U.S. retail and mail-order pharmacies, by age group, from 2019 to 2023, annually.

We used the Symphony Health Integrated Dataverse (IDV®) database, an all-payor prescription transaction database, to identify a sample of patients with OA prescriptions dispensed during a study period of 2021 to 2022. Patients were followed for 1 year and classified into four mutually exclusive groups based upon the number of dispensed OA prescriptions as detailed below:

1. Presumed short-term OA therapy: two or fewer ER/LA and/or two or fewer IR OA prescriptions
2. Presumed long-term OA therapy
    a. Predominantly IR OA long-term therapy: three or more IR and either no ER/LA or one to two ER/LA OA prescriptions
    b. Predominantly ER/LA OA long-term therapy: three or more ER/LAs and either no IR or one to two IR OA prescriptions
    c. Both IR and ER/LA OA long-term therapy: three or more IR and three or more ER/LA OA prescriptions

[49] Drug use mentions refer to office-based visits where a health care practitioner discussed a specified drug or drug class with a patient. These discussions may not necessarily have resulted in prescriptions being generated or drugs being dispensed to patients.
[50] The ICD-10 is a medical classification list by the World Health Organization that contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases.
[51] IR denotes immediate-release or short-acting

These analyses were performed for patients with any OA use during the study period as well as patients with incident OA use during the study period, defined as no OA prescriptions dispensed within the previous 365 days.

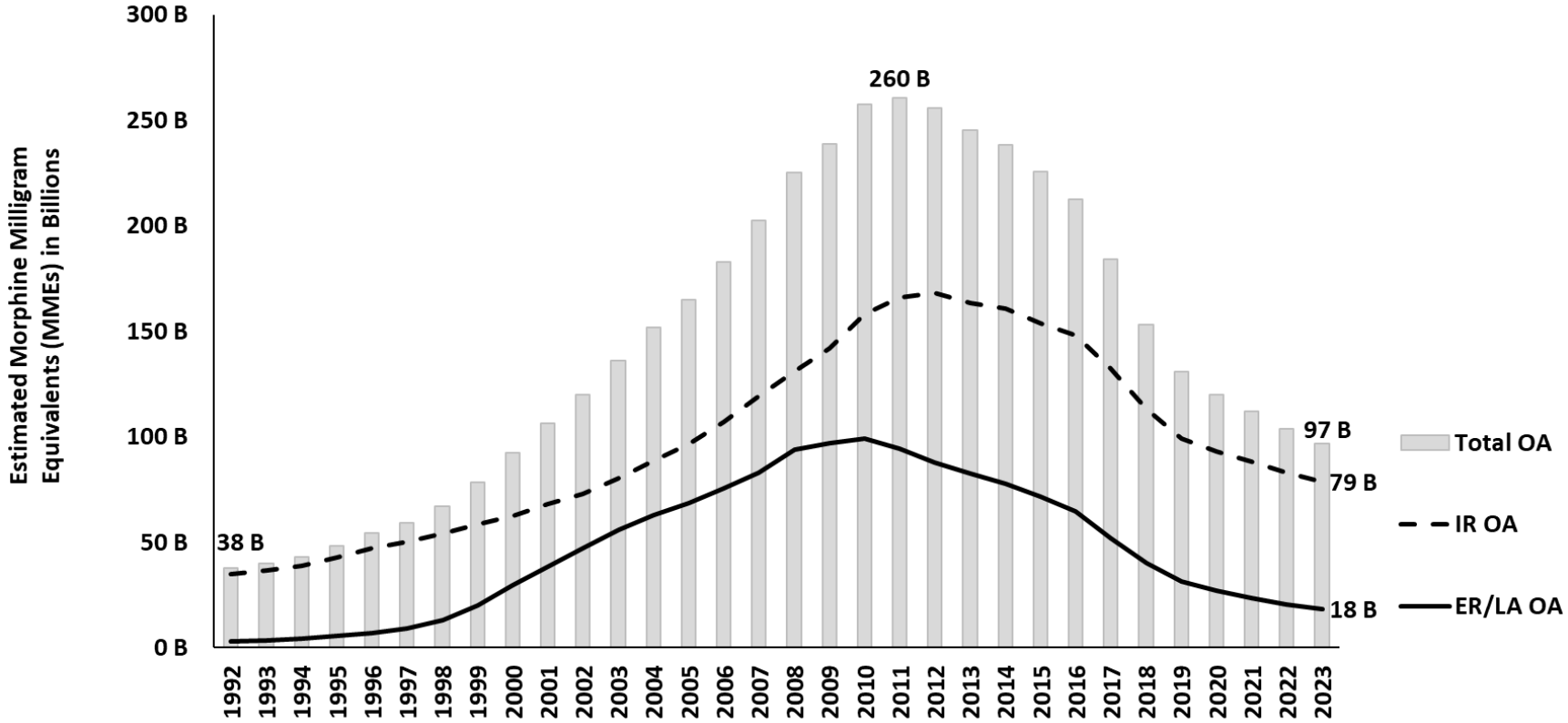
Lastly, we used the IDV database to evaluate average ER/LA OA starting daily doses among a sample of patients with new ER/LA OA therapy during two study periods: September 2017 to August 2018 and September 2022 to August 2023. New ER/LA OA therapy was defined as no ER/LA OA prescriptions dispensed in the previous 90 days. Patients were classified based upon having had IR OA therapy in the previous 90 days or not. Daily dose was calculated as total MMEs in the prescription divided by days' supply, using the days' supply on the prescription transaction. Patients were followed for 6 months and classified into two groups based upon the number of ER/LA OA dispensed prescriptions during that time:

1. One or two ER/LA OA prescriptions, including the initial prescription
2. Three or more ER/LA OA prescriptions.

6.2.2 Drug Utilization Results

Appendix Figure 8 shows the estimated annual number of morphine milligram equivalents (MMEs) for OAs, stratified by formulation, dispensed from U.S. retail and mail-order pharmacies from 1992 to 2023. In 2023, pharmacies dispensed approximately 97 billion MMEs, a 63% decrease from a peak of 260 billion MMEs in 2011. In 2023, pharmacies dispensed 18 billion MMEs of ER/LA OA products (representing 19% of all MMEs), an 82% decrease from a peak of 99 billion MMEs in 2010. In 2023, pharmacies dispensed 79 billion MMEs for IR OA products (81% of all MMEs), a 53% decrease from a peak of 168 billion MMEs in 2012.

Figure 8. Estimated Annual MMEs for Opioid Analgesics Dispensed From U.S. Retail and Mail-Order Pharmacies, Stratified by Formulation, 1992 to 2023

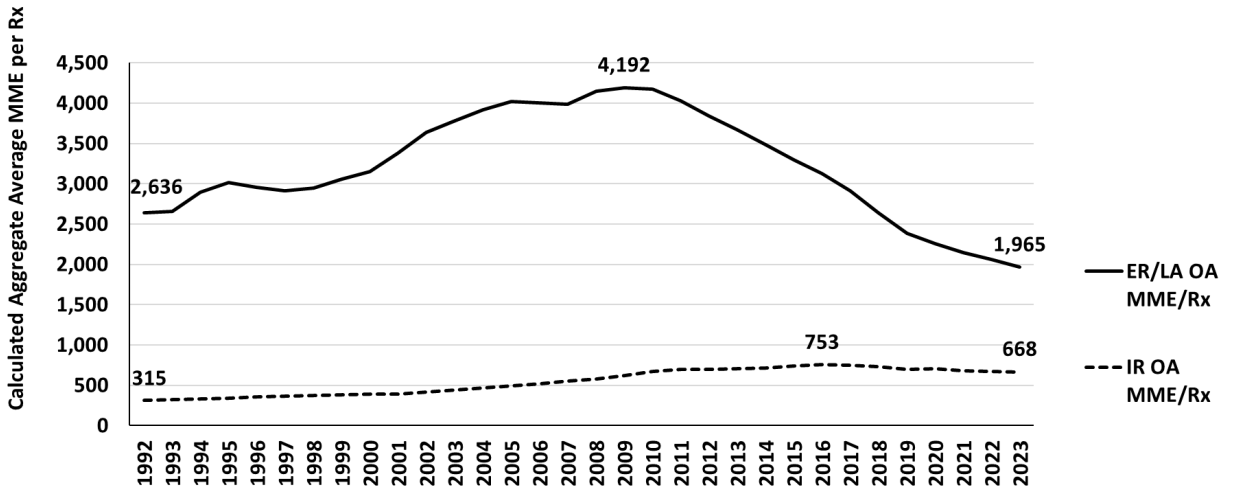


Source: IQVIA National Prescription Audit™, U.S. Launch edition. Data years 1992-2023. Data extracted July 2024. Sources for MME conversion factors: Centers for Disease Control and Prevention, NDC and Oral MME Conversion File, 2019 version, https://archive.cdc.gov/www_cdc_gov/opioids/data-resources/index.html. McPherson ML, *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, 2nd Edition, American Society of Health-System Pharmacists, 2018. GlobalRPh, Opioid conversions calc (single agent) equianalgesic, http://globalrph.com/narcoticonv.htm. Medscape, Opioid Equivalents and Conversions, https://emedicine.medscape.com/article/2138678-overview.

Abbreviations: B, billions; ER/LA OA, extended-release/long-acting opioid analgesics; IR OA, immediate-release or short-acting opioid analgesics; MME, morphine milligram equivalent; OA, opioid analgesic; total OA, total opioid analgesics; U.S., United States

Appendix Figure 9 shows the estimated aggregate, average MMEs per OA prescription, by formulation, dispensed from U.S. Retail and Mail-Order Pharmacies from 1992 to 2023. In 2023, ER/LA OA prescriptions had an average of 1,965 MMEs per prescription, a decrease from a peak of 4,192 MMEs per prescription in 2009. In 2023, IR OA prescriptions had an average of 668 MMEs per prescription, a decrease from a peak of 753 MMEs per prescription in 2016.

Figure 9. Estimated Aggregate, Average MMEs per Prescription for Opioid Analgesics Dispensed from U.S. Retail and Mail-Order Pharmacies, Stratified by Formulation, 1992 to 2023 Annually



Source: IQVIA National Prescription Audit™, U.S. Launch edition. Data years 1992-2023. Data extracted July 2024. Sources for MME conversion factors: Centers for Disease Control and Prevention, NDC and Oral MME Conversion File, 2019 version, https://archive.cdc.gov/www_cdc_gov/opioids/data-resources/index.html. McPherson ML, *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, 2nd Edition, American Society of Health-System Pharmacists, 2018. GlobalRPh, Opioid conversions calc (single agent) equianalgesic, http://globalrph.com/narcoticonv.htm. Medscape, Opioid Equivalents and Conversions, https://emedicine.medscape.com/article/2138678-overview.

Abbreviations: ER/LA OA, extended-release/long-acting opioid analgesics; IR OA, immediate-release or short-acting opioid analgesics; MME, morphine milligram equivalent; OA, opioid analgesics; Rx, prescription; U.S., United States

Appendix Table 23 shows the estimated annual number of OA prescriptions, stratified by formulation and patient age group, dispensed from U.S. retail and mail-order pharmacies from 2019 to 2023. During the study period, OA prescriptions were most commonly dispensed to adult patients 18 years old or older. In 2023, patients aged 18 to 64 years were dispensed approximately 5 million ER/LA OA prescriptions (55% of all ER/LA OA prescriptions) and patients 65 years or older were dispensed 3.8 million ER/LA OA prescriptions (42%). For IR OA prescriptions, 67 million prescriptions (57%) were dispensed to patients 18 to 64 years old in 2023, and 46 million prescriptions (39%) were dispensed to patients 65 years or older in 2023.

Table 23. Estimated Number of Opioid Analgesic Prescriptions Dispensed From U.S. Retail and Mail-Order Pharmacies, Stratified by Formulation and Age Group, 2019 to 2023, Annually

	2019		2020		2021		2022		2023	
	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)
Total OA	**155,431,068**	**100%**	**144,823,176**	**100%**	**137,939,003**	**100%**	**131,003,147**	**100%**	**125,863,403**	**100%**
ER/LA OA	13,525,561	9%	12,142,956	8%	10,812,829	8%	9,889,802	8%	9,172,234	7%
≤17 years old	12,631	<1%	11,476	<1%	9,945	<1%	8,243	<1%	7,801	<1%
18-64 years old	8,535,070	63%	7,478,852	62%	6,399,544	59%	5,621,260	57%	5,048,932	55%
65+ years old	4,391,661	32%	4,264,497	35%	4,002,078	37%	3,893,300	39%	3,834,192	42%
Unknown age	586,199	4%	388,131	3%	401,262	4%	366,999	4%	281,309	3%
IR OA	141,905,507	91%	132,680,220	92%	127,126,174	92%	121,113,345	92%	116,691,169	93%
≤17 years old	1,948,678	1%	1,593,743	1%	1,529,190	1%	1,422,157	1%	1,404,466	1%
18-64 years old	90,157,289	64%	83,133,474	63%	77,585,216	61%	71,397,034	59%	66,810,194	57%
65+ years old	45,250,839	32%	44,805,273	34%	44,552,883	35%	45,150,283	37%	45,886,392	39%
Unknown age	4,548,701	3%	3,147,730	2%	3,458,885	3%	3,143,871	3%	2,590,117	2%

Source: Symphony Health Metys™. Data years 2019-2023. Data extracted August 2024.

Abbreviations: ER/LA OA, extended-release/long-acting opioid analgesics; IR OA, immediate-release or short-acting opioid analgesics; N, number; OA, opioid analgesics; U.S., United States

Appendix Table 24 shows national estimates generated from U.S. office-based practitioner survey data where IR or ER/LA OA products were mentioned in association with a diagnosis during patient office visits, by indication, from 2019 to 2023, aggregated.

During the study period, *diseases of the musculoskeletal system and connective tissue* (ICD-10 M00-M99) accounted for 64% of the total use mentions for ER/LA OA products, followed by *diseases of the nervous system* at 12% (ICD-10 G00-G99), *mental and behavioral disorders* at 7% (ICD-10 F00-F99) and *neoplasms* at 7% (ICD-10 C00-D49).[52] For IR OA products, *diseases of the musculoskeletal system and connective tissue* accounted for 43% of total use mentions, followed by *injury, poisoning and certain external cause consequences* at 16% (ICD-10 S00-T98) and *diseases of the digestive system* at 8% (ICD-10 K00-K95).[53]

[52] Some examples of *diseases of the musculoskeletal system and connective tissue* (ICD-10 M00-M99) include *dorsalgia* (ICD-10 M54) and *osteoarthritis of the knee* (ICD-10 M17); examples of *diseases of the nervous system* (ICD-10 G00-G99) include *pain, not elsewhere classified* (ICD-10 G89) and *disorders of autonomic nervous system* (ICD-10 G90); examples of *mental and behavioral disorders* (ICD-10 F00-F99) include *opioid related disorders* (ICD-10 F11) and *bipolar disorder* (ICD-10 F31); examples of *neoplasms* (ICD-10 C00-D49) include *malignant neoplasm of bronchus and lung* (ICD-10 C34) and *malignant neoplasm of prostate* (ICD-10 C61).

[53] Some examples of *injury, poisoning and certain external cause consequences* (ICD-10 S00-T98) include *fracture of femur* (ICD-10 S72) and *fracture of lower leg, including ankle* (ICD-10 S82); examples of *diseases of the digestive system* include *inguinal hernia* (ICD-10 K40) and *cholelithiasis* (ICD-10 K80).

Table 24. Estimated Number and Proportion of Drug Use Mentions[1] for ER/LA or IR Opioid Analgesics Made During Office Visits, by Indication, as Reported by U.S. Office-Based Practitioner Surveys From 2019 to 2023, Aggregated

	2019-2023, aggregated
	Share (%) Uses (000)
Extended-release/Long-acting opioid analgesics	**100% (28,714)**
M00-M99 Diseases of the musculoskeletal system and connective tissue	64%
G00-G99 Diseases of the nervous system	12%
F00-F99 Mental and behavioral disorders	7%
C00-D49 Neoplasms	7%
S00-T98 Injury, poisoning and certain other causes of external consequences	3%
R00-R99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	2%
Z00-Z99 Factors influencing health status and health services	1%
E00-E90 Endocrine, nutritional and metabolic diseases	1%
K00-K95 Diseases of the digestive system	1%
N00-N99 Diseases of the genitourinary system	1%
All others	2%
Immediate-release opioid analgesics	**100% (227,595)**
M00-M99 Diseases of the musculoskeletal system and connective tissue	43%
S00-T98 Injury, poisoning and certain external cause consequences	16%
K00-K95 Diseases of the digestive system	8%
N00-N99 Diseases of the genitourinary system	7%
G00-G99 Diseases of the nervous system	6%
Z00-Z99 Factors influencing health status and health services	5%
C00-D49 Neoplasms	5%
R00-R99 Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	4%
L00-L99 Diseases of the skin and subcutaneous tissue	1%
J00-J99 Diseases of the respiratory system	1%
All others	5%

Source: Syneos Health Research & Insights, LLC, TreatmentAnswers with Pain Panel™. Data years 2019-2023. Data extracted August 2024.
[1] Drug use mentions refer to an office-based visit where a health care practitioner discussed a drug with a patient. These discussions may not necessarily have resulted in a prescription being generated or dispensed to a patient. Projections are based on a monthly survey of approximately 3,500 practitioners. Share (%) refers to the percentage of drug use mentions for a particular diagnosis category, out of the total. Diagnoses are using the International Classification of Diseases, Tenth Revision (ICD-10), a medical classification list that contains codes for diseases, signs and symptoms, abnormal findings, complaints, social circumstances, and external causes of injury or diseases.
Abbreviations: ER/LA, extended-release/long-acting opioid analgesic; IR, immediate-release or short-acting opioid analgesic

Appendix Table 25 shows the number of patients with new ER/LA OA therapy during the study periods of September 2017 to August 2018 (referred to as the 2018 study period) compared to September 2022 to August 2023 (referred to as the 2023 study period), assessed from a sample of dispensed prescriptions. In 2018, 947,879 patients started ER/LA OA therapy, of whom 400,066 patients (42%) did not have evidence of recent prior IR OA therapy. Of these, 249,041 patients (62%) received one to two ER/LA OA prescriptions during the 6-month follow-up period, including the first prescription, while 151,025 patients (38%) received three or more prescriptions. Among the 547,813 patients (58% of total patients) with evidence of prior IR OA therapy, 281,674 patients (51%) received one to two ER/LA OA prescriptions within the next 6 months, and 266,139 patients (49%) received three or more. For most groups assessed, median daily doses for starting ER/LA OA therapy were around 30 MME per day. Results were similar for the 2023 study period.

Table 25. Patients With New Extended-Release/Long-Acting Opioid Analgesic Prescription Utilization Assessed From a Nationally Representative Sample of Prescriptions Dispensed From U.S. Retail, Mail-Order, Specialty, and Long-Term Care Pharmacies, 2018[1] and 2023[1]

	2018 [1]			2023 [1]		
	Patients (n)	Share (%)	Starting daily dose MME/day (median, IQR)	Patients (n)	Share (%)	Starting daily dose MME/day (median, IQR)
Patients starting ER/LA opioid analgesic therapy	947,879	100%		534,535	100%	
No prior IR opioid analgesic therapy	400,066	42%		200,895	38%	
1-2 ER/LA opioid analgesic prescriptions[2]	249,041	62%	30 (30-60)	116,484	58%	30 (27-60)
3+ ER/LA opioid analgesic prescriptions[2]	151,025	38%	60 (30-90)	84,411	42%	36 (20-60)
With prior IR opioid analgesic therapy	547,813	58%		333,640	62%	
1-2 ER/LA opioid analgesic prescriptions[2]	281,674	51%	30 (30-60)	166,468	50%	30 (28-60)
3+ ER/LA opioid analgesic prescriptions[2]	266,139	49%	30 (30-60)	167,172	50%	30 (20-60)

Sources: Symphony Health's Integrated Dataverse®. Study period September 2017 to August 2018 and September 2022 to August 2023. Data for June 2017 to February 2019 and June 2022 to February 2024 extracted in February 2024. Sources for morphine milligram equivalent (MME) conversion factors: Centers for Disease Control and Prevention, NDC and Oral MME Conversion File, 2019 version, https://archive.cdc.gov/www_cdc_gov/opioids/data-resources/index.html. McPherson ML, *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, 2nd Edition, American Society of Health-System Pharmacists, 2018. GlobalRPh, Opioid conversions calc (single agent) equianalgesic, http://globalrph.com/narcoticonv.htm. Medscape, Opioid Equivalents and Conversions, https://emedicine.medscape.com/article/2138678-overview. Starting daily dose defined as MMEs per day at ER/LA opioid analgesic initiation, e.g., oxycodone 10 mg twice daily would be 30 MME/day. Starting ER/LA opioid analgesic therapy defined as no ER/LA opioid analgesic dispensed prescriptions in the prior 90 days. Prior IR opioid analgesic therapy defined as one or more IR opioid analgesic prescriptions dispensed in the 90 days before starting ER/LA opioid analgesic therapy.

[1] Due to data availability at the time of the study, the 2018 study period was September 2017 to August 2018 and the 2023 study period was September 2022 to August 2023.

[2] During a 6-month follow-up period.

Abbreviations: ER/LA, extended-release/long-acting opioid analgesic; IQR, interquartile range; IR, immediate-release or short-acting opioid analgesic; MME, morphine milligram equivalent; n, number; OA, opioid analgesic; U.S., United States

Appendix Table 26 shows the number of patients with OA prescriptions dispensed during the study period of 2021 to 2022, assessed from a sample of dispensed prescriptions. Of the 55.2 million patients with any OA therapy during the study period, 40.5 million patients (73%) had presumed short-term OA therapy and 14.7 million patients (27%) had presumed long-term therapy. Among patients with presumed long-term therapy, 13.6 million patients (93%) received predominantly IR OA long-term therapy, 237,376 patients (1.6%) received predominantly ER/LA OA long-term therapy, and 827,908 patients (6%) received both IR and ER/LA OA long-term therapy.

Among a subset of approximately 45.2 million patients starting OA therapy, 37.6 million patients (83%) had presumed short-term therapy and 7.7 million patients (17%) had presumed long-term therapy. Among patients with presumed long-term therapy, 7.4 million patients (97%) received predominantly IR OA long-term therapy, 55,729 patients (0.7%) received predominantly ER/LA OA long-term therapy, and 194,347 patients (2.5%) received both IR and ER/LA OA long-term therapy.

Table 26. Patients With Opioid Analgesic Prescription Utilization Assessed From a Sample of Prescriptions Dispensed From U.S. Retail, Mail-Order, Specialty, and Long-Term Care Pharmacies, 2021 to 2022, Aggregated

	Patients (n)	Share (%)
Any opioid analgesic therapy	55,245,686	100%
Presumed short-term OA therapy	40,540,041	73%
Presumed long-term OA therapy	14,705,645	27%
Predominantly IR OA long-term therapy	13,640,361	93%
Predominantly ER/LA OA long-term therapy	237,376	1.6%
Both IR OA long-term and ER/LA OA long-term therapy	827,908	6%
Incident opioid analgesic therapy	45,248,304	100%
Presumed short-term OA therapy	37,551,804	83%
Presumed long-term OA therapy	7,696,500	17%
Predominantly IR OA long-term therapy	7,446,424	97%
Predominantly ER/LA OA long-term therapy	55,729	0.7%
Both IR OA long-term and ER/LA OA long-term therapy	194,347	2.5%

Source: Symphony Health's Integrated Dataverse®. Study period January 2021 to December 2022. Data for January 2020 to December 2023 extracted February 2024.

Presumed short-term OA therapy defined as two or fewer ER/LA opioid analgesic prescriptions and/or two or fewer IR opioid analgesic prescriptions during the 1-year follow-up. *Presumed long-term OA therapy* defined as three or more ER/LA opioid analgesic prescriptions or three or more IR opioid analgesic prescriptions during the 1-year follow-up. *Incident use* defined as no opioid analgesic prescriptions dispensed within the previous 365 days. *Predominantly IR OA long-term therapy* defined as three or more IR opioid analgesic prescriptions and either no ER/LA or 1-2 ER/LA opioid analgesic prescriptions during the 1-year follow-up. *Predominantly ER/LA OA long-term therapy* defined as three or more ER/LA opioid analgesic prescriptions and either no IR or 1-2 IR opioid analgesic prescriptions during the 1-year follow-up. *Both IR OA long-term and ER/LA OA long-term therapy* defined as three or more ER/LA opioid analgesic prescriptions and three or more IR opioid analgesic prescriptions during the 1-year follow-up.

Abbreviations: ER/LA OA, extended-release/long-acting opioid analgesic; IR OA, immediate-release or short-acting opioid analgesic; OA, opioid analgesic; U.S., United States

Appendix Table 27 shows the estimated number of ER/LA OA prescriptions dispensed from U.S. retail and mail-order pharmacies, stratified by prescriber specialty, from 2019 to 2023, annually. In 2023, *nurse practitioners* and *physician assistants*[54] prescribed 34% of ER/LA OA dispensed prescriptions. Prescribers in the *general practitioner* category, comprising physician specialties for family practice, general practice, internal medicine, and osteopathic medicine, prescribed 28%, while *anesthesiology/pain medicine specialists* prescribed 21% of the total ER/LA OA prescriptions dispensed in 2023.

[54] Mid-level practitioners are categorized as nurse practitioners or physician assistants in this data source irrespective of whether they practice in a medical specialty, such as neurology or oncology.

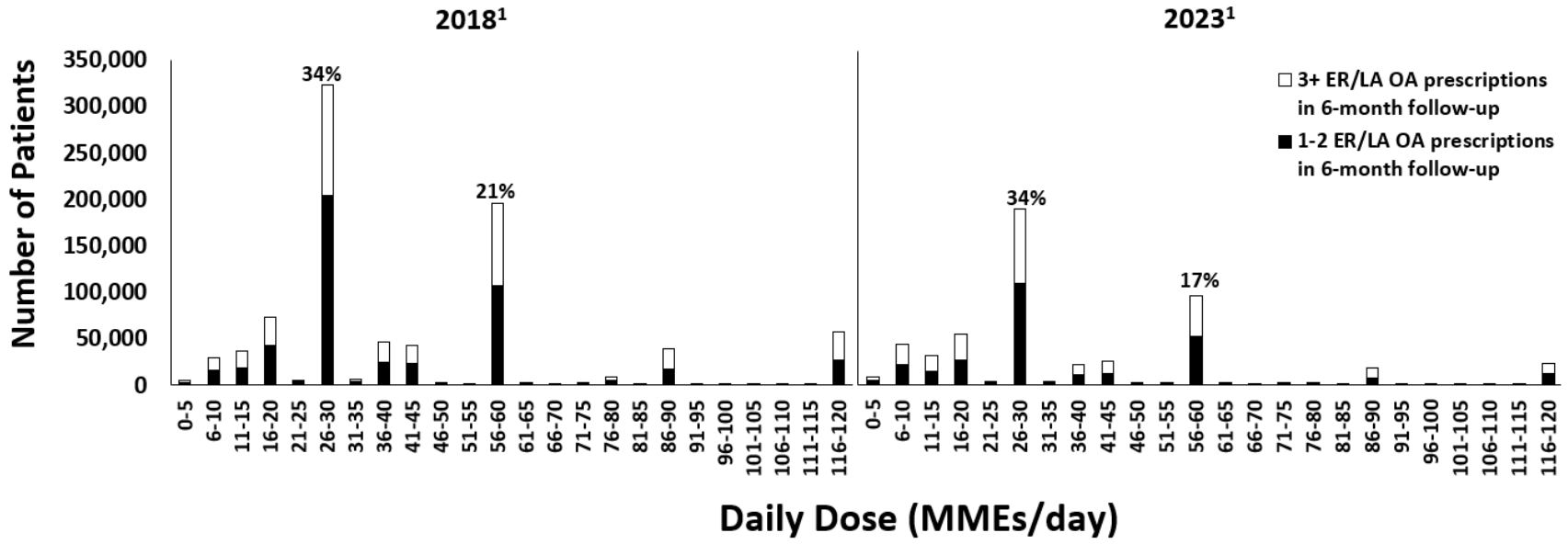
Table 27. Nationally Estimated Number of Extended-Release/Long-Acting Opioid Analgesic Prescriptions Dispensed From U.S. Retail and Mail-Order Pharmacies, by Prescriber Specialty, 2019 to 2023, Annually

	2019		2020		2021		2022		2023	
	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)	Prescriptions (N)	Share (%)
	13,087,382	**100%**	**11,892,872**	**100%**	**10,911,850**	**100%**	**9,945,582**	**100%**	**9,173,950**	**100%**
NURSE PRACTITIONER/PHYSICIAN ASSISTANT	3,615,678	28%	3,477,230	29%	3,418,539	31%	3,266,813	33%	3,137,361	34%
GENERAL PRACTITIONER	4,296,980	33%	3,731,887	31%	3,299,394	30%	2,909,213	29%	2,614,139	28%
ANESTHESIOLOGY/PAIN MEDICINE	2,722,966	21%	2,510,275	21%	2,262,719	21%	2,065,810	21%	1,887,235	21%
PHYSICAL MEDICINE & REHAB	985,377	8%	851,715	7%	723,239	7%	623,023	6%	569,703	6%
ONCOLOGY	438,202	3%	408,058	3%	370,760	3%	330,255	3%	294,675	3%
NEUROLOGY	209,979	2%	172,993	1%	148,078	1%	129,094	1%	115,284	1%
HOSPICE & PALLIATIVE MED	56,846	<1%	62,472	1%	71,252	1%	74,954	1%	73,912	1%
RHEUMATOLOGY	128,439	1%	108,075	1%	93,050	1%	76,999	1%	64,275	1%
ORTHOPEDIC SURGERY	80,544	1%	54,368	<1%	46,502	<1%	42,597	<1%	34,557	<1%
GERIATRICS	57,723	<1%	49,559	<1%	43,611	<1%	38,073	<1%	34,273	<1%
ALL OTHERS	494,648	4%	466,240	4%	434,706	4%	388,751	4%	348,536	4%

Source: IQVIA National Prescription Audit™. Data years 2019-2023. Data extracted August 2024.
General practitioner includes physician specialties for family practice, general practice, internal medicine, and osteopathic medicine.
Midlevel practitioners are categorized as nurse practitioners or physician assistants in this data source irrespective of whether they practice in a medical specialty, such as neurology or oncology.
Abbreviations: N, number; U.S., United States

Appendix Figure 10 shows the distribution of the starting daily dose for ER/LA OA therapy among a sample of patients newly ER/LA OA starting therapy in 2018 or 2023. In 2018, 323,664 patients (34% of total patients) started ER/LA OA therapy in the range of 26 to 30 MMEs/day, of whom around two-thirds (204,467 patients) received one or two ER/LA OA prescriptions within a 6-month follow-up period. Twenty-one percent of patients (195,373 patients) started therapy in the range of 56 to 60 MMEs/day, of whom just over half (106,549 patients) received one or two ER/LA OA prescriptions within a 6-month period. Similar results were seen for the 2023 period, but with fewer patients overall starting ER/LA OA therapy.

Figure 10. Distribution of ER/LA Opioid Analgesic Starting Daily Dose Among a Sample of Patients Starting ER/LA Opioid Analgesic Therapy, Assessed From a Nationally Representative Sample of Prescriptions Dispensed From U.S. Retail, Mail-Order, Specialty, and Long-Term Care Pharmacies, 2018[1] and 2023[1]



Sources: Symphony Health's Integrated Dataverse®. Study periods September 2017 to August 2018 and September 2022 to August 2023, data extracted February 2024 and April 2024 for June 2017 to February 2019 and June 2022 to February 2024. Sources for morphine milligram equivalent (MME) conversion factors: Centers for Disease Control and Prevention. NDC and Oral MME Conversion File, 2019 version, available at https://archive.cdc.gov/www_cdc_gov/opioids/data-resources/index.html. McPherson ML, *Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing*, 2nd Edition. American Society of Health-System Pharmacists, 2018. GlobalRPh. Opioid conversions calc (single agent) equianalgesic. https://globalrph.com/medcalcs/opioid-pain-management-converter-advanced/. Accessed February 13, 2019. Medscape. Opioid Equivalents and Conversions https://emedicine.medscape.com/article/2138678-overview. Sample sizes: 947,879 patients in 2018 and 534,535 patients in 2023. Patients with a daily dose over 120 MME/day not shown for 65,834 patients in 2018 (7%) and 22,409 patients in 2023 (4%). Daily dose defined as MMEs per day. For example, oxycodone 10 mg twice daily would be 30 MMEs/day. Starting ER/LA opioid analgesic therapy was defined as no ER/LA opioid analgesic dispensed prescriptions in the prior 90 days.

[1] Due to data availability at the time of the study, the 2018 study period was September 2017 to August 2018 and the 2023 study period was September 2022 to August 2023.

Abbreviations: ER/LA, extended-release/long-acting opioid analgesic; IR, immediate release or short-acting opioid analgesic; MME, morphine milligram equivalent; OA, opioid analgesic; U.S., United States

6.2.3 Drug Utilization Limitations

The analyses of OA utilization patterns have some limitations for consideration. Some drug utilization analyses were for national estimates (OA prescription counts, MMEs dispensed, OA prescriptions by age group and by prescriber specialty, diagnoses associated with OA use) while others were from a robust, nationally representative sample of dispensed prescriptions (patients with presumed long- or short-term use, patients starting ER/LA OA therapy, ER/LA OA starting daily dose). However, no statistical tests were performed to determine any significant statistical changes over time or between products.

Analyses were focused on utilization patterns discerned from dispensed prescriptions in the outpatient settings and did not include other settings of care where OA products are used, such as hospitals and clinics. Therefore, some patients may have been misclassified as new users when they actually had received recent ER/LA OA therapy. Similarly, some patients may have received more OA prescriptions during the study period than reported in the data source. This could have resulted in underestimation of OA therapy. The duration of OA therapy is challenging to assess due to as-needed (PRN) use. Therefore, we instead assessed counts of dispensed ER/LA or IR OA prescriptions within specified time frames to identify patients with likely short-term or long-term use. There is no standard definition for short-term versus long-term OA therapy. Thus, the methods in these analyses are a general tool for classifying patient therapy but may have misclassified some patients.

In the prescriber survey analysis, some ER/LA OA use appeared to be possibly related to treating OUD. The survey data do not specify which product was related to the condition being treated, or if the health-care practitioner mentioned OUD treatment as an addition to a patient's OA therapy. These data result from monthly surveys of 3,500 office-based practitioners' practitioner-patient discussions/encounters and may not necessarily represent dispensed prescription data. Due to the small sample size, the results may not be representative of all practitioners' prescribing behaviors.

6.2.4 Drug Products Selected and Drug Utilization Database Descriptions

Drug Products Selected for Drug Utilization Analyses

For the DEPI II analyses involving ER/LA OA prescriptions, we selected brand and generic OA products which are extended-release or long-acting, listed below. These selected products may differ from the products included in the ER/LA OA PMR studies.

- Acetaminophen/oxycodone extended-release tablet
- Buprenorphine injectable, oral strip, or transdermal system (not labeled for OUD)
- Fentanyl transdermal system
- Hydrocodone delayed-release, extended-release, or sustained-release capsule or tablet
- Hydromorphone sustained-release capsule or tablet
- Methadone injectable, oral liquid, or tablet (not obtained from a treatment center)
- Morphine sustained-release capsule or tablet
- Morphine/naltrexone sustained-release capsule
- Oxycodone sustained-release capsule or tablet

- Oxymorphone sustained-release tablet
- Tapentadol sustained-release tablet
- Tramadol sustained-release capsule or tablet

Descriptions of Databases Used for Drug Utilization Analyses

IQVIA National Prescription Audit™

National Prescription Audit (NPA) is the industry standard source of national prescription activity for all pharmaceutical products. It measures demand for prescription drugs, including dispensed pharmaceuticals to consumers across three unique channels: retail, mail service, and long-term care pharmacies. From the selected pharmacies, IQVIA collects new and refilled prescription data daily. Data can be analyzed and stratified by patient age, patient sex, co-payment, and four methods of payment: cash, commercial third party, Medicare Part D, and Medicaid. NPA is used to address a variety of research topics examining pharmaceuticals, especially investigations that focus on prescription drug utilization, prescription size, average consumption, and more than 90 prescriber specialty groupings representing over 170 specialties. NPA represents and captures over 94% of all outpatient prescription activity in the US and covers all products, classes, and manufacturers. Although the NPA provides data at a national level, NPA provides data that is at a more granular geographic level of detail. Data are available in IQVIA's business intelligence tool SMART for 72-rolling months and are updated monthly. Launch provides a complete repository on the U.S. marketplace from 1992 to present, capturing both prescription (NPA) and sales data (NSP). Data are available in IQVIA's business intelligence tool SMART and are updated quarterly.

Symphony Health Metys™

Powered by IDV®, Metys® is a web-based tool that intelligently integrates prescription, payer, and anonymized patient data through one single access point – all while delivering insights faster than any other tool in the industry. Metys® accesses over 60 terabytes of automatically included weekly and monthly data, reflecting our breadth of patient-level data and advancements in machine learning. The dispensed prescriptions in the sample represent approximately 85% of all U.S. retail prescriptions, 74% of all U.S. mail order prescriptions, 73% of all U.S. specialty prescriptions, and 50% of all U.S. Long Term Care prescriptions. The retail, mail order, specialty, and long-term care prescriptions are projected to the national level. In addition, the database captures approximately 96% of pharmaceutical distribution into non-retail outlets in the U.S. The non-retail data is not projected to the national level. Metys® Managed Markets metrics, such as rejections and reversals are calculated using a 50% sample of pharmacy adjudicated claims projected to the national level.

Syneos Health Research & Insights LLC., TreatmentAnswers™

Syneos Health Research & Insights, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,500 office-based physicians, physician assistants and nurse practitioners representing 32 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists' physicians each month. With the inclusion of visits to pain specialists, this will allow

additional insight into the pain market. In August 2019, the nurse practitioner and physician assistant specialties were added to the panel. This enhancement provides a more precise view of prescribing habits since nurse practitioners and physician assistants are increasingly playing an important role in patient care. All data collected, is projected nationally by physician specialty and region to reflect national prescribing patterns.

Symphony Health's IDV® (Integrated Dataverse)

The Integrated Dataverse (IDV®) from Symphony Health is the most comprehensive and longitudinal source of healthcare data in the industry, bringing together our vast claims resources – medical, hospital, and prescription – with our rich point-of-sale prescription data, non-retail invoice data, and demographic data. IDV® is the foundation of all Source® data products and offers one consistent market view across prescriber, payer, and patient dimensions. The Integrated Dataverse (IDV®) includes more than 10 years of historical data and accumulates new transactions on a daily basis. Historical capture includes over 50 billion healthcare transactions linked to over 317 million unique patients in the United States. On an annual average basis, the sample includes approximately 3.7 billion prescription transactions from 72,000+ pharmacies and 1.2 billion medical transactions tied to nearly 1.7 million active healthcare practitioners.

6.3 Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) and Final Scoring Algorithm

Note: Revised following Phase II; March 21, 2019

Source: Coyne et al. (2022)

Intentionality of patient responses are coded below for the questions where intentionality is asked. Coding is as follows: M, misuse; A, abuse, D, diversion; TBD, to be determined based on open text provided by the patient; Aberrant Signal, not misuse, abuse, or diversion, but may be an indicator for future misuse or abuse or an "at risk" patient. Note that diversion behavior was not assessed further in the ER/LA PMR studies.

If no code is provided with the specific intentionality, then the intentionality is an acceptable reason for the recorded behavior. Any misuse/abuse/diversion intentionality response on any item indicates that the individual has a misuse/abuse/diversion behavior.

1. In the past 3 months, what prescription opioid pain medications have you taken that were prescribed to you by your doctor or healthcare provider? (You may choose more than 1 answer.)

- □ Hydrocodone alone or in combination with another medication (e.g., Zohydro® ER, Hysingla™ ER, Vicodin®, Anexsia®, Rezira®, Vicoprofen®, Norco®)
- □ Hydromorphone (e.g., Exalgo®, Dilaudid®)
- □ Oxycodone alone or in combination with another medication (e.g., OxyContin®, Xartemis™ XR, Percocet®, Percodan®, Oxecta®, Oxycet®, Roxicodone®, Roxicet®)
- □ Methadone (e.g., Dolophine®, Methadose®)
- □ Codeine alone or in combination with another medication (e.g., acetaminophen, promethazine, guaifenesin) in tablet or solution (e.g., Tylenol® with codeine, Robitussin®, Prometh® with codeine)
- □ Oxymorphone (e.g., Opana®, Opana® ER)
- □ Morphine (e.g., Avinza®, Kadian®, MS Contin®, Embeda®, Duramorph®)
- □ Fentanyl (e.g., Duragesic®, Fentora®, Abstral®, Actiq®, Lazanda®, Onsolis®, Subsys®)
- □ Buprenorphine (e.g., Butrans®, Subutex®, Suboxone®, Zubsolv®, Belbuca®, Bunavail®)
- □ Tramadol alone or in combination with another medication (e.g., Ultram®, Ultram ER®, Ultracet®)

□ Tapentadol (e.g., Nucynta®, Nucynta® ER)
□ Other opioids (e.g., Butorphanol, Levorphanol, Meperidine /Demerol®)
□ Other prescription opioid pain medication (please specify): _____
□ None of the above

2. In the past 3 months, have you taken any other prescription opioid pain medications that were NOT prescribed to you by your doctor or healthcare provider?
□ Yes (Go to 2a)
□ No (Go to 3)
□ I am not sure (Go to 2a)

2a. In the past 3 months, what other prescription opioid pain medications have you taken that were NOT prescribed to you? (You may choose more than 1 answer.)
□ Hydrocodone alone or in combination with another medication (e.g., Zohydro® ER, Hysingla™ ER, Vicodin®, Anexsia®, Rezira®, Vicoprofen®, Norco®)
□ Hydromorphone (e.g., Exalgo®, Dilaudid®)
□ Oxycodone alone or in combination with another medication (e.g., OxyContin®, Xartemis™ XR, Percocet®, Percodan®, Oxecta®, Oxycet®, Roxicodone®, Roxicet®)
□ Methadone (e.g., Dolophine®, Methadose®)
□ Codeine alone or in combination with another medication (e.g., acetaminophen, promethazine, guaifenesin) in tablet or solution (e.g., Tylenol® with codeine, Robitussin®, Prometh® with codeine)
□ Oxymorphone (e.g., Opana®, Opana® ER)
□ Morphine (e.g., Avinza®, Kadian®, MS Contin®, Embeda®, Duramorph®)
□ Fentanyl (e.g., Duragesic®, Fentora®, Abstral®, Actiq®, Lazanda®, Onsolis®, Subsys®)
□ Buprenorphine (e.g., Butrans®, Subutex®, Suboxone®, Zubsolv®, Belbuca®, Bunavail®)
□ Tramadol alone or in combination with another medication (e.g., Ultram®, Ultram ER®, Ultracet®)
□ Tapentadol (e.g., Nucynta®, Nucynta® ER)
□ Other opioids (e.g., Butorphanol, Levorphanol, Meperidine /Demerol®)
□ Other prescription opioid pain medication (please specify): _____
□ None of the above

3. In the past year, did you take less of your prescription opioid pain medication than was prescribed to you?
□ Yes (Go to 3a)
□ No (Go to 4)
□ I am not sure (Go to 3a)

3a. In the past 3 months, did you take less of your prescription opioid pain medication than was prescribed to you?
□ Yes (Go to 3b and 3c)
□ No (Go to 4)

3b. In the past 3 months, why did you take less prescription opioid pain medication than was prescribed to you? (You may choose more than 1 answer.)
□ The dose my healthcare provider prescribed was too strong to treat my pain
□ I had less pain
□ To avoid getting constipated
□ To reduce the side effects of the opioid pain medication
□ I forgot to take my opioid pain medication
□ Began taking other drugs (e.g., heroin, marijuana) **A**
□ To save some opioid pain medication for later in case my pain gets worse
□ To save the opioid pain medication to sell it **D**
□ To save the opioid pain medication for a relative or friend **D**
□ To save the opioid pain medication to use more of it at once to get high **A**
□ I misunderstood how much to take
□ Other reason (please specify): _____ **TBD**

3c. In the past 1 month, how many times did you take less of your prescription opioid pain medication than was prescribed to you?
□ None
□ 1 time

□ 2-5 times
□ 6-10 times
□ 11-15 times
□ More than 15 times

4. In the past year, did you take more of your prescription opioid pain medication than was prescribed to you?

□ Yes (Go to 4a)
□ No (Go to 5)
□ I am not sure (Go to 4a)

4a. In the past 3 months, did you take more of your prescription opioid pain medication than was prescribed to you?

□ Yes (Go to 4b and 4c)
□ No (Go to 5)

4b. In the past 3 months, why did you take more prescription opioid pain medication than was prescribed to you? (You may choose more than 1 answer.)

□ The dose my healthcare provider prescribed was not strong enough to treat my pain **M (only if >2-5 times per month)**
□ To feel high or stoned **A (regardless of frequency)**
□ To treat my pain faster **M**
□ To feel less depressed or nervous **M**
□ To sleep better **M**
□ To unwind after a hard day **M**
□ To feel more talkative or outgoing **A (regardless of frequency)**
□ To treat other medical problems **M**
□ I did not realize how much I was taking **M**
□ To prevent withdrawal **M**
□ To relax or feel mellow **M**
□ To reduce my stress **M**
□ I had more pain **M (only if >2-5 times per month)**
□ To treat the emotional hurt I was feeling **M 0**
□ I misunderstood how much to take **M**
□ Other reason (please specify): **TBD**
_____

4c. In the past 1 month, how many times did you take more of your prescription opioid pain medication than was prescribed to you?

□ None
□ 1 time
□ 2-5 times
□ 6-10 times
□ 11-15 times
□ More than 15 times

5. In the past year, have you changed or tampered with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication?

□ Yes (Go to 5a-5b)
□ No (Go to 6)
□ I am not sure (Go to 5a-5b)

5a. In the past year, which of the following ways have you changed or tampered with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication? (You may choose more than 1 answer.)

□ Chewed my opioid pain medication
□ Crushed and then swallowed my opioid pain medication
□ Dissolved and then swallowed my opioid pain medication
□ Cut my opioid medication pill
□ Snorted my opioid pain medication **A**
□ Smoked my opioid pain medication **A**
□ Inhaled my opioid pain medication **A**
□ Injected my opioid pain medication **A**
□ Sucked a patch of opioid pain medication **A**
□ Swallowed an opioid patch **A**
□ Cut my opioid patch **M**
□ Scratched the skin under my opioid patch **A**
□ Extracted the pain medication from my opioid patch **A**
□ Applied heat to an opioid patch **M**
□ Placed under the tongue (but not prescribed this way) **A**
□ Inserted rectally (but not prescribed this way) **A**
□ Other reason (please specify): **TBD**
_____

5b. **<u>In the past 3 months</u>, have you changed or tampered with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication?**

□ Yes (Go to 5c–5e)
□ No (Go to 6)

5c. **<u>In the past 3 months</u>, which of the following ways have you changed or tampered with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication? (You may choose more than 1 answer.)**

□ Chewed my opioid pain medication
□ Crushed and then swallowed my opioid pain medication
□ Dissolved and then swallowed my opioid pain medication
□ Cut my opioid medication pill
□ Snorted my opioid pain medication **A**
□ Smoked my opioid pain medication **A**
□ Inhaled my opioid pain medication **A**
□ Injected my opioid pain medication **A**
□ Sucked a patch of opioid pain medication **A**
□ I have not changed or tampered with my opioid pain medication in the past 3 months
□ Swallowed an opioid patch **A**
□ Cut my opioid patch **M**
□ Scratched the skin under my opioid patch **A**
□ Extracted the pain medication from my opioid patch **A**
□ Applied heat to an opioid patch **M**
□ Placed under the tongue (but not prescribed this way) **A**
□ Inserted rectally (but not prescribed this way) **A**
□ Other (please specify): _____ **TBD**

5d. **<u>In the past 3 months</u>, why did you change or tamper with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication? (You may choose more than 1 answer.)**

□ To treat my pain faster **M**
□ To help me swallow my opioid pain medication
□ The dose my healthcare provider prescribed was not strong enough to treat my pain **M**
□ To feel less depressed or nervous **M**
□ To sleep better **M**
□ To unwind after a hard day **M**
□ To reduce my stress **M**
□ To feel more talkative or outgoing **A**
□ To prevent withdrawal **M**
□ To relax or feel mellow **M**
□ I had more pain **M**
□ To feel high or stoned **A**
□ To treat the emotional hurt I was feeling **M**
□ I misunderstood the instructions on how to take **M**
□ Other reason (please specify): **TBD**

5e. **<u>In the past 1 month</u>, how many times have you changed or tampered with (that is, crushed, chewed, dissolved, snorted, smoked, or injected) your prescription opioid pain medication?**

□ None
□ 1 time
□ 2-5 times
□ 6-10 times
□ 11-15 times
□ More than 15 times

6. <u>In the past year</u>, did you drink alcohol while taking your prescription opioid pain medication?

□ Yes (Go to 6a)
□ No (Go to 7)
□ I am not sure (Go to 6a)

6a. <u>In the past 3 months</u>, did you drink alcohol while taking your prescription opioid pain medication?

□ Yes (Go to 6b-6d)
□ No (Go to 7)

6b. <u>In the past 3 months</u>, why did you drink alcohol while taking your prescription opioid pain medication? (You may choose more than 1 answer.)

□ I do not think it is a problem to have a drink while taking an opioid pain medication **M (if amount and frequency criteria met)**
□ To celebrate a special occasion (e.g., a birthday, a wedding) **M (if amount and frequency criteria met)**
□ I forgot I was taking an opioid pain medication **M (if amount and frequency criteria met)**
□ I happened to have a drink close to the time of taking my opioid pain medication **M (if amount and frequency criteria met)**
□ To feel high or stoned **A (regardless of amount or frequency)**
□ To reduce my stress **M (if amount and frequency criteria met)**
□ To unwind after a hard day **M (if amount and frequency criteria met)**
□ To treat the emotional hurt I was feeling **M (if amount and frequency criteria met)**
□ To feel less depressed or nervous **M (if amount and frequency criteria met)**
□ To sleep better **M (if amount and frequency criteria met)**
□ To feel more talkative or outgoing **A (regardless of amount or frequency)**
□ To get a better feeling or high **A (regardless of amount or frequency)**
□ To boost the effect of my opioid pain medication **A (regardless of amount or frequency)**
□ To relax or feel mellow **M (if amount and frequency criteria met)**
□ The dose my healthcare provider prescribed was not strong enough to treat my pain **M (if amount and frequency criteria met)**
□ Other reason (please specify):_____ **TBD**

6c. <u>In the past 3 months</u>, on those occasions when you drank while taking your prescription opioid pain medication, how many drinks did you have on <u>average</u> (1 drink=1 standard bottle/can of beer, 1 glass of wine, 1 mixed drink, 1 shot of liquor)? (*see end of POMAQ for response classification*)

□ 1 drink
□ 2 drinks
□ 3 drinks
□ 4 drinks
□ 5 or more drinks

6d. **<u>In the past 1 month</u>, how many times did you drink alcohol while taking your prescription opioid pain medication?** ***(see end of POMAQ for response classification)***

- □ None
- □ 1 time
- □ 2-5 times
- □ 6-10 times
- □ 11-15 times
- □ More than 15 times

7. <u>In the past year</u>, were any of the following medications prescribed to you? (You may choose more than 1 answer.)

- □ Stimulants, such as, dextroamphetamine (Dexedrine®), methylphenidate, (Ritalin®, Concerta®) amphetamine and dextroamphetamine (Adderall®), methamphetamine (Desoxyn®), lisdexamfetamine (Vyvanse®)
- □ Anti-anxiety medications, for example, benzodiazepines such as diazepam (Valium®), alprazolam (Xanax®), clonazepam (Klonopin®), lorazepam (Ativan®)
- □ Sleeping pills such as zolpidem (Ambien®), eszopiclone (Lunesta®), temazepam (Restoril®), zaleplon (Sonata®), doxylamine (Unisom®)
- □ Antihistamines such as. promethazine (Phenergan®), diphenhydramine (Benadryl®)
- □ Barbiturates such as amobarbital (Amytal®), pentobarbital (Nembutal®), secobarbital (Seconal®)
- □ Antipsychotics or neuroleptics such as quetiapine (Seroquel®), olanzapine (Zyprexa®), risperidone (Risperdal®), aripiprazole (Abilify®), ziprasidone (Geodon®), asenapine (Saphris®)
- □ Other sedatives (please specify): _____
- □ None (Go to 8)

7a. **<u>In the past year</u>, did you take your prescription opioid pain medication with [autofill with above response from 7]?**

- □ Yes (Go to 7b)
- □ No (Go to 8)
- □ I am not sure (Go to 7b)

7b. **<u>In the past 3 months</u>, did you take your prescription opioid pain medication with [autofill with above response from 7]?**

- □ Yes (Go to 7c-7d)
- □ No (Go to 8)

7c. **<u>In the past 3 months</u>, why did you take your prescription opioid pain medication with [autofill with selection from 7a]? (You may choose more than 1 answer)** *<u>(see last page of POMAQ for classification of responses)</u>*

- □ My healthcare provider prescribed these medications to be taken together
- □ Different healthcare providers prescribed these medications
- □ To feel high or stoned **A (for all concomitant meds)**
- □ The dose my healthcare provider prescribed was not strong enough to treat my pain
- □ To feel less depressed or nervous
- □ To sleep better
- □ To feel more talkative or outgoing
- □ To treat my pain faster
- □ To reduce my stress
- □ To treat the emotional hurt I was feeling
- □ To boost the effect of my opioid pain medication
- □ I misunderstood the instructions on how to take my medications **M (for all concomitant meds)**
- □ To relax or feel mellow
- □ Other reason (please specify): **TBD (for all concomitant meds)**

_____

7d. **<u>In the past 1 month</u>, how many times did you take your prescription opioid pain medication with [autofill with selection from 7]?**

- □ None
- □ 1 time
- □ 2-5 times
- □ 6-10 times
- □ 11-15 times
- □ More than 15 times

8. In the past year, did you get any opioid pain medication from someone who was NOT a doctor or healthcare provider?

□ Yes (Go to 8a)
□ No (Go to 9)
□ I am not sure (Go to 8a)

8a. In the past 3 months, did you get any opioid pain medication from someone who was NOT a doctor or healthcare provider?

□ Yes (Go to 8b)
□ No (Go to 9)

8b. In the past 3 months, how did you get opioid pain medication from someone who was NOT a doctor or healthcare provider? (You may choose more than 1 answer.)

□ I asked a friend or relative to give me some of their prescription opioid pain medication (Go to 8c and 8e)
□ I took some pills from the prescription of a friend or relative (Go to 8c and 8e)
□ I took the prescription of a friend or relative and filled it (Go to 8c and 8e)
□ I took the prescription opioid pain medication of somebody I do not know (Go to 8c and 8e)
□ I bought the opioid pain medication without a prescription on the internet (Go to 8c and 8e) A
□ I got some opioid pain medication from someone on the street (Go to 8d and 8e) A
□ I got it from a friend or relative who had some opioid pain medication from the street (Go to 8d and 8e) A
□ Other reason (please specify): _____ (Go to 8c and 8e)

8c. In the past 3 months, what other prescription opioid pain medications did you get that were NOT prescribed to you? (You may choose more than 1 answer.)

□ Hydrocodone alone or in combination with another medication (e.g., Zohydro® ER, Hysingla™ ER, Vicodin®, Anexsia®, Rezira®, Vicoprofen®, Norco®)
□ Hydromorphone (e.g., Exalgo®, Dilaudid®)
□ Oxycodone alone or in combination with another medication (e.g., OxyContin®, Xartemis™ XR, Percocet®, Percodan®, Oxecta®, Oxycet®, Roxicodone®, Roxicet®)
□ Methadone (e.g., Dolophine®, Methadose®)
□ Codeine alone or in combination with another medication (e.g., acetaminophen, promethazine, guaifenesin) in tablet or solution (e.g., Tylenol® with codeine, Robitussin®, Prometh® with codeine)
□ Oxymorphone (e.g., Opana®, Opana® ER)
□ Morphine (e.g., Avinza®, Kadian®, MS Contin®, Embeda®, Duramorph®)
□ Fentanyl (e.g., Duragesic®, Fentora®, Abstral®, Actiq®, Lazanda®, Onsolis®, Subsys®)
□ Buprenorphine (e.g., Butrans®, Subutex®, Suboxone®, Zubsolv®, Belbuca®, Bunavail®)
□ Tramadol alone or in combination with another medication (e.g., Ultram®, Ultram ER®, Ultracet®)
□ Tapentadol (e.g., Nucynta®, Nucynta® ER)
□ Other opioids (e.g., Butorphanol, Levorphanol, Meperidine (Demerol®)
□ Other opioid medication (please specify): _____
□ None of the above

8d. **<u>In the past 3 months</u>, what opioid street pain medication did you get? (You may choose more than 1 answer.)**

□ Hydrocodone (e.g., Vike, Watson-387, Zohydro® ER, Hysingla™ ER, Vicodin®, Anexsia®, Rezira®, Vicoprofen®, Norco®)
□ Hydromorphone (e.g., Juice, Smack, D, Footballs, Dillies, Exalgo®, Dilaudid®)
□ Oxycodone (e.g., Oxy, OC, Oxycotton, Hillbilly, Percs, OxyContin®, Xartemis™ XR, Percocet®, Percodan®, Oxecta®, Oxycet®, Roxicodone®, Roxicet®)
□ Methadone (e.g., Fizzies, Amidone, Dolophine®, Methadose®)
□ Codeine (e.g., Prometh, Captain Cody, Cody, Schoolboy, Tylenol®, Robitussin®)
□ Oxymorphone (e.g., Biscuits, Blue Heaven, Blues, Mrs O, Octagons, Stop signs, O bomb, Opana®, Opana® ER)
□ Morphine (e.g., M, Miss Emma, Monkey, White stuff, Avinza®, Kadian®, MS Contin®, Embeda®, Duramorph®)
□ Fentanyl (e.g., Apache, China girl, Dance fever, Friend, Goodfella, Jackpot, Murder 8, TNT, Tango and Cash, Duragesic®, Fentora®, Abstral®, Actiq®, Lazanda®, Onsolis®, Subsys®)
□ Buprenorphine (e.g., Subs, Bupe, Subbies, Oranges, Sobos, Box, Stop signs, Butrans®, Subutex®, Suboxone®, Zubsolv®, Belbuca®, Bunavail®)
□ Tramadol (e.g., Trammies, Chill Pill, Ultra, Ultram®, Ultram ER®, Ultracet®)
□ Tapentadol (e.g., Nucynta®, Nucynta® ER)
□ Meperidine (Demmies, Pain killer, Demerol®)
□ Other opioid medication (please specify): _____
□ None of the above

8e. **<u>In the past 3 months</u>, why did you get opioid pain medication from someone who was <u>NOT</u> a doctor or healthcare provider? (You may choose more than 1 answer.)**

□ I lost my opioid pain medication **Aberrant signal**
□ My prescription was stolen **Aberrant signal**
□ I wanted to make sure I had enough of my opioid pain medication in case I needed it **M**
□ I needed more opioid pain medication to treat my pain **M**
□ I wanted to get more opioid pain medication to get high on **A**
□ I wanted to get more opioid pain medication to sell **D**
□ I wanted to get more opioid pain medication to help a friend or relative **D**
□ Other reason (please specify): _____ **TBD**

8f. **<u>In the past 1 month</u>, how many times did you get opioid pain medication from someone who was <u>NOT</u> a doctor or healthcare provider?**

□ None
□ 1 time
□ 2 times
□ 3 times
□ 4 times
□ More than 4 times

9. **<u>In the past year</u>, have you taken any of the following street drugs? (You may choose more than 1 answer.)**

□ Marijuana (Blunt, Dope, Ganja, Grass, Herb, Joint, Bud, Mary Jane, Pot, Reefer, Green, Trees, Smoke, Simsemilla, Skunk, Weed)
□ Hashish (Boom, Gangster, Hash, Hash oil, Hemp)
□ Synthetic cannabis (K2, Spice, Cloud 9, Relax, Crown, Mojo, Scooby Snax, bath salts)
□ Anabolic Steroids (Roids, Juice, Gym candy, Pumpers, Stackers)
□ Barbiturates (Barbs, Reds, Red birds, Phennies, Tooies, Yellows, Yellow Jackets)
□ Benzodiazepines (Diazepam (Valium®), alprazolam (Xanax®), clonazepam (Klonopin®), temazepam (Restoril®), flurazepam (Dalmane®), chlordiazepoxide (Librium®), lorazepam (Ativan®), triazolam (Halcion®), Candy, Downers, Sleeping pills, Tranks) **If anti-anxiety medications recorded on Q7 and no abuse intent noted, then this Q9 response will not be considered abuse**
□ Sleeping pills (e.g., Ambien®, Lunesta®, Restoril®, Sonata®, Unisom®) **If sleeping pills recorded on Q7 and no abuse intent noted, then this Q9 response will not be considered abuse**
□ Antipsychotics or neuroleptics (Seroquel®, Quell, Susie-Q, Baby heroin, Zyprexa ®, Risperdal ®)

□ Amphetamine (Bennies, Black beauties, Crosses, Hearts, LA turnaround, Speed, Truck drivers, Uppers)
□ Caffeine powder
□ Methamphetamine (Meth, Ice, Crank, Chalk, Crystal, Fire, Glass, Go fast, Speed)
□ Methylphenidate (Ritalin, JIF, MPH, R-ball, Skippy, Smart drug, Vitamin R)
□ Cocaine (Blow, Bump, C, Candy, Charlie, Coke, Crack, Flake, Rock, Snow, Toot)
□ MDMA (Ecstasy, E, X, XTC, Molly, Adam, Eve, Clarity, Peace, Uppers, Lover's speed)
□ GHB (Date-rape drug, G, Georgia home-boy, Grievous bodily harm, Liquid ecstasy, Soap, Scoop, Goop, Liquid X)
□ Flunitrazepam (Rohypnol, Roofies, Forget-me pill, Mexican valium, R2, Roach, Roche, Roofinol, Rope, Rophies)
□ Dextromethorphan (DXM, Robo, Robotripping, Triple C)
□ Phencyclidine (PCP, Angel dust, Boat, Hog, Love boat, Peace pill)
□ Salvia divinorum (Salvia, Shepherdess's herb, Maria Pastora, Magic mint, Sally-D)
□ Ketamine (K, Special K, Vitamin K, Cat Valium)
□ Inhalants (paint thinner, gasoline, glues, gases, laughing gases, poppers, snappers, whippets)
□ LSD (Acid, Blotter, Cubes, Microdot, Yellow sunshine, Blue heaven)
□ Mescaline (Buttons, Cactus, Mesc, Peyote)
□ 5-MeO-DMT (5-Methoxy-N-N-dimethyltryptamine)
□ Psilocybin (Magic mushroom, Purple passion, Shrooms, Little smoke)
□ Substituted phenethylamine (N-bomb, Legal acid, Smiles, 25I)
□ Prescription-strength cough syrup with codeine and promethazine (Syrup, Purple Drank, Sizzurp, Lean)
□ Heroin (Smack, Junk, Horse, Brown sugar, Dope, H, Skag, Skunk, White horse, China white, Cheese)
□ Opium (Big O, Black stuff, Block, Gum, Hop)
□ Desomorphine (Krokodil)
□ Other (please specify):_____ **TBD – Must review and hard code as needed – may not be street drug**
□ None (Go to 10)

9a. **In the past year, have you taken your prescription opioid pain medication with [autofill with selection from 9]? (PAST YEAR responses not used to determine intentionality)**
□ Yes (Go to 9b)
□ No (Go to 10)
□ I am not sure (Go to 9b)

9b. **In the past 3 months, have you taken your prescription opioid pain medication with [autofill with selection from 9]?**
□ Yes (Go to 9c) **MUST say yes to 3-month use to be considered misuse or abuse**
□ No (Go to 10)

9c. **In the past 3 months, why did you take your prescription opioid pain medication with [autofill with selection from 9]?**
(You may choose more than 1 answer) (if A or M intent taken in the PAST 3 MONTHS, will count as A, excluding Marijuana unless otherwise noted)

□ To feel high or stoned **A (including marijuana)**
□ The dose my healthcare provider prescribed was not strong enough to treat my pain **M**
□ To feel less depressed or nervous **M**
□ To unwind after a hard day **M**
□ To sleep better **M**
□ To treat other medical problems **M**
□ To feel more talkative or outgoing **A (including marijuana)**
□ It is better to get high on my prescription opioid pain medication when on another drug **A (including marijuana)**
□ To treat my pain faster **M**
□ To prevent withdrawal **M**
□ To relax or feel mellow **M**
□ I had more pain **M**
□ Other reason (please specify): _____ **TBD**

9d. **<u>In the past 1 month</u>, how many times have you taken your prescription opioid pain medication with [autofill with selection from 9]?**

□ None
□ 1 time
□ 2-5 times
□ 6-10 times
□ 11-15 times
□ More than 15 times

10. <u>In the past year</u>, have you visited more than 1 doctor or healthcare provider to get more prescription opioid pain medication?

□ Yes (Go to 10a)
□ No (Go to 11)
□ I am not sure (Go to 10a)

10a. **<u>In the past 3 months</u>, have you visited more than 1 doctor or healthcare provider to get more prescription opioid pain medication?**

□ Yes (Go to 10b and 10c)
□ No (Go to 11)

10b. **<u>In the past 3 months</u>, why did you visit more than 1 doctor or healthcare provider to get more prescription opioid pain medication? (You may choose more than 1 answer.)**

□ I see different healthcare providers for different health problems, so I ask for an opioid prescription when seeing each healthcare provider **Aberrant signal**
□ I needed more opioid pain medication to treat my pain than 1 doctor would give me **Aberrant signal**
□ I wanted to get more opioid pain medication to get high on **A**
□ I wanted to get more opioid pain medication to sell **D**
□ I wanted to get more opioid pain medication to help a friend or relative **D**
□ I lost my opioid pain medication **Aberrant signal**
□ I wanted to make sure I had enough opioid pain medication in case I needed it **M**
□ My insurance, employment or place of residence changed, and I had to change my doctor
□ My doctor stopped prescribing opioid pain medication **Aberrant signal**
□ I was referred to another doctor
□ My doctor does not understand my pain level **Aberrant signal**
□ My doctor thinks I may be faking my pain **Aberrant signal**
□ Other reason (please specify): _____**TBD**_____

10c. **<u>In the past 1 month</u>, how many doctors or healthcare providers have you visited to get more prescription opioid pain medication?**

□ None
□ 1
□ 2
□ 3
□ 4
□ More than 4

11. <u>In the past year</u>, have you gone to more than 1 pharmacy to obtain your prescription opioid pain medication?

□ Yes (Go to 11a)
□ No (Go to 12)
□ I am not sure (Go to 11a)

11a. <u>In the past 3 months</u>, have you gone to more than 1 pharmacy to obtain your prescription opioid pain medication?

□ Yes (Go to 11b and 11c)
□ No (Go to 12)

11b. <u>In the past 3 months</u>, why did you go to more than 1 pharmacy to obtain your prescription opioid pain medication? (You may choose more than 1 answer.)

□ I lost my opioid pain medication **Aberrant signal**
□ A pharmacy refused to fill my opioid pain prescription
□ My prescription was changed to a different dose or medication
□ I use several different pharmacies for convenience
□ I wanted to make sure I had enough of my opioid pain medication in case I needed it **M**
□ My regular pharmacy did not have enough of my opioid pain medication
□ My insurance changed, and I had to change my pharmacy
□ I do not want the pharmacist to know how much opioid pain medication I take per month **Aberrant signal**
□ I needed more opioid pain medication to treat my pain **M**
□ I always try to get the best price, so I go to different pharmacies
□ I wanted to get more opioid pain medication and did not want to get caught **A**
□ Other reason (please specify): **TBD** _____

11c. <u>In the past 1 month</u>, how many pharmacies have you gone to in order to obtain your prescription opioid pain medication?

□ None
□ 1
□ 2
□ 3
□ 4
□ More than 4

12. <u>In the past year</u>, has your prescription for opioid pain medication or your prescription opioid pain medication been lost?

□ Yes (Go to 12a)
□ No (Go to 13)
□ I am not sure (Go to 12a)

12a. <u>In the past 3 months</u>, has your prescription for opioid pain medication or your prescription opioid pain medication been lost?

□ Yes
□ No

13. <u>In the past year</u>, has your prescription for opioid pain medication or your prescription opioid pain medication been stolen?

□ Yes (Go to 13a)
□ No (Go to 14)
□ I am not sure (Go to 13a)

13a. <u>In the past 3 months</u>, has your prescription for opioid pain medication or your prescription opioid pain medication been stolen?

□ Yes
□ No

14. In the past year, have you requested refills for your prescription opioid pain medication earlier than they were due?

□ Yes (Go to 14a)
□ No (Go to 15)
□ I am not sure (Go to 14a)

14a. In the past 3 months, have you requested refills for your prescription opioid pain medication earlier than they were due?

□ Yes (Go to 14b and 14c)
□ No (Go to 15)

14b. In the past 3 months, why did you request refills on your prescription opioid pain medication earlier than they were due? (You may choose more than 1 answer.)

□ I lost my opioid pain medication **Aberrant signal**
□ My prescription was changed to a different dose
□ My prescription was stolen **Aberrant signal**
□ I wanted to make sure I had enough of my opioid pain medication in case I needed it **M (if ≥2 times in past 1 month)**
□ I needed more opioid pain medication to treat my pain **M (if ≥2 times in past 1 month)**
□ I did not realize how much medication I was taking, and I ran out **M (if ≥2 times in past 1 month)**
□ I wanted to get more opioid pain medication to get high on **A**
□ I wanted to get more opioid pain medication to sell **D**
□ I wanted to get more opioid pain medication to help a friend or relative **D**
□ Other reason (please specify): _____ **TBD**

14c. In the past 1 month, how many times have you requested refills on your prescription opioid pain medication earlier than they were due?

□ None
□ 1 time
□ 2 times
□ 3 times
□ 4 times
□ More than 4 times

15. In the past year, have you visited an emergency room (ER) or Urgent Care clinic to get more prescription opioid pain medication?

□ Yes (Go to 15a)
□ No (Go to 16)
□ I am not sure (Go to 15a)

15a. In the past 3 months, have you visited an emergency room (ER) or Urgent Care clinic to get more prescription opioid pain medication?

□ Yes (Go to 15b)
□ No (Go to 16)

15b. In the past 1 month, how many times have you visited an emergency room (ER) or Urgent Care clinic to get more prescription opioid pain medication?

□ None
□ 1 time
□ 2 times
□ 3 times
□ 4 times
□ More than 4 times

16. In the past year, have you used or tried to use a fake or changed prescription for opioid pain medication?

□ Yes (Go to 16a)
□ No (Go to 17)
□ I am not sure (Go to 16a)

16a. In the past 3 months, have you used or tried to use a fake or changed prescription for opioid pain medication?

□ Yes (Go to 16b)
□ No (Go to 17)

16b. In the past 3 months, why did you use or try to use a fake or changed prescription for opioid pain medication? (You may choose more than 1 answer.)

□ I lost my opioid pain medication **Aberrant signal**
□ My prescription was stolen **Aberrant signal**
□ I wanted to make sure I had enough of my opioid pain medication in case I needed it **M**
□ I needed more opioid pain medication to treat my pain **M**
□ I wanted to get more opioid pain medication to get high on **A**
□ I wanted to get more opioid pain medication to sell **D**
□ I wanted to get more opioid pain medication to help a friend or relative **D**
□ Other reason (please specify): _____ **TBD**

17. In the past year, have you purchased or stolen a prescription or a prescription pad or part of a prescription pad?

□ Yes (Go to 17a)
□ No (Go to 18)
□ I am not sure (Go to 17a)

17a. In the past 3 months, have you purchased or stolen a prescription or a prescription pad or part of a prescription pad?

□ Yes (Go to 17b)
□ No (Go to 18)

17b. In the past 3 months, why did you purchase or steal a prescription or a prescription pad or part of a prescription pad? (You may choose more than 1 answer.)

□ I lost my opioid pain medication **Aberrant signal**
□ My prescription was stolen **Aberrant signal**
□ I wanted to make sure I had enough of my opioid pain medication in case I needed it **M**
□ I needed more opioid pain medication to treat my pain **M**
□ I wanted to get more opioid pain medication to get high on **A**
□ I wanted to get more opioid pain medication to sell **D**
□ I wanted to get more opioid pain medication to help a friend or relative **D**
□ I wanted to sell individual prescriptions of opioid pain medications to make money **D**
□ I wanted to sell individual prescriptions of other medications to make money **D**
□ Other reason (please specify): _____ **TBD**

18. In the past year, have you shared, sold, or traded your prescription opioid pain medication?

□ Yes (Go to 18a)
□ No (Go to 19)
□ I am not sure (Go to 18a)

18a. In the past 3 months, have you shared, sold, or traded your prescription opioid pain medication?

□ Yes **D**
□ No

19. Do you think you may have a problem with your prescription opioid pain medication?

□ Yes (Go to 19a)
□ No
□ I am not sure (Go to 19a)

19a. What problem(s) do you think you may have with your prescription opioid pain medication? (You may choose more than 1 answer.)

□ Problems refilling my prescription
□ The medication does not control my pain well
□ An unwanted side effect (for example, constipation or nausea)
□ I think I may be addicted to the opioid pain medication
□ I have problems controlling the amount of opioid pain medication I take
□ I may have a problem stopping my opioid pain medication
□ Other reason (please specify):

Question 6: Classification of Alcohol Use Amount and Frequency Responses

	1 drink	2 drinks	3 drinks	4 drinks	5 or more drinks
None	-	-	-	-	-
1 time	Not M but can be A if marked as intention	Not M but can be A if marked as intention	Not M but can be A if marked as intention	Code as intention reason	Code as intention reason
2-5 times	Not M but can be A if marked as intention	Not M but can be A if marked as intention	Not M but can be A if marked as intention	Code as intention reason	Code as intention reason
6-10 times	Not M but can be A if marked as intention	Code as intention reason	Code as intention reason	A regardless of intention	A regardless of intention
11-15 times	Not M but can be A if marked as intention	Code as intention reason	Code as intention reason	A regardless of intention	A regardless of intention
More than 15 times	Not M but can be A if marked as intention	Code as intention reason	Code as intention reason	A regardless of intention	A regardless of intention

Question 7c: Classification of POMAQ Responses

	Stimulants	**Anti-anxiety**	**Sleeping Pills**	**Antihistamines**	**Barbiturates**	**Antipsychotics**	**Other**
1. HCP prescribed medications to be taken together				-			
2. Different HCPs prescribed medications				-			
3. To feel high or stoned				**A for all**			
4. Dose prescribed not strong enough to treat pain				**M** if #1 or #2 not selected			
5. To feel less depressed or nervous	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected

		Stimulants	Anti-anxiety	Sleeping Pills	Antihistamines	Barbiturates	Antipsychotics	Other
6.	To sleep better	**M**	-	-	-	-	**M**	**M** if #1 or #2 not selected
7.	To feel more talkative or outgoing	**A**	-	**A**	**A**	-	**A**	**A**
8.	To treat my pain faster				**M** if #1 or #2 not selected			
9.	To reduce my stress	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected
10.	To treat the emotional hurt	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected
11.	To boost effect of opioid pain medication				**A for all** if #1 not selected			
12.	Misunderstood instructions				**M**			
13.	To relax or feel mellow	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected	-	**M** if #1 or #2 not selected	**M** if #1 or #2 not selected
14.	Other				**TBD**			

6.4 Definitions and Operationalization of Potential Risk Factors Included in PMR 3033-1 Studies

Table 28. Details on Measurement of the Risk Factors Included in Risk Factor Analysis for PMR 3033-1 Studies

Potential Risk Factor	Data Source	Definition/Operationalization	Timeframe
Sociodemographic factors			
Age	Semistructured interview	18-39, 40-49, 50-59, ≥60 years	Date of interview
Sex	Semistructured interview	Male, female	Date of interview
Race[1]	Semistructured interview	White, Black, other/mixed	Date of interview
Ethnicity[1]	Semistructured interview	Hispanic, not Hispanic	Date of interview
Highest education level	Semistructured interview	<High school degree, high school or general equivalency degree, any college, any graduate school	Date of interview
Annual income	Semistructured interview	≤$25,000, $25,001-50,000, $50,001-75,000, $75,001-100,000, $100,001-150,000, >$150,000, prefer not to report	Date of interview
Insurance type	EHR or claims	Medicaid vs. other	Past 12 months
Predominant place of care	EHR or claims	IDS with care only, IDS with care and insurance, or network fee for service	Past 12 months
OA-related factors			
Predominant opioid moiety	EHR or claims	Based on prescription dispensing; "predominant" defined as longest cumulative days' supply in the past 12 months or most prescriptions in case of a tie. Oxycodone, morphine, hydrocodone, fentanyl, methadone, oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, butorphanol, other	Past 6 months (prospective study), Past 12 months (cross-sectional study)
Predominant opioid formulation (i.e., ER/LA or IR/SA)	EHR or claims	Based on prescription dispensing; "predominant" defined as type with the most days' supply; categorized as ER/LA vs. IR/SA	Past 6 months (prospective study), Past 12 months (cross-sectional study)
Use of abuse-deterrent formulation	EHR or claims	Based on prescription dispensing; dichotomized as yes vs. no	Past 6 months (prospective study), Past 12 months (cross-sectional study)

Potential Risk Factor	Data Source	Definition/Operationalization	Timeframe
Average daily opioid dose	EHR or claims	Based on prescription dispensing; MME calculated for each opioid dispensed by multiplying quantity by strength (i.e., mg. per unit dispensed) by drug-specific conversion factors published by the CDC. For drugs or formulations where the CDC does not have recommendations for conversion (e.g., tramadol, levorphanol, buprenorphine), used CMS conversion factors.[2] Total MME for an episode calculated by adding the MMEs for each opioid dispensed during the episode; average daily dose for an episode calculated as total MMEs divided by episode duration. If there were opioids from multiple dispensations on the same day, daily MMEs were summed for that day. <50, 50-89, 90-119, ≥120 MME per day	Past 6 months (prospective study), Past 12 months (cross-sectional study)
Duration of Schedule II OA therapy in the 6-month baseline period, prospective study only)	EHR or claims	Based on prescription dispensing; estimated by summing duration of each episode. Because patients prescribed opioid types or doses may change over time, captured duration of exposure to each opioid type (e.g., ER/LA, IR/SA), as well as cumulative and average daily doses of opioid exposure in MME. Operationalized as number of weeks.	Past 6 months
History of substance use disorders			
Nonopioid, non-nicotine substance-use disorders *in the past year*[2]	Semistructured interview	Any disorder related to hallucinogens, sedatives, cocaine, stimulants, alcohol, cannabis, or other drugs, based on data collected in PRISM-5-Op	Past 12 months
Prior nonopioid, non-nicotine substance-use disorders *prior to the past year*[2]	Semistructured interview	See above	Prior to past 12 months
Health- and pain-related factors			
Number of inpatient visits	EHR or claims	Count of visits, categorized as 0, 1-2, ≥3	Past 12 months
Number of emergency department visits	EHR or claims	Count of visits, categorized as 0, 1-2, ≥3	Past 12 months
Other medication use (antidepressants, antipsychotics, gabapentinoids, muscle relaxers, naloxone, sedative hypnotics, stimulants)	EHR or claims	Medication use defined as ≥2 dispensings in the prior year, except naloxone, where use was defined as ≥1 dispensings or ≥1 procedure codes. Each medication assessed separately and dichotomized as yes vs. no	Past 12 months
Number of pain conditions	EHR or claims	Count of conditions[3] based on diagnosis codes; categorized as 0, 1-2, or ≥3	Past 12 months
Elixhauser Comorbidity Index	EHR or claims	Calculated from algorithm[4] based on diagnosis codes; categorized as 0, 1, or ≥2	Past 12 months
Body mass index category	EHR	Calculated from recorded height and weight; categorized as underweight/normal, overweight, obese	Past 12 months*
Fibromyalgia from patient-reported symptoms	Questionnaire	Based on criteria in the 2011 modification of the American College of Rheumatology Preliminary Diagnostic Criteria for Fibromyalgia	Current, past 6 months

Potential Risk Factor	Data Source	Definition/Operationalization	Timeframe
Pain severity	Questionnaire	Brief Pain Inventory-Short Form [BPI-SF], continuous score 0-10	Current, past 3 months
Pain interference	Questionnaire	The extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. BPI-SF, continuous score 0-10	Current, past 3 months
Physical capability	Questionnaire	12-item Short Form Health Survey [SF-12], continuous score 0-100	Past 1 month
Mental capability	Questionnaire	SF-12, continuous score 0-100	Past 1 month
Mental health and social factors			
Major depressive disorder *in the past year*	Semistructured interview	Based on data collected in PRISM-5-Op	Past 12 months
Major depressive disorder *prior to the past year*	Semistructured interview	Based on data collected in PRISM-5-Op	Prior to past 12 months
ADHD	Questionnaire	Adult ADHD Self-Report Scale, v. 1.1, score ≥11	Past 6 months
Borderline personality disorder	Questionnaire	Maclean Borderline Personality Disorder Screener, score ≥7	Current*
GAD	Questionnaire	7-item GAD Screener [GAD-7], score ≥10	Past 2 weeks
PTSD	Questionnaire	5-item PTSD Checklist [PCL-5], score ≥33	Past 1 month
History of parental substance use	Questionnaire	Unknown	Reported on date of questionnaire
Adverse childhood experiences	Questionnaire	Number of experiences of: neglect, emotional, physical, or sexual abuse, or domestic violence before age 18 years	Lifetime
Poor sleep quality	Questionnaire	Pittsburgh Sleep Quality Index, score ≥6	Past 1 month
Stress	Questionnaire	Perceived Stress Scale, continuous score 0-40	Past 1 month
Social support	Questionnaire	Medical Outcome Survey, continuous score 0-100	Current*
Genetic factors			
Genetic burden scores (OPRM1, CYP3A4, CYP2D6)	Saliva sample	SNPs sequenced in a subset of patients across 3 genes: OPRM1 (3 SNPs), CYP3A4 (4 SNPs), and CYP2D6 (2 SNPs). SNPs coded 0/1/2; weighted sum calculated per gene, with SNP-specific weights derived based on minor allele frequencies.	Not applicable

Source: FDA-generated table from information provided in final study reports, Final Report on the Prospective Study Results: December 16, 2022 and 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022.

* Exact timeframe not specified.

[1] Race and ethnicity were available from both EHR and questionnaire data, but the questionnaire data were used for the risk factor analysis.

[2] The conversion factors for tramadol, hydromorphone, and methadone changed during the prospective PMR 3033-1 study (2019); however, it is unclear if these changes affected the dose calculations. These changes occurred after data collection for cross-sectional PMR 3033-1 was completed.

[2] Substance use disorders, including nicotine use disorder, were also assessed as individual risk factors in unadjusted and demographically adjusted models (but not the fully adjusted models).

[3] Pain conditions included abdominal and bowel; limb/extremity, joint, arthritic disorders; back; musculoskeletal and chest; fractures, contusions, sprains and strains; fibromyalgia; headache; neck; neuropathy; orofacial, ear, and temporomandibular; other; systemic disorders or diseases causing pain; urogenital, pelvic and menstrual; other (i.e., acquired deformities [excluding back], cancer-related, general, postoperative, post-trauma, restless leg syndrome, spinal cord injury, bone infections, infectious arthritic diseases).

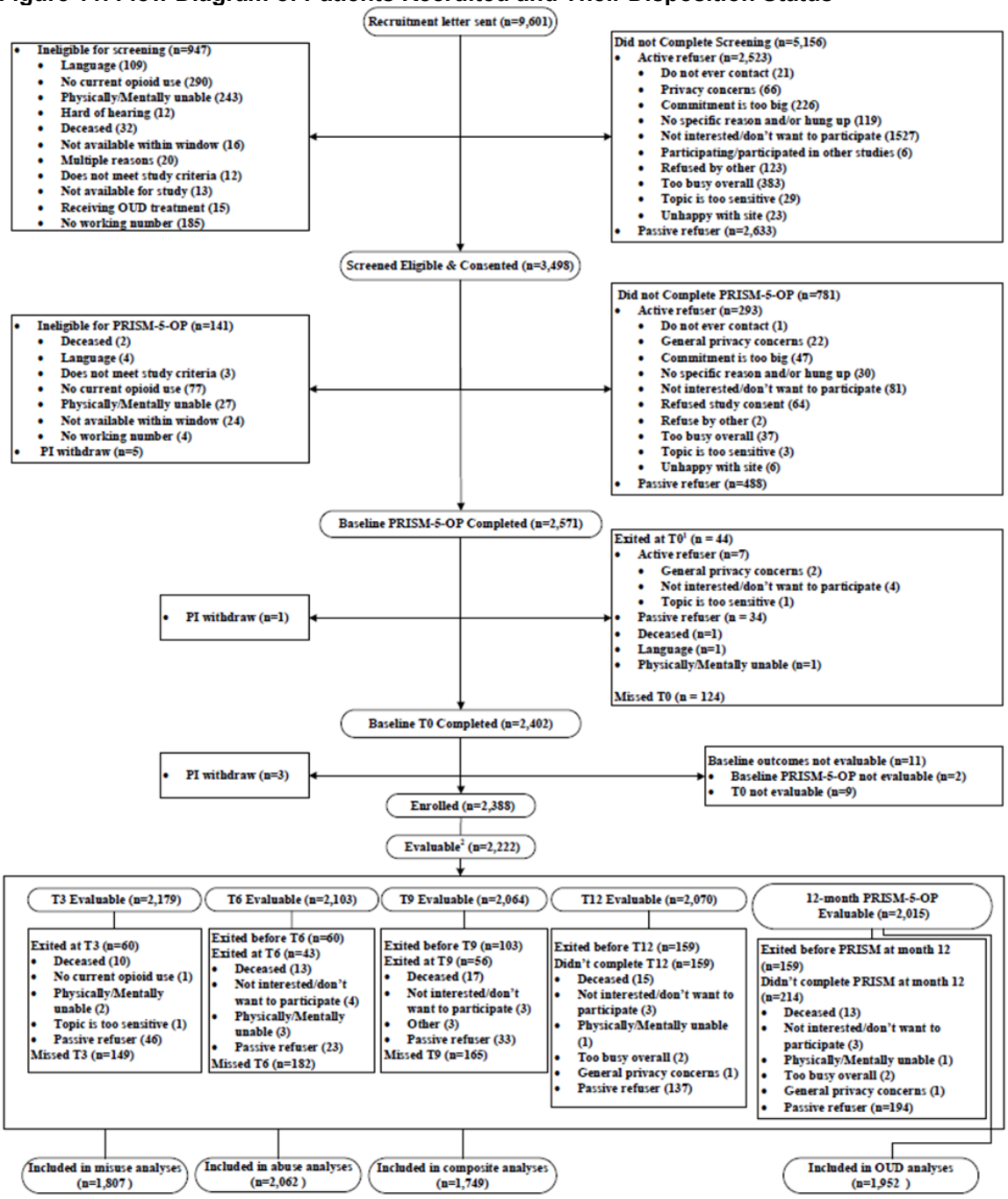
[4] Details of the algorithm, such as included comorbidities are published elsewhere (Thompson et al. 2015).

[4] Substance use disorders, including nicotine use disorder, were assessed as individual risk factors in unadjusted and demographically adjusted models.

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; CMS, Centers for Medicare and Medicaid Services; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EHR, electronic health records; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; IDS, integrated delivery system; MME: morphine milligram equivalent; OA, opioid analgesic; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; SNP, single nucleotide polymorphism

6.5 Prospective PMR 3033-1 Study Figures and Tables

Figure 11. Flow Diagram of Patients Recruited and Their Disposition Status



Source: Figure 2, Final Report on the Prospective Study Results

[1] All T surveys included for the POMAQ and other survey instruments.

[2] Definition of "evaluable" at a given timepoint: the measure (based on POMAQ or PRISM-5-Op) was able to be scored at the particular timepoint. Patients must have completed at least two evaluable POMAQ follow-up measures and must not have had the given outcome at baseline to be included in the misuse or abuse analyses; they must have completed the follow-up PRISM-5-Op and not have had OUD at baseline to be included in the OUD analysis. 2,222 unique patients were included in any outcome analysis. Patients could be included in multiple outcome analyses.

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM 5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; T0, time zero (baseline); T3, 3-month survey; T6, 6-month survey; T9, 9-month survey; T-12, 12-month survey

Table 29. Baseline Characteristics of the ER/LA and LtOT Cohorts, by Incident Opioid Misuse or Opioid Abuse Outcome Status,[1] Prospective 3033-1 Study

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Study site										
1	12.6	13.7	4.1	11.1	9.3	13.5	5.1	10.0	12.9	9.3
2	7.7	6.8	21.7	20.0	14.0	6.5	17.2	19.6	6.9	19.3
3	6.6	6.8	15.2	17.9	3.5	7.2	19.2	16.5	6.6	16.8
4	38.8	41.1	16.6	12.6	45.3	40.6	18.2	13.6	41.4	14.0
5	10.4	10.6	11.1	9.3	5.8	10.7	7.1	9.6	10.4	9.3
6	1.1	1.8	1.4	1.8	0.0	1.6	3.0	1.9	1.3	2.1
7	3.3	1.4	1.8	1.4	2.3	1.7	1.0	1.8	1.8	1.8
8	3.3	2.6	11.1	5.7	3.5	2.7	8.1	6.7	2.6	6.8
9	1.1	1.0	0.5	0.4	1.2	0.7	0.0	0.4	0.8	0.6
10	15.3	14.3	16.6	19.8	15.1	14.9	21.2	20.0	15.2	19.9
Age group, years										
18-39	6.6	10.5	9.2	10.4	14.0	10.5	15.2	10.2	10.6	10.6
40-49	14.2	12.6	14.7	17.4	16.3	12.8	15.2	17.1	13.5	17.2
50-59	25.1	28.2	33.2	26.0	22.1	28.4	24.2	27.9	27.4	27.3
≥60	54.1	48.8	42.9	46.2	47.7	48.2	45.5	44.8	48.5	44.9
Sex										
Female	53.0	59.6	64.5	61.2	54.7	58.5	53.5	61.0	56.9	59.4
Male	47.0	40.4	35.5	38.8	45.3	41.5	46.5	39.0	43.1	40.6
Race										
White	79.2	84.1	73.3	77.6	76.7	83.9	79.8	77.6	83.4	78.1
Black	10.4	8.9	19.8	14.5	8.1	9.5	15.2	15.0	9.1	14.8
Other/mixed	10.4	6.6	6.5	6.7	14.0	6.3	5.1	6.5	7.0	6.4
Missing	0.0	0.5	0.5	1.1	1.2	0.4	0.0	1.0	0.5	0.8
Hispanic/Latino ethnicity	8.7	11.0	8.8	9.9	8.1	11.0	9.1	9.5	10.8	9.2
BMI (kg/m^2)										
Underweight/normal	16.4	19.2	12.0	12.8	23.3	17.2	17.2	12.4	18.4	13.1
Overweight	21.9	22.9	24.4	22.1	27.9	22.2	26.3	22.3	22.9	22.8
Obese	47.5	48.0	50.7	49.9	39.5	50.4	42.4	50.6	48.2	49.4
Missing	14.2	10.0	12.9	15.1	9.3	10.2	14.1	14.7	10.5	14.7
Medicaid insurance	23.5	17.7	25.8	20.0	20.9	19.5	25.3	20.4	19.7	20.8

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Predominant place of care										
Care and insurance in an integrated delivery system	73.2	76.5	60.4	63.7	68.6	76.2	64.6	63.2	76.2	63.2
Care only in an integrated delivery system	18.0	17.7	26.7	26.8	24.4	17.8	27.3	26.3	17.7	26.4
Network or fee-for-service providers	8.7	5.8	12.9	9.4	7.0	5.9	8.1	10.5	6.1	10.4
ED visits (n)										
0	56.3	51.9	59.0	63.1	55.8	51.8	60.6	61.8	53.0	61.7
1-2	27.3	33.0	30.4	28.0	31.4	31.5	34.3	28.5	30.9	28.9
≥3	16.4	15.1	10.6	8.9	12.8	16.7	5.1	9.7	16.2	9.4
Inpatient stays (n)										
0	74.9	67.1	78.8	74.4	81.4	68.6	74.7	75.1	69.3	75.2
1	16.9	21.7	15.2	20.2	12.8	20.1	18.2	18.7	19.6	18.5
≥2	8.2	11.1	6.0	5.3	5.8	11.3	7.1	6.2	11.0	6.3
Predominant OA formulation[4]										
IR/SA opioid	66.1	56.2	97.7	97.5	65.1	59.3	98.0	97.7	60.2	97.6
ER/LA opioid	33.9	43.5	2.3	2.2	34.9	40.5	2.0	2.0	39.6	2.2
Predominant opioid moiety[4]										
Oxycodone	32.8	24.2	32.7	35.8	25.6	27.5	30.3	35.2	27.5	34.6
Morphine	23.5	28.5	1.8	2.3	20.9	27.2	3.0	1.8	26.5	2.0
Hydrocodone	23.5	18.2	60.8	56.4	27.9	18.9	61.6	57.8	19.4	57.8
Fentanyl	2.2	7.2	0.0	0.1	5.8	6.1	0.0	0.1	5.8	0.1
Methadone	2.7	5.8	0.0	0.3	4.7	5.3	0.0	0.2	5.4	0.2
Oxymorphone	1.1	0.3	0.0	0.0	1.2	0.5	0.0	0.0	0.5	0.0
Hydromorphone	3.8	2.6	0.5	1.3	3.5	2.2	4.0	0.9	2.5	1.3
Tramadol	4.9	8.4	1.8	2.4	3.5	8.5	1.0	2.3	8.0	2.3
Buprenorphine[5]	3.3	2.9	0.5	0.4	3.5	2.4	0.0	0.5	2.6	0.4
Codeine	1.6	1.4	1.8	0.5	2.3	1.1	0.0	0.8	1.3	0.7
Tapentadol	0.5	0.0	0.0	0.1	1.2	0.0	0.0	0.2	0.2	0.2
Meperidine	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.1	0.0	0.1
Butorphanol	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0
Abuse deterrent opioid exposure[4]	12.0	9.7	1.8	0.8	8.1	10.7	1.0	1.0	10.1	1.0

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Average daily dose, MMEs[4]										
<50	43.2	49.8	86.6	86.5	47.7	46.9	84.8	86.4	46.2	86.1
50-89	32.8	31.6	10.1	9.7	31.4	31.5	10.1	10.2	32.2	10.3
90-119	11.5	9.3	1.8	1.9	10.5	10.2	4.0	1.6	10.1	1.9
≥120	12.6	9.0	1.4	1.5	10.5	11.2	1.0	1.5	11.2	1.4
Other medication use[6]										
Antidepressants	68.3	59.1	55.8	45.4	62.8	61.0	58.6	47.8	60.9	49.5
Tricyclic antidepressants	13.1	13.5	12.0	8.0	14.0	14.1	3.0	9.3	13.5	8.9
Nontricyclic antidepressants	63.4	52.5	53.0	40.5	55.8	54.8	55.6	43.0	54.9	44.9
Antipsychotics	11.5	6.0	7.8	5.7	9.3	7.5	17.2	6.6	7.7	7.4
Buprenorphine	1.6	0.6	0.5	0.3	0.0	1.2	1.0	0.2	1.3	0.2
Gabapentinoids	54.1	45.9	42.9	38.0	50.0	47.4	43.4	39.1	47.3	39.7
Muscle relaxers	38.3	36.6	33.6	37.2	40.7	38.5	35.4	36.5	37.8	35.9
Naloxone	20.8	19.3	13.4	13.6	20.9	20.2	15.2	13.3	20.0	13.6
Sedative hypnotics	35.0	31.4	32.3	24.4	32.6	31.9	28.3	26.0	32.2	26.5
Benzodiazepines	31.1	26.1	26.7	20.0	25.6	27.4	27.3	21.1	27.5	21.9
Nonbenzodiazepine sedative hypnotics	8.7	8.1	8.8	7.6	8.1	8.0	2.0	7.8	7.9	7.6
Stimulants	4.4	3.1	3.7	2.9	1.2	3.6	4.0	3.4	3.7	3.4
Pain conditions from EHR										
Abdominal and bowel	19.7	24.2	19.4	19.1	18.6	23.9	14.1	19.7	23.1	18.6
Limb/extremity, joint, noninflammatory arthritic disorders	71.0	67.6	67.3	65.3	60.5	69.1	60.6	66.7	68.4	66.3
Back	67.8	64.3	60.8	58.4	60.5	65.5	65.7	58.6	64.9	59.2
Musculoskeletal and chest	13.1	11.9	7.4	9.2	10.5	12.1	10.1	8.9	11.8	8.9
Fractures, contusions, sprains, strains	14.2	19.6	16.1	14.4	12.8	18.7	15.2	14.1	18.4	14.4
Fibromyalgia	16.4	15.5	5.5	9.8	19.8	15.2	2.0	9.4	15.4	8.5
Headache	13.1	14.8	15.2	13.0	11.6	15.4	14.1	12.7	14.5	12.6
Neck	29.0	22.5	24.0	22.5	20.9	24.2	23.2	22.8	24.4	22.5
Neuropathy	23.5	23.3	15.7	16.3	18.6	24.0	22.2	15.9	23.2	16.2
Orofacial, ear, and temporomandibular	0.5	1.3	1.4	1.0	3.5	1.5	0.0	1.2	1.5	1.0
Other	78.7	74.2	66.8	58.5	88.4	75.3	76.8	58.7	76.5	60.5
Systemic disorders or diseases causing pain	8.7	13.2	5.5	5.7	16.3	11.5	3.0	5.8	11.9	5.3
Urogenital, pelvic, and menstrual	2.2	3.7	5.1	2.7	4.7	3.4	6.1	2.9	3.3	3.1

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Number of pain conditions recorded in EHR										
0	2.2	3.1	2.8	5.6	2.3	2.7	1.0	4.9	2.5	4.7
1-2	29.5	26.6	33.6	35.2	30.2	26.9	38.4	36.4	27.7	36.7
≥3	68.3	70.4	63.6	59.2	67.4	70.4	60.6	58.7	69.8	58.6
ECI score										
0	9.8	6.4	6.9	11.1	12.8	6.5	9.1	10.5	7.5	10.4
1	7.7	12.4	12.4	13.4	8.1	11.6	17.2	12.9	11.6	13.6
≥2	81.4	80.5	80.6	75.3	79.1	81.1	73.7	76.4	80.4	75.8
Missing	1.1	0.6	0.0	0.3	0.0	0.7	0.0	0.2	0.6	0.2
Annual household income, $										
$25,000 or less	29.0	26.6	35.0	28.5	30.2	27.2	34.3	29.1	27.5	30.0
$25,001-$50,000	23.0	20.8	21.2	22.4	19.8	20.2	24.2	22.0	19.7	21.9
$50,001-$75,000	17.5	17.2	16.1	15.9	17.4	17.2	15.2	16.3	16.9	15.9
$75,001-$100,000	8.2	15.0	10.1	14.5	8.1	13.0	10.1	13.8	13.0	13.6
$100,001-$150,000	8.7	8.4	10.6	9.9	10.5	9.8	8.1	10.1	10.1	9.9
Greater than $150,000	6.0	7.6	4.1	5.6	8.1	7.8	3.0	5.4	7.9	5.2
Prefer not to report	7.7	4.5	2.8	3.2	5.8	4.8	5.1	3.3	4.9	3.5
Education										
<High school degree	7.1	5.2	12.4	8.8	4.7	5.2	19.2	8.7	5.3	9.2
High school or General Equivalency Degree	15.8	22.1	21.2	24.6	9.3	21.2	17.2	25.1	19.7	24.7
Any college	67.8	59.3	55.3	57.3	75.6	60.7	52.5	56.6	62.4	56.3
Any graduate school	9.3	13.5	11.1	9.4	10.5	12.8	11.1	9.7	12.6	9.8
Substance use disorders from baseline PRISM-5-Op interviews										
Nonopioid and non-nicotine substance use disorder, past year	9.3	4.2	14.3	4.3	15.1	4.2	15.2	6.1	6.5	8.3
Nonopioid and non-nicotine substance use disorder, prior to past year	37.7	22.4	33.6	29.0	41.9	26.5	47.5	31.6	29.0	34.1
Hallucinogen use disorder, past year	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Hallucinogen use disorder, prior to past year	3.3	1.4	1.8	2.2	1.2	1.9	6.1	2.3	1.8	2.9
Sedative use disorder, past year	0.5	0.2	0.0	0.0	0.0	0.5	0.0	0.1	0.4	0.2
Sedative use disorder, prior to past year	3.8	0.6	0.9	1.5	4.7	1.1	5.1	1.7	1.4	2.3
Cocaine use disorder, past year	0.0	0.3	1.4	0.0	0.0	0.1	2.0	0.2	0.2	0.5

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Cocaine use disorder, prior to past year	11.5	4.3	12.4	7.0	10.5	5.9	18.2	8.6	6.4	10.4
Stimulant use disorder, past year	0.5	0.0	0.0	0.1	0.0	0.1	0.0	0.1	0.1	0.2
Stimulant use disorder, prior to past year	6.0	3.4	4.6	3.8	7.0	4.5	9.1	4.3	4.6	5.2
Alcohol use disorder, past year	6.6	2.1	8.8	2.0	7.0	2.8	9.1	3.3	4.2	4.7
Alcohol use disorder, prior to past year	28.4	18.2	26.3	22.5	32.6	21.7	35.4	24.1	23.7	26.0
Cannabis use disorder, past year	4.4	2.1	5.1	2.5	8.1	1.5	6.1	2.9	2.7	3.9
Cannabis use disorder, prior to past year	12.0	6.0	9.7	8.9	11.6	7.2	12.1	9.4	8.0	10.2
Other drug use disorder, past year	0.0	0.2	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0
Other drug use disorder, prior to past year	0.0	0.0	0.0	0.0	1.2	0.2	0.0	0.0	0.3	0.0
Nicotine use disorder, past year	26.2	13.0	22.1	18.3	31.4	14.3	26.3	19.7	16.3	21.0
Nicotine use disorder, prior to past year	40.4	27.1	36.4	36.6	41.9	29.6	40.4	38.2	31.1	38.3
OUD,[7] past year	1.1	1.8	1.8	0.6	5.8	2.8	9.1	1.0	3.1	1.6
OUD-H, past year	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
OUD-P, past year	1.1	1.8	1.8	0.6	5.8	2.8	9.1	1.0	3.1	1.6
OUD,[7] prior to past year	7.1	4.5	7.4	2.8	11.6	5.9	14.1	4.6	6.7	5.9
OUD-H, prior to past year	2.7	1.8	1.8	1.3	1.2	1.8	3.0	1.6	1.6	1.9
OUD-P, prior to past year	4.9	3.2	6.0	1.8	10.5	4.6	13.1	3.4	5.5	4.7
Other measures from baseline PRISM-5-Op										
Major depressive disorder, past year	16.9	13.5	11.1	10.6	20.9	14.5	20.2	12.2	15.1	12.8
Major depressive disorder, prior to past year	26.2	24.6	20.7	19.1	33.7	25.3	30.3	20.1	25.6	20.7
History of parental substance use	48.6	40.4	53.0	43.6	55.8	42.1	57.6	45.0	44.2	46.5
Prescription opioid misuse and prescription opioid abuse from baseline POMAQ questionnaire										
Prescription opioid misuse, past 3 months	Not applicable		Not applicable		32.6	13.5	37.4	14.0	16.3	18.1
Prescription opioid abuse, past 3 months	6.6	3.2	9.2	2.0	Not applicable		Not applicable		5.2	6.1
Participant-reported questionnaires: categorical or binary measures										
ACE										
0	15.3	22.2	18.9	24.7	11.6	21.3	15.2	22.2	19.9	21.6
1	12.6	17.7	16.6	17.8	15.1	16.4	14.1	17.5	16.1	17.0
2	16.9	13.7	10.1	11.6	5.8	14.7	8.1	12.2	13.7	11.6
3	13.1	12.1	13.8	11.1	11.6	13.0	16.2	12.6	13.0	12.9
4+	41.5	34.1	40.1	34.4	55.8	34.3	44.4	35.2	37.0	36.5
Missing	0.5	0.2	0.5	0.5	0.0	0.4	2.0	0.3	0.3	0.4

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
ADHD[8]										
0-10	79.8	87.3	87.1	87.4	77.9	85.3	84.8	86.9	84.7	86.2
11-20	19.7	12.6	12.4	12.5	20.9	14.2	14.1	12.9	14.8	13.5
Missing	0.5	0.2	0.5	0.1	1.2	0.5	1.0	0.2	0.5	0.3
Borderline personality disorder	13.1	5.6	9.7	6.1	26.7	7.2	14.1	7.6	8.7	8.6
GAD	28.4	17.9	27.2	20.4	36.0	20.2	30.3	22.1	21.9	23.6
Fibromyalgia from patient-reported symptoms	9.8	7.2	8.3	7.0	12.8	8.0	8.1	7.8	8.6	7.6
Poor sleep quality	79.8	76.8	78.3	78.2	86.0	78.3	83.8	78.9	78.8	79.7
PTSD	16.4	11.9	18.9	8.8	30.2	13.6	18.2	11.4	14.7	12.5
SNPs collected from genetic testing[9]										
OPRM1 SNPs										
rs1799971 minor allele										
0	56.8	57.8	51.6	50.5	67.4	57.2	53.5	51.0	57.4	51.6
1	13.7	15.6	18.0	13.2	8.1	15.2	14.1	14.0	14.9	13.6
2	0.5	1.1	1.4	1.7	0.0	1.1	1.0	1.4	1.0	1.4
Missing[9]	29.0	25.4	29.0	34.6	24.4	26.5	31.3	33.6	26.7	33.4
rs3778150 minor allele										
0	48.1	52.8	52.5	45.8	44.2	51.8	49.5	47.0	51.1	46.6
1	20.8	18.7	18.0	17.7	29.1	18.9	18.2	17.7	19.6	18.1
2	2.2	3.1	0.9	2.2	2.3	2.8	1.0	2.0	2.6	2.1
Missing[9]	29.0	25.4	28.6	34.4	24.4	26.5	31.3	33.4	26.7	33.2
rs9479757 minor allele										
	55.7	62.5	58.5	53.6	55.8	61.3	55.6	55.1	60.6	54.6
1	14.2	11.8	12.4	10.1	19.8	11.5	12.1	10.1	12.2	10.7
2	1.1	0.8	0.5	1.7	0.0	1.0	1.0	1.1	0.8	1.2
Missing[9]	29.0	25.0	28.6	34.7	24.4	26.2	31.3	33.7	26.4	33.5
Cytochrome P450 2D6 SNPs										
rs133333 minor allele										
0	42.6	40.7	41.0	34.7	46.5	41.1	37.4	36.4	41.5	36.7
1	24.6	28.7	26.7	24.3	24.4	28.1	24.2	24.2	27.2	24.3
2	4.4	5.3	4.1	6.5	4.7	4.5	7.1	6.1	4.7	5.9
Missing[9]	28.4	25.3	28.1	34.5	24.4	26.3	31.3	33.3	26.6	33.1

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
rs5758550 minor allele										
0	42.6	41.1	40.6	34.9	46.5	41.2	37.4	36.4	41.7	36.7
1	24.6	28.3	26.3	23.7	24.4	27.9	24.2	23.8	27.0	23.7
2	4.4	5.5	4.1	6.6	4.7	4.6	7.1	6.2	4.8	5.9
Missing[9]	28.4	25.1	29.0	34.9	24.4	26.3	31.3	33.7	26.5	33.6
Cytochrome P450 3A4 SNPs										
rs4646440 minor allele										
0	69.4	71.3	68.2	61.8	73.3	70.3	66.7	62.6	70.3	63.3
1	2.2	3.2	3.2	3.7	2.3	3.3	2.0	3.8	3.1	3.5
2	0.0	0.2	0.0	0.3	0.0	0.1	0.0	0.2	0.1	0.2
Missing[9]	28.4	25.3	28.6	34.2	24.4	26.3	31.3	33.4	26.5	33.1
rs2242480 minor allele										
0	52.5	53.6	45.6	41.6	48.8	53.9	48.5	43.2	52.7	44.1
1	14.8	15.6	17.1	16.2	22.1	14.5	13.1	15.9	15.7	15.4
2	3.3	5.2	8.3	6.9	3.5	4.6	7.1	6.7	4.5	6.6
Missing[9]	29.5	25.6	29.0	35.4	25.6	26.9	31.3	34.2	27.1	34.0
rs4987161 minor allele										
0	71.6	74.9	71.0	65.6	75.6	73.7	68.7	66.4	73.4	66.7
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Missing[9]	28.4	25.1	29.0	34.4	24.4	26.3	31.3	33.6	26.6	33.3
rs4646438 minor allele										
0	71.0	74.1	71.4	65.1	73.3	73.0	67.7	66.3	72.7	66.5
1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Missing[9]	29.0	25.9	28.6	34.9	26.7	27.0	32.3	33.7	27.3	33.5
Duration of Schedule II OA therapy during baseline period,[4] mean (SD) days	138.9 (44.5)	127.5 (45.1)	110.0 (29.6)	105.7 (24.1)	140.7 (42.8)	130.8 (45.7)	109.0 (28.9)	107.4 (25.3)	131.7 (45.4)	107.7 (25.6)
Participant-reported questionnaires: continuous measures, mean (SD)										
Pain severity	5.8 (1.8)	5.3 (2.1)	5.9 (2.0)	5.5 (2.1)	5.8 (1.9)	5.5 (2.0)	5.8 (1.9)	5.6 (2.0)	5.5 (2.0)	5.6 (2.0)
Pain interference	6.4 (2.1)	5.9 (2.4)	6.0 (2.5)	5.7 (2.5)	6.6 (2.3)	6.0 2.3)	6.2 (2.3)	5.8 (2.5)	6.1 (2.3)	5.9 (2.5)
Stress	17.3 (7.6)	14.4 (7.8)	15.5 (8.4)	13.5 (7.9)	17.8 (8.4)	15.1 (7.8)	15.9 (7.9)	14.1 (8.1)	15.4 (7.9)	14.4 (8.1)

	ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]		LtOT Cohort[3]		ER/LA Cohort[2]	LtOT Cohort[3]
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Total Cohort	Total Cohort
	Yes	No	Yes	No	Yes	No	Yes	No	-	-
	N=183	N=621	N=217	N=786	N=86	N=825	N=99	N=1,052	N=978	N=1,244
Baseline Characteristic	%	%	%	%	%	%	%	%	%	%
Social support	66.4	74.0	69.1	73.9	63.9	72.8	65.6	73.3 (25.9)	71.8	71.8
	(26.6)	(24.9)	(27.0)	(25.7)	(25.9)	(25.4)	(26.8)		(25.6)	(26.3)
SF-12 physical score	29.6	30.8 (9.1)	33.4	32.3	31.7	30.6 (8.8)	33.1	32.5	30.7	32.6
	(7.7)		(8.4)	(9.2)	(8.3)		(9.1)	(9.0)	(8.7)	(9.0)
SF-12 mental score	46.2	49.3	47.1	50.2	44.6	48.4	47.3	49.3 (11.4)	47.9	48.9
	(10.6)	(10.8)	(11.7)	(11.2)	(11.8)	(10.7)	(11.3)		(10.9)	(11.5)
Gene-specific burden scores based on SNPs collected from genetic testing,[7] mean (SD)										
OPRM1 burden score	2.4 (2.8)	2.2 (2.8)	2.3 (2.4)	2.4 (2.9)	2.4 (2.7)	2.2 (2.7)	2.2 (2.5)	2.3 (2.8)	2.3 (2.7)	2.3 (2.8)
Cytochrome P450 2D6 burden score	2.1 (2.8)	2.4 (2.9)	2.2 (2.8)	2.6 (3.0)	2.0 (2.8)	2.3 (2.8)	2.5 (3.1)	2.5 (3.0)	2.3 (2.8)	2.4 (3.0)
Cytochrome P450 3A4 burden score	1.0 (2.0)	1.2 (2.4)	1.4 (2.4)	1.6 (2.7)	1.1 (2.0)	1.1 (2.4)	1.2 (2.3)	1.5 (2.6)	1.1 (2.3)	1.4 (2.6)

Source: FDA-generated table adapted from data provided in Final Prospective Tables, Table 7a and Table 7b, FDA IR Response dated July 19, 2023.

[1] Total number of individuals included for each study outcome varies because individuals were excluded from follow-up analysis of an outcome of interest (e.g., opioid misuse) if they were positive for that outcome at baseline.

[2] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[3] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[4] Baseline opioid exposure is measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominant opioid moiety and predominant OA formulation are based on the predominant OA, defined as the OA with the greatest total days' supply, or most prescriptions if there was a tie.

[5] Does not include buprenorphine formulations used to treat opioid use disorder.

[6] Other medication use defined as two or more dispensings in the prior year except for buprenorphine and naloxone where use defined as one or more dispensings or one or more procedure codes.

[7] All OUD measures in this table use the pain-adjusted DSM-5-OUD definition.

[8] ADHD was missing for 0.5% of the ER/LA cohort and 0.3% of the LtOT cohort. Percentage with ADHD is based on all participants, including those missing ADHD status.

[9] Genetic analyses include the subset of eligible individuals who provided evaluable genetic samples. The amount of missingness for each individual SNP for each outcome is reported.

Abbreviations: ACE, adverse childhood experiences; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; ED, emergency department; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, immediate-release/short-acting; kg/m^2, kilogram/meter^2; LtOT, long-term opioid use; MME, morphine milligram equivalent; n, number; OA, opioid analgesic; OPRM1, opioid receptor mu 1; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; SD, standard deviation; SF-12, 12-item Short Form Health Survey; SNP, single nucleotide polymorphism

Table 30. Odds Ratios and 95% CIs From Unadjusted Models for Incident Opioid Misuse, Opioid Abuse, and Moderate-to-Severe Pain-Adjusted DSM-5-OUD for the ER/LA and LtOT Cohorts, Prospective 3033-1 Study

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Sociodemographic factors												
Age group, years												
18-39	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
40-49	1.8	**0.0402**	0.9	0.8682	1.0	0.8511	0.6	0.2897	0.2	**0.0080**	0.8	0.7389
50-59	1.4	**0.0620**	1.4	0.4067	0.6	**0.0467**	0.6	0.1811	0.4	**0.0757**	0.9	0.9346
≥60	1.8	**0.0148**	1.0	0.9241	0.7	**0.0628**	0.7	0.3476	0.1	**0.0008**	0.6	0.4497
Sex												
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.3	0.1301	0.9	0.2708	1.2	0.3108	1.4	0.1709	1.3	0.5691	1.5	0.4584
Race												
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.2	0.4055	1.4	**0.0148**	0.9	0.8329	1.0	0.9093	1.0[5]	0.9570[5]	1.2	0.7169
Other/mixed	1.6	**0.0346**	1.0	0.9830	2.4	**0.0129**	0.8	0.2016			1.0	0.9841
Hispanic/Latino ethnicity												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.8	0.1325	0.8	0.4096	0.7	0.2131	1.0	0.9887	2.9	**0.0001**	2.2	**0.0070**
Annual household income, $												
≤25,000	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
25, 001-50,000	1.0	0.9522	0.8	**0.0438**	0.9	0.7315	0.9	0.7320	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
50, 001-75,000	0.9	0.7783	0.8	0.4955	0.9	0.7978	0.8	0.4488	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
75, 001-100,000	0.5	**0.0061**	0.6	**0.0007**	0.6	0.1494	0.6	**0.0288**	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
100, 001-150,000	1.0	0.8843	0.9	0.5062	0.9	0.8911	0.7	0.3836	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
>150,000	0.7	0.4128	0.6	0.1437	0.9	0.8763	0.5	**0.0683**	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Prefer not to report	1.6	0.1168	0.7	0.2964	1.1	0.7396	1.3	0.5540	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Education												
<High school degree	1.9	**0.0574**	1.6	**0.0453**	2.0	0.2181	3.2	**0.0015**	Not estimable[6]	Not estimable[6]	0.8	0.7782
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Any college	1.6	**0.0112**	1.1	0.4780	2.8	**0.0348**	1.4	0.2045	Not estimable[6]	Not estimable[6]	0.4	**0.0533**
Any graduate school	0.9	0.8412	1.3	0.3243	1.9	0.3755	1.7	0.1194	Not estimable[6]	Not estimable[6]	0.7	0.5921
Medicaid insurance												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.4	**0.0943**	1.4	0.1681	1.1	0.7681	1.3	0.4742	0.8	0.7486	1.3	0.5150
Predominant place of care												
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	1.1	0.4299	1.0	0.9287	1.8	**0.0145**	0.9	0.4419	Not estimable[6]	Not estimable[6]	1.2	0.8003
Network or fee-for-service providers	1.6	**0.0711**	1.4	0.3562	1.6	0.1776	0.7	**0.0370**	Not estimable[6]	Not estimable[6]	0.7	0.7069
OA-related factors												
Predominant opioid formulation[7]												
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	0.7	**0.0038**	1.1	0.8064	0.8	**0.0903**	1.0	0.9992	1.1	0.9118	NE[6]	NE[6]
Baseline average daily dose, MME[7]												
<50	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
50-89	1.2	0.1128	1.0	0.8539	1.0	0.9083	1.0	0.9764	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
90-119	1.4	**0.0584**	1.0	0.9818	1.0	0.9542	2.5	**0.0184**	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
≥120	1.6	**0.0006**	0.9	0.9253	0.9	0.8643	0.7	0.7203	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Predominant opioid moiety[7,8]												
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.6	**0.0316**	0.9	0.7053	0.8	0.3294	2.0	**0.0426**	0.8	0.7700	*	*
Hydrocodone	0.9	0.8104	1.2	0.2766	1.6	**0.0198**	1.2	0.2817	*	*	1.5	0.4219
Fentanyl	0.2	**0.0170**	*	*	1.0	0.9508	*	*	*	*	*	*
Methadone	0.3	**0.0323**	*	*	0.9	0.8607	*	*	*	*	*	*
Oxymorphone	*	*	*	*	*	*	*	*	*	*	*	*
Hydromorphone	1.1	0.7627	*	*	1.7	0.2172	5.5	**<0.0001**	*	*	*	*
Tramadol	0.4	**0.0006**	0.8	0.6608	0.4	0.1407	*	*	*	*	*	*
Buprenorphine	0.9	0.6274	*	*	1.6	0.6424	*	*	*	*	*	*
Codeine	0.8	0.8189	4.1	**0.0417**	*	*	*	*	*	*	*	*
Tapentadol	*	*	*	*	*	*	*	*	*	*	*	*
Meperidine	*	*	*	*	*	*	*	*	*	*	*	*
Butorphanol	*	*	*	*	*	*	*	*	*	*	*	*
Other[9]	2.5	0.3268	0.4	0.1303	2.9	**0.0102**	0.3	0.2033	0.4	**0.0431**	0.9	0.8690
Use of an ADF OA[7] (any vs. none)	1.3	0.4216	2.6	0.2163	0.7	0.2895	0.9	0.9028	1.9	0.5141	Not estimable[6]	Not estimable[6]
Duration of Schedule II OA therapy during baseline period[7]												
Per 7-day increase	1.0	**0.0287**	1.0	**0.0139**	1.0	**0.0836**	1.0	0.1547	1.0	0.8975	1.1	0.1691
SUD history												
Past-year nonopioid, non-nicotine SUD (yes vs. no)	2.4	**0.0403**	3.6	**<0.0001**	4.0	**0.0002**	2.8	**<0.0001**	3.1	0.1097	11.3	**0.0002**
Nonopioid, non-nicotine SUD, prior to the past year (yes vs. no)	2.1	**<0.0001**	1.2	0.1277	2.0	**0.0187**	2.0	**0.0036**	2.6	0.2033	9.5	**<.0001**
Hallucinogen use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Hallucinogen use disorder, prior to the past year (yes vs. no)	2.3	0.2163	0.9	0.8787	0.6	0.6606	2.8	**0.0703**	Not estimable[6]	Not estimable[6]	1.9	0.5005
Sedative use disorder, past year (yes vs. no)	3.4	0.3860	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Sedative use disorder, prior to the past year (yes vs. no)	6.1	**0.0080**	0.6	0.4280	4.4	**0.0035**	3.0	**0.0502**	Not estimable[6]	Not estimable[6]	12.0	**<0.0001**
Cocaine use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	10.3	**0.0006**	Not estimable[6]	Not estimable[6]	17.2	**0.0224**
Cocaine use disorder, prior to the past year (yes vs. no)	2.9	**<0.0001**	1.9	**0.0134**	1.9	0.1555	2.4	**0.0001**	Not estimable[6]	Not estimable[6]	6.9	**<0.0001**

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Stimulant use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	30.1	**<0.0001**
Stimulant use disorder, prior to the past year (yes vs. no)	1.8	0.1710	1.2	0.1940	1.6	0.1817	2.4	**0.0053**	Not estimable[6]	Not estimable[6]	6.9	**<0.0001**
Alcohol use disorder, past year (yes vs. no)	3.3	**0.0047**	4.5	**0.0017**	2.6	**0.0273**	2.9	**<0.0001**	5.1	**0.0258**	16.2	**<0.0001**
Alcohol use disorder, prior to the past year (yes vs. no)	1.8	**0.0021**	1.2	0.1139	1.7	**0.0331**	1.7	**0.0157**	2.5	0.1435	4.3	**<0.0001**
Cannabis use disorder, past year (yes vs. no)	2.2	0.2574	2.0	**0.0742**	6.0	**<0.0001**	2.2	**0.0291**	Not estimable[6]	Not estimable[6]	7.5	**0.0007**
Cannabis use disorder, prior to the past year (yes vs. no)	2.2	**0.0289**	1.1	0.6565	1.7	**0.0087**	1.4	0.2180	1.1	0.9117	3.3	**0.0005**
Other drug use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Other drug use disorder, prior to the past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	4.8	**<0.0001**	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Nicotine use disorder, past year (yes vs. no)	2.3	**0.0002**	1.3	0.1623	2.8	**<0.0001**	1.4	0.1089	1.0	0.9656	2.6	**0.0274**
Nicotine use disorder, prior to the past year (yes vs. no)	1.8	**<0.0001**	1.0	0.9840	1.8	**0.0152**	1.1	0.7610	1.7	0.5718	2.0	**0.0489**
POMAQ-classified misuse (yes vs. no)	Not applicable		Not applicable		3.1	**<0.0001**	3.7	**<0.0001**	4.3	**0.0508**	3.6	**0.0018**
POMAQ-classified abuse (yes vs. no)	2.1	**0.0312**	4.8	**<0.0001**	Not applicable		Not applicable		1.5	0.6815	7.1	**<0.0001**
OUD, past year (yes vs. no)	0.6	0.2914	2.7	**0.0237**	2.2	**0.0590**	9.3	**<0.0001**	Not applicable		Not applicable	
OUD-H, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not applicable		Not applicable	
OUD-P,[10] past year (yes vs. no)	0.6	0.2914	2.7	**0.0237**	2.2	**0.0590**	9.3	**<0.0001**	Not applicable		Not applicable	
OUD, prior to the past year (yes vs. no)	1.6	**0.0154**	2.7	**0.0015**	2.1	**<0.0001**	3.4	**<0.0001**	1.8	0.5506	7.9	**<0.0001**
OUD-H, prior to the past year (yes vs. no)	1.6	0.2479	1.4	0.5024	0.6	0.6423	1.9	0.2003	NE[6]	NE[6]	NE[6]	NE[6]
OUD-P,[10] prior to the past year (yes vs. no)	1.6	**0.0097**	3.4	**<0.0001**	2.4	**<0.0001**	4.3	**0.0008**	2.6	0.3393	11.6	**<0.0001**

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Health- and pain-related factors												
Emergency department visits												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1-2	0.8	**0.0149**	1.2	0.3462	0.9	0.3517	1.2	0.3650	0.9	0.8723	0.2	**0.0429**
≥3	1.0	0.9920	1.3	0.4255	0.7	0.4298	0.5	0.2881	1.7	0.2954	2.9	0.1652
Inpatient stays												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	0.7	**0.0026**	0.7	**0.0086**	0.5	**0.0027**	1.0	0.8421	Not estimable[6]	Not estimable[6]	1.1	0.8597
≥2	0.7	0.1159	1.1	0.6370	0.4	0.1098	1.1	0.6826	Not estimable[6]	Not estimable[6]	2.1	0.2723
Other medication use[11] (any vs. none)												
Antidepressants	1.5	**0.0295**	1.6	**<0.0001**	1.1	0.7193	1.5	0.1604	1.2	0.7619	1.9	**0.0038**
Antipsychotics	2.1	**0.0227**	1.4	0.0948	1.3	0.4733	2.9	**0.0453**	1.1	0.8978	0.8	0.7756
Gabapentinoids	1.4	**0.0036**	1.2	0.1051	1.1	0.3969	1.2	0.6387	2.2	**0.0003**	1.2	0.6586
Muscle relaxers	1.1	0.7491	0.9	0.2914	1.1	0.6493	0.9	0.6159	2.3	**0.0552**	1.2	0.7000
Naloxone	1.1	0.5619	0.9	0.8702	1.0	0.9016	1.2	0.4258	0.3	0.2946	3.3	**0.0324**
Sedative hypnotics	1.2	0.4915	1.5	**<0.0001**	1.0	0.9461	1.1	0.7423	0.2	0.1299	1.9	**0.0911**
Stimulants	1.5	0.1715	1.3	0.5810	0.3	**0.0867**	1.2	0.7421	Not estimable[6]	Not estimable[6]	1.8	0.3935
Number of pain conditions recorded in EHR												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1-2	1.5	0.4806	1.9	0.1744	1.3	0.6967	5.7	0.1131	Not estimable[6]	Not estimable[6]	1.1	0.9464
≥3	1.3	0.6059	2.1	0.1626	1.1	0.8926	5.6	0.1199	Not estimable[6]	Not estimable[6]	0.7	0.7303
ECI score												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	0.4	**0.0139**	1.5	0.1965	0.4	**<0.0001**	1.5	0.1441	0.2	**0.0002**	1.7	0.1874
≥2	0.7	0.1088	1.7	**0.0915**	0.5	**0.0137**	1.1	0.8083	0.2	**0.0291**	0.7	0.5488
Fibromyalgia from patient-reported symptoms												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.4	0.2660	1.2	0.5829	1.7	**0.0308**	1.0	0.9590	1.0	0.9822	NE[6]	NE[6]
BMI (kg/m^2)												
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	1.1	0.6619	1.2	0.5137	0.9	0.7608	0.8	0.5108	1.1	0.8992	0.6	0.5091
Obese	1.2	0.2494	1.1	0.7683	0.6	**0.0034**	0.6	**0.0015**	1.1	0.9051	0.9	0.8865
Missing	1.6	**0.0260**	0.9	0.7764	0.7	0.4025	0.7	0.1244	0.9	0.8574	0.5	0.3675

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Mental health conditions and social risk factors												
Major depressive disorder, past year (yes vs. no)	1.3	0.1269	1.0	0.8910	1.6	0.1394	1.8	**0.0079**	2.9	**0.0409**	0.9	0.8470
Major depressive disorder, prior to the past year (yes vs. no)	1.1	0.5328	1.1	0.5561	1.5	**0.0056**	1.8	**0.0065**	2.1	0.1586	1.5	0.2344
ADHD (yes vs. no)	1.7	**0.0015**	1.0	0.9921	1.6	0.1013	1.1	0.8159	1.2	0.6958	3.5	**0.0184**
Borderline personality disorder (yes vs. no)	2.5	**0.0003**	1.7	**0.0975**	4.8	**<0.0001**	2.0	**0.0164**	1.1	0.9277	3.3	**<0.0001**
GAD (yes vs. no)	1.8	**0.0129**	1.4	**0.0578**	2.3	**0.0600**	1.5	0.1385	Not estimable[6]	Not estimable[6]	2.7	**0.0220**
PTSD (yes vs. no)	1.5	**0.0934**	2.4	**<0.0001**	2.8	**<0.0001**	1.7	**0.0467**	2.4	**0.0634**	4.0	**<0.0001**
ACE												
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	1.0	0.9139	1.2	0.4247	1.7	0.1065	1.2	0.5776	3.6	0.1070	NE[6]	NE[6]
2	1.8	**0.0458**	1.2	0.4351	0.7	0.5035	1.0	0.9205	4.4	**0.0578**	NE[6]	NE[6]
3	1.6	**0.0126**	1.6	**0.0486**	1.6	0.1638	1.9	0.1159	1.6	0.7617	NE[6]	NE[6]
4+	1.8	**0.0012**	1.5	**0.0782**	3.0	**<0.0001**	1.9	**0.0072**	2.1	0.5531	NE[6]	NE[6]
History of parental substance use												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.4	**0.0048**	1.4	**0.0082**	1.7	**<0.0001**	1.6	**<0.0001**	0.8	0.7732	1.5	0.3186
Poor sleep quality												
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.1	0.2896	1.2	**0.0191**	2.0	0.2317	1.4	**0.0504**	2.1	0.2527	1.3	0.6360
Other patient-reported measures (per 1-unit change worse)												
Pain severity	1.1	**<0.0001**	1.1	**0.0053**	1.1	0.1806	1.1	0.1167	1.2	**0.0115**	1.1	0.1184
Pain interference	1.1	**<0.0001**	1.1	0.1398	1.1	**0.0291**	1.1	**0.0626**	1.1	0.7100	1.3	**0.0001**
Stress	1.0	**<0.0001**	1.0	**<0.0001**	1.0	**0.0113**	1.0	**0.0121**	1.0	0.4175	1.1	**<0.0001**
Social support	1.0	**<0.0001**	1.0	**<0.0001**	1.0	**0.0131**	1.0	**<0.0001**	1.0	0.9497	1.0	**0.0053**
SF-12 physical score	1.0	**0.0195**	1.0	**0.0719**	1.0	**0.0265**	1.0	0.2404	1.0	0.8016	1.0	0.7588
SF-12 mental score	1.0	0.0009	1.0	**<0.0001**	1.0	**0.0945**	1.0	0.0561	1.0	0.8768	1.1	**0.0039**

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Opioid Misuse		Opioid Misuse		Opioid Abuse		Opioid Abuse		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]		Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	
Risk Factor	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**	**Unadjusted OR**	**p[4]**
Genetic factors[12] (per 1 standard deviation increase gene-specific burden scores)												
OPRM1 burden score	1.1	0.6157	1.0	0.5319	1.1	0.5599	1.0	0.8736	0.6	0.3042	1.1	0.7879
Cytochrome P450 2D6 burden score	0.9	0.3375	0.9	**0.0781**	0.9	0.4182	1.0	0.8850	0.8	0.1836	1.1	0.7600
Cytochrome P450 3A4 burden score	0.9	**0.0853**	1.0	0.4224	1.0	0.9539	0.9	0.1472	0.5	**0.0053**	1.1	0.6293

Source: FDA-generated table from data provided in Appendix 1 Q5 Table D and Q5 Table G, FDA IR Response dated June 04, 2024.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] For this table (unadjusted models), factors with p≤0.10 are **bolded** and considered statistically significant. These factors were entered into the fully adjusted model for each outcome in addition to age, sex, race, and ethnicity.

[5] There were no Black participants with the OUD outcome. To achieve model convergence, Black race was combined with other/mixed race for this outcome.

[6] For cells denoted "not estimable," odds ratios could not be estimated due to a lack of model convergence arising from the small number of participants with this outcome.

[7] Baseline opioid exposure was measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominance was based on greatest total days' supply or most prescriptions if there was a tie.

[8] The following opioid moieties were not prescribed in this study population are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene.

[9] The *other* category for predominant opioid moiety combines all ingredients where there were ≤2 events for a given outcome. * indicates ingredients included in other, by outcome.

[10] Pain-adjusted.

[11] Other medication use defined as two or more dispensings in the prior year except for naloxone where use defined as one or more dispensings or one or more procedure codes.

[12] Genetic analyses include the subset of eligible individuals who provided evaluable genetic samples: 822 for OPRM1, 829 for Cytochrome P450 2D6, and 821 for Cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experience; ADF, abuse-deterrent formulation; ADHD, attention deficit/hyperactivity disorder; BMI, body mass index; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, immediate release/short-acting; LtOT, long-term opioid therapy; MME, morphine milligram equivalent; NE, not estimable; OA, opioid analgesic; OPRM1, opioid receptor mu 1; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; Ref, reference; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-OP, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; Ref, reference value; SF-12, 12-item Short Form Health Survey; SUD, substance use disorder

Table 31. Odds Ratios and 95% CIs From Demographically Adjusted Models for Incident Opioid Misuse, Opioid Abuse, and Moderate-to-Severe Pain-Adjusted DSM-5-OUD for the ER/LA and LtOT Cohorts, Prospective 3033-1 Study

	ER/LA Cohort[1]	LtOT Cohort[2]	ER/LA Cohort[1]	LtOT Cohort[2]	ER/LA Cohort[1]	LtOT Cohort[2]
	Opioid Misuse	Opioid Misuse	Opioid Abuse	Opioid Abuse	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]
Risk Factor	**Demographically Adjusted[4] OR (95% CI)**	**Demographically Adjusted[4] OR (95% CI)**	**Demographically Adjusted[4] OR (95% CI)**	**Demographically Adjusted[4] OR (95% CI)**	**Demographically Adjusted[4] OR (95% CI)**	**Demographically Adjusted[4] OR (95% CI)**
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	**2.0 (1.1, 3.4)**	0.9 (0.4, 2.0)	1.1 (0.7, 1.6)	0.6 (0.2, 1.6)	**0.2 (0.0, 0.7)**	0.8 (0.3, 2.7)
50-59	1.5 (1.0, 2.2)	1.4 (0.6, 3.1)	0.6 (0.4, 1.1)	0.6 (0.3, 1.3)	0.4 (0.2, 1.2)	0.8 (0.2, 3.1)
≥60	**1.8 (1.2, 2.9)**	1.0 (0.5, 2.0)	0.8 (0.6, 1.1)	0.7 (0.3, 1.5)	**0.1 (0.0, 0.3)**	0.7 (0.2, 2.1)
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.3 (0.9, 1.8)	0.9 (0.7, 1.2)	1.2 (0.9, 1.6)	1.4 (0.9, 2.1)	1.4 (0.6, 3.4)	1.7 (0.6, 4.4)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.4 (0.9, 2.1)	**1.3 (1.0, 1.7)**	0.9 (0.5, 1.6)	1.0 (0.6, 1.8)	0.8 (0.2, 4.1)[5]	1.3 (0.5, 3.3)
Other/mixed	**1.8 (1.1, 3.0)**	1.0 (0.6, 1.5)	**2.5 (1.3, 5.0)**	0.8 (0.5, 1.1)		0.8 (0.1, 5.5)
Hispanic/Latino ethnicity						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	0.8 (0.6, 1.1)	0.9 (0.6, 1.4)	0.6 (0.3, 1.2)	1.1 (0.6, 1.9)	**2.1 (1.0, 4.5)**	1.7 (0.5, 5.8)
Annual household income, $						
≤25,000	Ref	Ref	Ref	Ref	Ref	Ref
25, 001-50,000	1.0 (0.6, 1.8)	0.8 (0.7, 1.1)	0.8 (0.4, 1.7)	0.9 (0.7, 1.2)	Not estimable[6]	Not estimable[6]
50, 001-75,000	0.9 (0.5, 1.3)	0.8 (0.5, 1.5)	0.8 (0.4, 1.6)	0.8 (0.4, 1.3)	Not estimable[6]	Not estimable[6]
75, 001-100,000	**0.5 (0.3, 0.8)**	**0.6 (0.4, 0.8)**	0.5 (0.2, 1.2)	**0.6 (0.4, 0.9)**	Not estimable[6]	Not estimable[6]
100, 001-150,000	0.9 (0.5, 1.7)	0.9 (0.6, 1.5)	0.9 (0.4, 2.0)	0.7 (0.3, 1.6)	Not estimable[6]	Not estimable[6]
>150,000	0.7 (0.3, 1.5)	0.6 (0.3, 1.2)	0.7 (0.3, 1.5)	0.5 (0.2, 1.1)	Not estimable[6]	Not estimable[6]
Prefer not to report	1.5 (0.9, 2.7)	0.7 (0.4, 1.5)	1.0 (0.6, 1.6)	1.3 (0.5, 3.1)	Not estimable[6]	Not estimable[6]
Education						
<High school degree	1.8 (0.9, 3.6)	1.6 (1.0, 2.6)	1.9 (0.6, 6.1)	**3.2 (1.5, 6.9)**	Not estimable[6]	0.9 (0.2, 3.9)
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	**1.6 (1.1, 2.3)**	1.2 (0.8, 1.6)	2.6 (1.0, 7.0)	1.4 (0.9, 2.2)	Not estimable[6]	0.5 (0.2, 1.2)
Any graduate school	0.9 (0.5, 1.7)	1.4 (0.8, 2.6)	1.7 (0.4, 6.7)	1.7 (0.8, 3.5)	Not estimable[6]	0.8 (0.2, 4.1)
Medicaid insurance						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**1.6 (1.0, 2.4)**	1.4 (0.8, 2.4)	1.2 (0.6, 2.2)	1.2 (0.6, 2.4)	0.5 (0.1, 2.6)	1.2 (0.6, 2.4)

Risk Factor	ER/LA Cohort[1] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	1.1 (0.9, 1.2)	0.9 (0.6, 1.5)	**2.0 (1.4, 2.9)**	0.9 (0.7, 1.1)	Not estimable[6]	1.2 (0.3, 4.4)
Network or fee-for-service providers	1.6 (1.0, 2.6)	1.4 (0.7, 2.7)	1.6 (0.8, 3.2)	0.7 (0.4, 1.0)	Not estimable[6]	0.7 (0.1, 4.5)
OA-related factors						
Predominant opioid formulation[7]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	**0.7 (0.5, 0.9)**	1.1 (0.6, 2.1)	0.8 (0.6, 1.1)	1.0 (0.2, 3.9)	1.0 (0.3, 3.1)	Not estimable[6]
Baseline average daily dose, MME[7]						
<50	Ref	Ref	Ref	Ref	Ref	Ref
50-89	1.2 (0.9, 1.5)	1.0 (0.7, 1.3)	1.0 (0.7, 1.5)	1.0 (0.4, 2.2)	Not estimable[6]	Not estimable[6]
90-119	1.4 (0.9, 2.1)	0.9 (0.4, 2.1)	1.0 (0.7, 1.5)	**2.7 (1.2, 6.2)**	Not estimable[6]	Not estimable[6]
≥120	**1.6** (1.1, 2.2)	1.0 (0.3, 3.9)	0.9 (0.4, 2.2)	0.7 (0.1, 6.1)	Not estimable[6]	Not estimable[6]
Predominant opioid moiety[7,8]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	**0.6 (0.4, 0.9)**	0.9 (0.4, 1.9)	0.8 (0.5, 1.2)	**2.0 (1.2, 3.5)**	0.7 (0.2, 2.7)	*
Hydrocodone	0.9 (0.5, 1.6)	1.2 (0.9, 1.5)	**1.5 (1.1, 2.2)**	1.3 (0.9, 1.8)	*	1.3 (0.5, 3.4)
Fentanyl	**0.2 (0.1, 0.7)**	*	1.0 (0.4, 2.1)	*	*	*
Methadone	**0.3 (0.1, 0.9)**	*	1.0 (0.5, 2.0)	*	*	*
Oxymorphone	*	*	*	*	*	*
Hydromorphone	1.1 (0.7, 1.9)	*	2.0 (0.7, 5.2)	**5.8 (2.4, 13.9)**	*	*
Tramadol	**0.4 (0.2, 0.7)**	0.8 (0.3, 2.1)	0.5 (0.2, 1.4)	*	*	*
Buprenorphine	0.8 (0.5, 1.5)	*	1.6 (0.2, 9.9)	*	*	*
Codeine	0.8 (0.1, 4.6)	4.0 (0.9, 18.0)	*	*	*	*
Tapentadol	*	*	*	*	*	*
Meperidine	*	*	*	*	*	*
Butorphanol	*	*	*	*	*	*
Other[9]	2.2 (0.4, 13.3)	0.4 (0.2, 1.3)	**2.6 (1.2, 5.8)**	0.3 (0.0, 1.8)	0.4 (0.1, 1.1)	0.9 (0.2, 3.0)
Use of an ADF OA[7] (any vs. none)	1.3 (0.7, 2.5)	2.6 (0.5, 12.4)	0.7 (0.5, 1.2)	0.9 (0.1, 11.6)	1.9 (0.3, 12.9)	Not estimable[6]
Duration of Schedule II OA therapy during baseline period[7]						
Per 7-day increase	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	1.1 (1.0, 1.2)
SUD history						
Nonopioid and non-nicotine substance use disorder, past year (yes vs. no)	**2.4 (1.1, 5.3)**	**3.5 (2.7, 4.6)**	**4.2 (1.8, 9.8)**	**2.8 (2.1, 3.6)**	2.3 (0.6, 8.2)	**9.6 (2.5, 36.2)**

Risk Factor	ER/LA Cohort[1] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)
Nonopioid and non-nicotine substance use disorder, prior to past year (yes vs. no)	**2.0 (1.4, 2.9)**	1.3 (0.9, 1.8)	**2.0 (1.1, 3.6)**	**2.0 (1.3, 3.0)**	2.4 (0.6, 9.2)	**14.4 (5.8, 35.5)**
Hallucinogen use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Hallucinogen use disorder, prior to past year (yes vs. no)	2.0 (0.5, 8.4)	0.9 (0.3, 3.4)	0.5 (0.0, 5.2)	2.5 (0.8, 8.4)	Not estimable[6]	1.9 (0.3, 13.4)
Sedative use disorder, past year (yes vs. no)	3.1 (0.2, 42.0)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Sedative use disorder, prior to past year (yes vs. no)	**5.8 (1.4, 24.6)**	0.7 (0.2, 2.1)	**3.4 (1.2, 9.6)**	**2.9 (1.1, 8.2)**	Not estimable[6]	**13.4 (6.6, 27.3)**
Cocaine use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	**9.2 (3.4, 25.2)**	Not estimable[6]	**17.2 (2.0, 146.6)**
Cocaine use disorder, prior to past year (yes vs. no)	**2.7 (1.7, 4.6)**	**1.8 (1.1, 3.2)**	1.7 (0.6, 4.9)	**2.4 (1.6, 3.6)**	Not estimable[6]	**7.4 (2.2, 24.5)**
Stimulant use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	**31.5 (6.0, 166.8)**
Stimulant use disorder, prior to past year (yes vs. no)	1.8 (0.8, 4.2)	1.3 (1.0, 1.8)	1.6 (0.8, 3.0)	**2.4 (1.4, 4.2)**	Not estimable[6]	**8.4 (4.3, 16.4)**
Alcohol use disorder, past year (yes vs. no)	**3.6 (1.6, 8.1)**	**4.1 (1.7, 9.8)**	2.6 (0.9, 7.5)	**3.2 (2.0, 5.1)**	**4.1 (1.0, 16.1)**	**13.9 (4.4, 44.1)**
Alcohol use disorder, prior to past year (yes vs. no)	**1.7 (1.1, 2.5)**	1.3 (0.9, 1.8)	**1.8 (1.1, 3.0)**	**1.7 (1.1, 2.7)**	2.3 (0.8, 6.7)	**4.9 (1.9, 12.9)**
Cannabis use disorder, past year (yes vs. no)	2.2 (0.6, 8.2)	2.1 (1.0, 4.4)	**6.4 (2.3, 17.2)**	1.9 (0.9, 4.0)	Not estimable[5]	**7.4 (1.6, 35.0)**
Cannabis use disorder, prior to past year (yes vs. no)	**2.1 (1.1, 4.2)**	1.1 (0.7, 1.7)	**1.8 (1.2, 2.7)**	1.3 (0.8, 2.2)	1.1 (0.3, 3.8)	**3.4 (1.3, 8.9)**
Other drug use disorder, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]
Other drug use disorder, prior to past year (yes vs. no)	Not estimable[6]	Not estimable[6]	**9.1 (4.1, 20.1)**	Not estimable[6]	Not estimable[6]	Not estimable[6]
Nicotine use disorder, past year (yes vs. no)	**2.5 (1.6, 3.8)**	1.3 (0.9, 1.7)	**2.9 (1.8, 4.9)**	1.4 (1.0, 2.1)	0.8 (0.1, 5.8)	**2.7 (1.3, 5.9)**
Nicotine use disorder, prior to past year (yes vs. no)	**1.8 (1.4, 2.2)**	1.0 (0.7, 1.4)	**1.6 (1.0, 2.6)**	1.1 (0.7, 1.6)	1.8 (0.3, 12.9)	**2.4 (1.1, 5.1)**
POMAQ-classified misuse, past 3 months (yes vs. no)	Not applicable	Not applicable	**3.2 (2.3, 4.6)**	**3.5 (2.4, 5.2)**	4.0 (0.8, 20.4)	**4.0 (2.1, 7.6)**
POMAQ-classified abuse, past 3 months (yes vs. no)	**2.1 (1.2, 3.7)**	**4.9 (3.0, 7.8)**	Not applicable	Not applicable	1.7 (0.2, 12.2)	**8.2 (4.6, 14.7)**
OUD, past year (yes vs. no)	0.6 (0.2, 1.7)	2.3 (0.9, 5.8)	2.3 (1.0, 5.5)	**10.9 (6.1, 19.5)**	Not applicable	Not applicable
OUD-H, past year (yes vs. no)	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not applicable	Not applicable
OUD-P,[10] past year (yes vs. no)	0.6 (0.2, 1.7)	2.3 (0.9, 5.8)	2.3 (1.0, 5.5)	**10.9 (6.1, 19.5)**	Not applicable	Not applicable

Risk Factor	ER/LA Cohort[1] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)
OUD, prior to past year (yes vs. no)	**1.5 (1.0, 2.2)**	**2.6 (1.4, 4.9)**	**2.0 (1.4, 2.8)**	**3.4 (1.9, 6.2)**	1.8 (0.3, 12.7)	**8.4 (4.5, 15.7)**
OUD-H, prior to past year (yes vs. no)	1.4 (0.6, 3.0)	1.4 (0.5, 3.7)	0.6 (0.1, 3.9)	1.7 (0.6, 4.4)	Not estimable[6]	Not estimable[6]
OUD-P,[10] prior to past year (yes vs. no)	**1.5 (1.0, 2.0)**	**3.4 (2.0, 5.8)**	**2.3 (1.8, 3.0)**	**4.4 (1.9, 10.1)**	2.4 (0.3, 18.1)	**12.0 (6.4, 22.6)**
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	**0.7 (0.6, 0.9)**	1.2 (0.9, 1.6)	0.9 (0.7, 1.0)	1.3 (0.8, 2.1)	0.7 (0.2, 2.4)	0.2 (0.0, 1.2)
≥3	1.0 (0.7, 1.5)	1.3 (0.7, 2.3)	0.7 (0.3, 1.7)	0.6 (0.2, 1.7)	1.1 (0.3, 4.5)	3.3 (0.7, 16.0)
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.7 (0.6, 0.9)**	**0.7 (0.6, 0.9)**	**0.6 (0.4, 0.8)**	1.0 (0.6, 1.5)	Not estimable[6]	1.2 (0.4, 4.0)
≥2	0.6 (0.4, 1.1)	1.1 (0.7, 1.7)	0.4 (0.2, 1.2)	1.1 (0.7, 1.8)	Not estimable[6]	2.3 (0.7, 7.8)
Other medication use[11] (any vs. none)						
Antidepressants	**1.6 (1.1, 2.2)**	**1.6 (1.4, 2.0)**	1.1 (0.7, 1.8)	1.7 (0.9, 3.1)	1.3 (0.3, 4.9)	**2.6 (1.3, 5.1)**
Antipsychotics	**2.1 (1.1, 3.9)**	1.4 (1.0, 2.1)	1.3 (0.6, 2.8)	**3.0 (1.0, 9.0)**	0.8 (0.3, 2.5)	0.8 (0.1, 5.9)
Gabapentinoids	**1.4 (1.1, 1.8)**	1.2 (1.0, 1.6)	1.2 (0.9, 1.6)	1.2 (0.6, 2.3)	**2.5 (1.5, 4.4)**	1.4 (0.4, 4.1)
Muscle relaxers	1.1 (0.8, 1.6)	0.8 (0.6, 1.1)	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)	1.8 (0.7, 4.6)	1.3 (0.5, 3.6)
Naloxone	1.1 (0.8, 1.6)	0.9 (0.5, 1.9)	1.1 (0.5, 2.3)	1.1 (0.8, 1.7)	0.3 (0.0, 2.2)	**3.6 (1.2, 10.2)**
Sedative hypnotics	1.3 (0.8, 2.1)	**1.5 (1.3, 1.8)**	1.1 (0.4, 2.9)	1.1 (0.7, 1.9)	0.2 (0.0, 1.1)	**2.2 (1.1, 4.4)**
Stimulants	1.6 (1.0, 2.5)	1.3 (0.6, 2.9)	Not estimable[6]	1.2 (0.4, 3.8)	Not estimable[6]	1.9 (0.4, 9.6)
Number of pain conditions recorded in EHR						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	1.6 (0.5, 5.5)	1.9 (0.8, 4.6)	1.3 (0.4, 4.9)	6.0 (0.6, 59.0)	Not estimable[6]	1.0 (0.2, 6.5)
≥3	1.4 (0.5, 4.5)	2.1 (0.8, 5.5)	1.2 (0.3, 4.8)	6.4 (0.7, 62.3)	Not estimable[6]	0.6 (0.1, 5.0)
ECI score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.4 (0.2, 0.9)**	1.4 (0.8, 2.6)	**0.3 (0.2, 0.5)**	1.6 (0.9, 2.9)	**0.3 (0.1, 0.7)**	1.3 (0.4, 4.0)
≥2	0.7 (0.4, 1.2)	1.6 (0.9, 3.0)	**0.5 (0.3, 1.0)**	1.2 (0.5, 2.9)	0.3 (0.1, 1.2)	0.7 (0.2, 2.4)
Fibromyalgia from patient-reported symptoms						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.4 (0.8, 2.5)	1.2 (0.6, 2.4)	**1.7 (1.1, 2.7)**	1.1 (0.5, 2.4)	1.2 (0.2, 9.9)	Not estimable[6]
BMI (kg/m^2)						
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	1.1 (0.6, 1.9)	1.2 (0.7, 2.0)	1.0 (0.6, 1.9)	0.8 (0.5, 1.4)	1.4 (0.1, 12.4)	0.6 (0.1, 2.8)
Obese	1.2 (0.9, 1.4)	1.1 (0.6, 1.8)	0.7 (0.4, 1.1)	**0.6 (0.5, 0.8)**	1.3 (0.2, 7.6)	0.8 (0.2, 3.4)
Missing	**1.6 (1.0, 2.4)**	0.9 (0.5, 1.6)	0.8 (0.3, 2.0)	0.7 (0.5, 1.1)	1.1 (0.2, 7.7)	0.5 (0.1, 2.3)

Risk Factor	ER/LA Cohort[1] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)
Mental health conditions and social risk factors						
Major depressive disorder, past year (yes vs. no)	1.4 (1.0, 2.0)	1.0 (0.6, 1.9)	1.7 (0.9, 3.2)	**2.0 (1.3, 2.9)**	2.8 (0.9, 8.8)	0.9 (0.3, 3.4)
Major depressive disorder, prior to the past year (yes vs. no)	1.2 (0.9, 1.7)	1.1 (0.7, 1.6)	**1.6 (1.2, 2.2)**	**1.9 (1.3, 2.8)**	2.1 (0.7, 6.6)	1.3 (0.7, 2.3)
ADHD (yes vs. no)	**1.8 (1.3, 2.4)**	1.0 (0.5, 1.8)	1.6 (1.0, 2.8)	1.1 (0.5, 2.6)	1.1 (0.4, 3.0)	**3.8 (1.4, 10.5)**
Borderline personality disorder (yes vs. no)	**2.6 (1.5, 4.7)**	1.8 (1.0, 3.2)	**5.2 (3.3, 8.0)**	**2.2 (1.1, 4.3)**	0.9 (0.3, 3.1)	**4.1 (2.1, 7.9)**
GAD (yes vs. no)	**1.9 (1.2, 3.1)**	1.4 (1.0, 2.0)	2.3 (0.9, 5.8)	1.6 (0.9, 2.7)	Not estimable[6]	**3.0 (1.2, 8.0)**
PTSD (yes vs. no)	**1.5 (1.0, 2.2)**	**2.4 (1.6, 3.4)**	**2.9 (2.4, 3.5)**	**1.8 (1.0, 3.3)**	1.8 (0.9, 3.7)	**4.5 (2.1, 9.5)**
ACE						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.0 (0.6, 1.6)	1.2 (0.7, 2.1)	1.7 (0.9, 3.2)	1.3 (0.7, 2.5)	3.7 (0.9, 15.5)	Not estimable[6]
2	**1.9 (1.1, 3.5)**	1.1 (0.8, 1.6)	0.7 (0.3, 1.9)	1.1 (0.6, 2.2)	4.0 (1.0, 15.9)	Not estimable[6]
3	**1.7 (1.1, 2.5)**	1.6 (1.0, 2.7)	1.7 (0.9, 3.4)	2.1 (1.0, 4.4)	1.5 (0.1, 18.4)	Not estimable[6]
4+	**1.9 (1.3, 2.8)**	1.5 (0.9, 2.3)	**3.1 (1.8, 5.1)**	**2.2 (1.4, 3.4)**	1.9 (0.2, 15.9)	Not estimable[6]
History of parental substance use						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	**1.5 (1.1, 2.0)**	**1.4 (1.1, 1.9)**	**1.8 (1.6, 2.0)**	**1.7 (1.4, 2.2)**	0.8 (0.3, 2.8)	1.4 (0.7, 2.9)
Poor sleep quality						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.2 (1.0, 1.6)	1.2 (1.0, 1.5)	2.1 (0.7, 6.6)	1.5 (1.0, 2.2)	1.7 (0.3, 8.7)	1.3 (0.4, 5.1)
Other patient-reported measures (per 1-unit change worse)						
Pain severity	**1.1 (1.1, 1.2)**	**1.1 (1.0, 1.1)**	1.1 (1.0, 1.2)	**1.1 (1.0, 1.2)**	**1.2 (1.0, 1.4)**	1.2 (1.0, 1.4)
Pain interference	**1.1 (1.1, 1.2)**	1.0 (1.0, 1.1)	**1.1 (1.0, 1.2)**	**1.1 (1.0, 1.2)**	1.0 (0.8, 1.4)	**1.3 (1.1, 1.6)**
Stress	**1.1 (1.0, 1.1)**	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.0)	**1.1 (1.1, 1.2)**
Social support	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)**
SF-12 physical score	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.1)	1.0 (0.9, 1.1)
SF-12 mental score	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.0)**	1.0 (0.9, 1.0)	**1.1 (1.0, 1.1)**

Risk Factor	ER/LA Cohort[1] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Abuse Demographically Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Demographically Adjusted[4] OR (95% CI)
Genetic factors[12] (per 1 standard deviation increase gene-specific burden scores)						
OPRM1 burden score	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	1.1 (0.9, 1.3)	1.0 (0.7, 1.4)	**0.6 (0.5, 0.9)**	Not estimable[6]
Cytochrome P450 2D6 burden score	0.9 (0.7, 1.1)	0.9 (0.7, 1.0)	0.9 (0.7, 1.2)	1.0 (0.8, 1.3)	0.6 (0.4, 1.1)	Not estimable[6]
Cytochrome P450 3A4 burden score	**0.8 (0.7, 0.9)**	0.9 (0.8, 1.1)	1.0 (0.8, 1.1)	0.9 (0.8, 1.1)	**0.3 (0.2, 0.4)**	Not estimable[6]

Source: FDA-generated table from data provided in Appendix 1 Q5 Table E and Q5 Table H, FDA IR Response dated June 04, 2024.

Note: Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] ORs adjusted for age, sex, race, and ethnicity.

[5] There were no Black participants with the OUD outcome. To achieve model convergence, Black was combined with other/mixed race for this outcome.

[6] For cells denoted "not estimable," odds ratios could not be estimated due to a lack of model convergence arising from the small number of participants with this outcome.

[7] Baseline opioid exposure was measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominance was based on greatest total days' supply or most prescriptions if there was a tie.

[8] The following opioid moieties were not prescribed in this study and are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene.

[9] The *other* category for predominant opioid moiety combines all ingredients where there were ≤2 events for a given outcome. * indicates ingredients included in other, by outcome.

[10] Pain-adjusted.

[11] Other medication use defined as two or more dispensings in the prior year except for naloxone where use defined as one or more dispensings or one or more procedure codes.

[12] Genetic analyses include the subset of eligible individuals who provided evaluable genetic samples: 822 for OPRM1, 829 for cytochrome P450 2D6, and 821 for cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experiences; ADF, abuse deterrent formulation; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/LA, immediate-release/short-acting; LtOT, long-term opioid therapy; MME morphine milligram equivalent; OA, opioid analgesic; OPRM1, opioid receptor mu 1; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, Post-traumatic stress disorder; Ref, reference value; SF-12, 12-item Short Form Health Survey; SNP, single nucleotide polymorphism; SUD, substance use disorder

Table 32. Odds Ratios and 95% CIs From Fully Adjusted Models for Incident Opioid Misuse, Opioid Abuse, and Moderate-to-Severe Pain-Adjusted DSM-5-OUD for the ER/LA and LtOT Cohorts, Prospective 3033-1 Study

	ER/LA Cohort[1]	LtOT Cohort[2]	ER/LA Cohort[1]	LtOT Cohort[2]	ER/LA Cohort[1]	LtOT Cohort[2]
	Opioid Misuse	Opioid Misuse	Opioid Abuse	Opioid Abuse	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3]
Risk Factor	**Fully Adjusted[4] OR (95% CI)**	**Fully Adjusted[4] OR (95% CI)**	**Fully Adjusted[4] OR (95% CI)[4]**	**Fully Adjusted[4] OR (95% CI)**	**Fully Adjusted[4] OR (95% CI)**	**Fully Adjusted[4] OR (95% CI)**
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	1.2 (0.5, 2.7)	1.0 (0.3, 2.7)	0.8 (0.5, 1.2)	0.6 (0.1, 2.3)	**0.1 (0.0, 0.4)**	0.9 (0.1, 6.6)
50-59	1.3 (0.7, 2.1)	1.5 (0.5, 4.6)	**0.5 (0.3, 0.7)**	0.5 (0.2, 1.2)	0.3 (0.1, 1.3)	0.8 (0.2, 3.5)
≥60	**1.8 (1.0, 3.0)**	1.3 (0.6, 2.8)	1.0 (0.5, 1.9)	1.0 (0.5, 2.3)	**0.0 (0.0, 0.5)**	0.9 (0.1, 4.9)
Sex						
Female	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.4 (0.9, 2.1)	1.0 (0.6, 1.7)	1.6 (1.0, 2.7)	1.2 (0.8, 1.8)	1.2 (0.4, 3.5)	1.0 (0.3, 3.2)
Race						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.8 (0.7, 4.2)	1.2 (0.7, 1.9)	0.8 (0.3, 1.9)	1.1 (0.7, 1.7)	1.04 (0.1, 8.0)[5]	**3.0 (1.3, 7.0)**
Other/mixed	**1.8 (1.1, 2.9)**	1.0 (0.6, 1.8)	**2.2 (1.5, 3.3)**	0.8 (0.5, 1.3)		0.8 (0.1, 7.9)
Hispanic/Latino ethnicity						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.0 (0.5, 1.8)	0.8 (0.6, 1.2)	0.7 (0.4, 1.0)	1.0 (0.5, 1.8)	1.4 (0.4, 5.0)	**3.6 (1.2, 10.9)**
Annual household income, $						
≤25,000	Ref	Ref	Ref	Ref	Ref	Ref
25,001-50,000	1.2 (0.5, 3.0)	0.9 (0.7, 1.2)	N/I	1.2 (0.7, 2.1)	N/I	N/I
50,001-75,000	1.4 (0.7, 2.7)	1.0 (0.7, 1.5)	N/I	1.0 (0.5, 2.0)	N/I	N/I
75,001-100,000	0.9 (0.4, 1.7)	0.7 (0.5, 1.1)	N/I	0.9 (0.5, 1.6)	N/I	N/I
100,001-150,000	1.5 (0.5, 4.2)	1.3 (0.7, 2.5)	N/I	1.1 (0.4, 3.2)	N/I	N/I
>150,000	1.4 (0.5, 4.4)	0.6 (0.3, 1.2)	N/I	1.2 (0.7, 2.0)	N/I	N/I
Prefer not to report	1.4 (0.7, 3.0)	1.3 (0.5, 3.6)	N/I	1.8 (0.5, 6.1)	N/I	N/I
Education						
<High school degree	1.2 (0.3, 4.3)	1.7 (1.0, 3.0)	1.3 (0.3, 4.7)	**4.0 (1.6, 10.2)**	N/I	1.5 (0.2, 10.9)
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	**1.8 (1.0, 3.0)**	1.3 (0.9, 1.8)	2.5 (0.9, 6.8)	1.4 (0.8, 2.4)	N/I	0.3 (0.1, 1.1)
Any graduate school	1.0 (0.6, 1.9)	1.5 (0.9, 2.3)	1.3 (0.3, 5.4)	1.6 (0.8, 3.2)	N/I	1.4 (0.3, 7.3)

Risk Factor	ER/LA Cohort[1] Opioid Misuse Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Fully Adjusted[4] OR (95% CI)[4]	LtOT Cohort[2] Opioid Abuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)
Medicaid insurance						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.7 (0.9, 3.2)	N/I	N/I	N/I	N/I	N/I
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	0.9 (0.7, 1.2)	N/I	**2.6 (1.5, 4.4)**	1.0 (0.8, 1.2)	N/I	N/I
Network or fee-for-service providers	0.8 (0.5, 1.5)	N/I	1.2 (0.2, 5.9)	**0.5 (0.3, 0.9)**	N/I	N/I
OA-related factors						
Predominant opioid formulation[6]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	1.3 (0.7, 2.2)	N/I	1.3 (0.7, 2.4)	N/I	N/I	N/I
Baseline average daily dose, MME[6]						
<50	Ref	Ref	Ref	Ref	Ref	Ref
50-89	1.2 (0.8, 1.7)	N/I	N/I	1.2 (0.6, 2.6)	N/I	N/I
90-119	**1.8 (1.0, 3.2)**	N/I	N/I	**2.7 (1.3, 5.6)**	N/I	N/I
≥120	**2.4 (1.2, 4.5)**	N/I	N/I	1.9 (0.2, 15.5)	N/I	N/I
Predominant active moiety[6,7]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.8 (0.3, 1.8)	0.8 (0.2, 2.8)	0.9 (0.4, 1.9)	2.3 (0.7, 7.4)	1.1 (0.5, 2.4)	*
Hydrocodone	1.1 (0.7, 1.9)	1.2 (0.9, 1.5)	1.8 (0.9, 3.5)	1.5 (1.0, 2.4)	*	2.4 (0.9, 6.4)
Fentanyl	0.3 (0.1, 1.2)	*	1.2 (0.5, 2.8)	*	*	*
Methadone	0.4 (0.1, 1.8)	*	1.0 (0.3, 3.4)	*	*	*
Oxymorphone	*	*	*	*	*	*
Hydromorphone	1.4 (0.7, 2.5)	*	**6.8 (3.3, 14.0)**	**6.9 (2.7, 17.6)**	*	*
Tramadol	**0.4 (0.2, 0.7)**	0.7 (0.3, 1.7)	0.5 (0.2, 1.0)	*	*	*
Buprenorphine	1.1 (0.6, 2.1)	*	2.1 (0.1, 31.5)	*	*	*
Codeine	1.1 (0.2, 6.7)	**3.2 (1.4, 7.4)**	*	*	*	*
Tapentadol	*	*	*	*	*	*
Meperidine	*	*	*	*	*	*
Butorphanol	*	*	*	*	*	*
Other[8]	4.4 (0.7,26.7)	0.4 (0.1, 1.6)	**4.1 (1.4, 12.6)**	0.4 (0.1, 3.4)	0.2 (0.0, 1.6)	**0.2 (0.0, 0.7)**

Risk Factor	ER/LA Cohort[1] Opioid Misuse Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Fully Adjusted[4] OR (95% CI)[4]	LtOT Cohort[2] Opioid Abuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)
Use of an ADF OA[6] (any vs. none)	N/I	N/I	N/I	N/I	N/I	N/I
Duration of Schedule II OA therapy during baseline period[6]						
Per 7-day increase	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.1)	N/I	N/I	N/I
SUD history						
Nonopioid and non-nicotine substance use disorder, past year (yes vs. no)	**2.7 (1.1, 6.7)**	**3.4 (2.3, 5.0)**	**5.5 (2.0, 15.6)**	**2.3 (1.5, 3.5)**	N/I	2.4 (0.5, 11.2)
Nonopioid and non-nicotine substance use disorder, prior to past year (yes vs. no)	1.6 (1.0, 2.7)	N/I	1.0 (0.5, 1.9)	1.2 (0.7, 2.0)	N/I	**9.8 (3.1, 30.8)**
POMAQ-classified prescription opioid misuse, past 3 months (yes vs. no)	Not applicable	Not applicable	**3.0 (1.8, 5.1)**	**2.2 (1.2, 3.8)**	3.4 (0.7, 16.8)	1.9 (0.6, 5.8)
POMAQ-classified prescription opioid abuse, past 3 months (yes vs. no)	1.3 (0.7, 2.4)	**3.6 (2.3, 5.6)**	Not applicable	Not applicable	N/I	**5.4 (2.3, 12.9)**
OUD-H, past year (yes vs. no)	N/I	N/I	N/I	N/I	Not applicable	Not applicable
OUD-P,[9] past year (yes vs. no)	N/I	1.1 (0.3, 3.9)	0.6 (0.1, 4.9)	**5.2 (1.9, 14.8)**	Not applicable	Not applicable
OUD-H, prior to past year (yes vs. no)	N/I	N/I	N/I	N/I	N/I	N/I
OUD-P,[9] prior to past year (yes vs. no)	0.7 (0.4,1.1)	**2.6 (1.2, 5.6)**	1.0 (0.4, 2.6)	1.8 (0.6, 4.9)	N/I	**9.0 (2.6, 31.0)**
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	**0.7 (0.6, 0.9)**	N/I	N/I	N/I	N/I	**0.0 (0.0, 0.1)**
≥3	1.0 (0.7, 1.6)	N/I	N/I	N/I	N/I	2.2 (0.5, 9.8)
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.7 (0.6, 1.0)**	0.7 (0.4, 1.1)	0.8 (0.4, 1.4)	N/I	N/I	N/I
≥2	**0.4 (0.2, 0.9)**	1.1 (0.8, 1.6)	0.4 (0.1, 1.4)	N/I	N/I	N/I

Risk Factor	ER/LA Cohort[1] Opioid Misuse Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Fully Adjusted[4] OR (95% CI)[4]	LtOT Cohort[2] Opioid Abuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)
Other medication use[10] (any vs. none)						
Antidepressants	1.3 (0.9, 1.9)	1.4 (0.9, 2.0)	N/I	N/I	N/I	**2.3 (1.3, 4.1)**
Antipsychotics	1.5 (1.0, 2.3)	0.7 (0.3, 1.6)	N/I	2.4 (0.8, 7.3)	N/I	N/I
Gabapentinoids	**1.3 (1.0, 1.8)**	N/I	N/I	N/I	**5.0 (2.1, 11.9)**	N/I
Muscle relaxers	N/I	N/I	N/I	N/I	1.8 (0.5, 6.1)	N/I
Naloxone	N/I	N/I	N/I	N/I	N/I	**9.0 (2.8, 28.4)**
Sedative hypnotics	N/I	1.3 (1.0, 1.7)	N/I	N/I	N/I	1.1 (0.5, 2.5)
Stimulants	N/I	N/I	Not estimable[11]	N/I	N/I	N/I
Number of pain conditions recorded in EHR						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	N/I	N/I	N/I	N/I	N/I	N/I
≥3	N/I	N/I	N/I	N/I	N/I	N/I
ECI score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**0.2 (0.1, 0.4)**	1.4 (0.6, 3.3)	**0.3 (0.1, 0.7)**	N/I	**0.2 (0.1, 0.3)**	N/I
≥2	**0.4 (0.3, 0.7)**	1.5 (0.7, 3.4)	**0.4 (0.2, 0.8)**	N/I	**0.1 (0.0, 0.6)**	N/I
Fibromyalgia from patient-reported symptoms						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	N/I	N/I	1.4 (0.7, 2.7)	N/I	N/I	N/I
BMI (kg/m^2)						
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	1.0 (0.6, 1.5)	N/I	0.9 (0.5, 1.3)	0.8 (0.3, 1.7)	N/I	N/I
Obese	0.9 (0.6, 1.5)	N/I	**0.5 (0.3, 0.8)**	**0.6 (0.4, 0.9)**	N/I	N/I
Missing	1.4 (0.7, 3.1)	N/I	0.8 (0.1, 4.1)	0.8 (0.3, 1.8)	N/I	N/I
Mental health conditions and social factors						
Major depressive disorder, past year (yes vs. no)	N/I	N/I	N/I	0.8 (0.5, 1.3)	2.6 (1.0, 6.8)	N/I
Major depressive disorder, prior to past year (yes vs. no)	N/I	N/I	1.2 (0.7, 2.0)	1.4 (0.9, 2.2)	N/I	N/I
ADHD (yes vs. no)	1.0 (0.6, 1.6)	N/I	N/I	N/I	N/I	1.8 (0.5, 6.4)
Borderline personality disorder (yes vs. no)	**1.9 (1.1, 3.3)**	1.1 (0.5, 2.7)	**2.5 (1.7, 3.6)**	1.2 (0.7, 2.2)	N/I	0.6 (0.1, 3.3)
GAD (yes vs. no)	1.1 (0.5, 2.2)	0.8 (0.5, 1.1)	1.3 (0.4, 3.8)	N/I	N/I	1.2 (0.3, 5.0)

Risk Factor	ER/LA Cohort[1] Opioid Misuse Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Opioid Misuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Opioid Abuse Fully Adjusted[4] OR (95% CI)[4]	LtOT Cohort[2] Opioid Abuse Fully Adjusted[4] OR (95% CI)	ER/LA Cohort[1] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)	LtOT Cohort[2] Moderate-to-Severe Pain-Adjusted DSM-5-OUD[3] Fully Adjusted[4] OR (95% CI)
PTSD (yes vs. no)	**0.6 (0.4, 0.9)**	**1.6 (1.0, 2.6)**	1.7 (0.7, 4.1)	0.8 (0.4, 2.0)	**1.4 (1.0, 2.0)**	1.4 (0.3, 7.0)
ACE						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	0.9 (0.4, 2.0)	1.3 (0.7, 2.3)	**1.8 (1.2, 2.9)**	0.7 (0.3, 1.9)	4.8 (1.0, 23.9)	N/I
2	1.8 (0.7, 4.2)	0.9 (0.6, 1.3)	0.8 (0.3, 2.2)	0.6 (0.2, 2.2)	1.3 (0.1, 14.6)[12]	N/I
3	1.4 (0.8, 2.6)	1.5 (0.8, 2.6)	1.6 (0.8, 3.5)	1.1 (0.4, 2.8)		N/I
4+	1.4 (0.7, 2.5)	1.0 (0.5, 1.9)	**2.3 (1.3, 4.0)**	1.1 (0.7, 2.0)	1.3 (0.1, 21.2)	N/I
History of parental substance use						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.1 (0.9, 1.4)	1.2 (0.8, 2.0)	1.1 (0.8, 1.4)	**1.4 (1.1, 1.7)**	N/I	N/I
Poor sleep quality						
No	Ref	Ref	Ref	Ref	Ref	Ref
Yes	N/I	1.0 (0.7, 1.5)	N/I	1.2 (0.7, 2.3)	N/I	N/I
Other patient-reported measures (per 1-unit change worse)						
Pain severity	**1.1 (1.0, 1.2)**	1.1 (1.0, 1.2)	N/I	N/I	1.1 (0.9, 1.3)	N/I
Pain interference	**0.9 (0.8, 1.0)**	N/I	1.0 (0.9, 1.2)	1.1 (1.0, 1.2)	N/I	1.2 (1.0, 1.4)
Stress	**1.0 (1.0, 1.1)**	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)	N/I	1.1 (1.0, 1.2)
Social support	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)**	**1.0 (1.0, 1.0)**	N/I	1.0 (1.0, 1.0)
SF-12 physical score	**1.0 (1.0, 1.1)**	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	N/I	N/I	N/I
SF-12 mental score	**1.0 (1.0, 1.0)**	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)	N/I	1.0 (0.9, 1.0)

Source: FDA-generated table adapted from data provided in Appendix 1 Q5 Table F REV and Q5 Table I REV, FDA IR Response dated June 04, 2024.

Note: For nonreference variables denoted "N/I", the variable did not reach statistical significance at p<0.10 in univariate analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] Moderate-to-severe pain-adjusted DSM-5 OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] Fully adjusted models were adjusted for all risk factors with ORs and 95% CIs presented in the corresponding column of this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.10), plus age, sex, race, and ethnicity.

[5] There were no Black participants with the OUD outcome. To achieve model convergence, Black was combined with other/mixed race for this outcome.

[6] Baseline opioid exposure is measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominance was based on greatest total days supply or most prescriptions if there was a tie.

[7] The following opioid moieties were not prescribed in this study and are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene.

[8] When an opioid moiety contained ≤2 events of a given outcome, it was collapsed into the "other" category. Opioid moieties included in the "other" category for a given outcome are indicated by *.

[9] Pain-adjusted.

[10] Other medication use defined as two or more dispensings in the prior year except naloxone where use was defined as one or more dispensings or one or more procedure codes.

[11] For cells denoted "not estimable," odds ratios could not be estimated due to a lack of model convergence arising from the small number of participants with this outcome.

[12] There were no participants with 3 ACEs with the OUD outcome. To achieve model convergence, participants who had 2 ACEs and 3 ACEs were combined for this outcome.

Abbreviations: ACE, adverse childhood experience; ADF, abuse deterrent formulation; ADHD, attention deficit/hyperactivity disorder; BMI, body mass index; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, intermediate-release/short-acting; LtOT, long-term opioid therapy; MME: milligram morphine equivalent; N/I, not included; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; Ref, reference value; PTSD, posttraumatic stress disorder; SF-12, 12-item Short Form Health Survey; SUD, substance use disorder

Table 33. Odds Ratios and 95% CIs From Fully Adjusted Models for Pain-Adjusted DSM-5-OUD and DSM-5-OUD (Any and Moderate-to-Severe) for the ER/LA and LtOT Cohorts, Prospective 3033-1 Study

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)	Fully Adjusted[7] OR (95% CI)
Sociodemographic factors								
Age group, years								
18-39	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
40-49	0.6 (0.3, 1.0)	1.1 (0.6, 2.1)	1.7 (0.6, 5.0)	**0.7 (0.5, 1.0)**	**0.1 (0.0, 0.4)**	0.7 (0.3, 1.5)	0.9 (0.1, 6.6)	0.7 (0.3, 1.4)
50-59	0.7 (0.4, 1.2)	1.1 (0.5, 2.3)	1.8 (0.7, 4.8)	0.8 (0.6, 1.1)	0.3 (0.1, 1.3)	0.5 (0.2, 1.6)	0.8 (0.2, 3.5)	0.6 (0.3, 1.3)
≥60	0.7 (0.5, 1.1)	1.4 (0.6, 3.3)	1.2 (0.4, 3.3)	**0.7 (0.5, 0.9)**	**0.0 (0.0, 0.5)**	0.5 (0.2, 1.2)	0.9 (0.1, 4.9)	0.7 (0.3, 1.8)
Sex								
Female	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Male	1.0 (0.6, 1.9)	0.9 (0.6, 1.5)	**2.2 (1.0, 4.8)**	1.5 (0.9, 2.3)	1.2 (0.4, 3.5)	1.0 (0.3, 3.2)	1.1 (0.4, 3.0)	1.4 (0.7, 2.9)
Race								
White	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.0 (0.4, 2.5)	**1.6 (1.1, 2.4)**	0.6 (0.2, 1.7)	1.0 (0.6, 1.7)	1.0 (0.1, 8.0)[8]	**3.4 (1.4, 7.9)**	**3.0 (1.3, 7.0)**	1.4 (0.8, 2.8)
Other/mixed	1.8 (0.9, 3.7)	**2.5 (1.5, 4.2)**	0.6 (0.2, 1.5)	**0.6 (0.3, 1.0)**		2.1 (0.5, 9.6)	0.8 (0.1, 7.9)	0.3 (0.0, 1.9)

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**
Hispanic/Latino ethnicity								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.1 (0.4, 3.1)	1.4 (0.8, 2.3)	**2.3 (1.5, 3.6)**	1.5 (0.9, 2.6)	1.4 (0.4, 5.0)	**2.5 (1.1, 5.8)**	**3.6 (1.2, 10.9)**	1.3 (0.6, 3.0)
Annual household income, $								
≤25,000	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
25,001-50,000	1.5 (0.8, 2.9)	1.1 (0.7, 1.5)	1.4 (0.6, 3.0)	1.0 (0.6, 1.7)	N/I	2.0 (0.7, 6.1)	N/I	N/I
51,000-75,000	1.3 (0.7, 2.4)	**1.6 (1.0, 2.4)**	**2.6 (1.0, 6.6)**	1.4 (0.8, 2.2)	N/I	2.1 (0.8, 5.8)	N/I	N/I
75,001-100,000	2.0 (0.5, 8.3)	1.7 (0.9, 3.1)	0.6 (0.2, 2.1)	0.9 (0.5, 1.5)	N/I	**2.2 (1.2, 4.0)**	N/I	N/I
100,001-150,000	**2.4 (1.2, 4.8)**	**1.6 (1.1, 2.4)**	1.5 (0.6, 3.7)	1.3 (0.6, 2.8)	N/I	1.5 (0.6, 3.8)	N/I	N/I
>150,000	1.4 (0.6, 3.2)	1.1 (0.7, 1.8)	0.9 (0.1, 10.4)	0.8 (0.2, 3.2)	N/I	1.0 (0.1, 6.5)	N/I	N/I
Prefer not to report	0.8 (0.4, 1.6)	0.4 (0.2, 1.0)	1.4 (0.3, 7.7)	1.2 (0.4, 3.6)	N/I	0.3 (0.0, 3.5)	N/I	N/I
Education								
<High school degree	**2.4 (1.0, 5.4)**	0.7 (0.3, 1.8)	3.1 (0.9, 10.8)	1.4 (0.7, 2.6)	N/I	N/I	1.5 (0.2, 10.9)	N/I
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Any college	1.4 (0.5, 3.7)	1.2 (0.8, 1.9)	0.8 (0.4, 1.6)	1.1 (0.7, 1.8)	N/I	N/I	0.3 (0.1, 1.1)	N/I
Any graduate school	1.3 (0.4, 4.9)	2.1 (0.9, 4.8)	2.6 (0.8, 8.3)	1.7 (0.7, 3.9)	N/I	N/I	1.4 (0.3, 7.3)	N/I
Medicaid insurance								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	N/I	N/I	1.2 (0.5, 3.0)	N/I	N/I	N/I	N/I	0.8 (0.5, 1.4)
Predominant place of care								
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	0.7 (0.5, 1.0)	0.9 (0.5, 1.5)	N/I	N/I	N/I	0.7 (0.3, 1.7)	N/I	N/I
Network or fee-for-service providers	1.3 (0.7, 2.6)	1.6 (1.0, 2.7)	N/I	N/I	N/I	**2.3 (1.3, 3.8)**	N/I	N/I

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**
OA-related factors								
Predominant opioid formulation[9]								
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	N/I	1.1 (0.8, 1.6)	N/I	N/I	N/I	N/I	N/I	N/I
Baseline average daily dose, MME[9]								
<50	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
50-89	N/I	1.0 (0.8, 1.1)	N/I	1.3 (0.8, 2.2)	N/I	0.4 (0.1, 1.4)	N/I	N/I
90-119	N/I	0.6 (0.3, 1.1)	N/I	1.9 (0.4, 10.0)	N/I	1.0 (0.5, 2.0)	N/I	N/I
≥120	N/I	1.0 (0.5, 1.8)	N/I	1.5 (0.5, 4.5)	N/I	1.2 (0.5, 3.1)	N/I	N/I
Predominant opioid moiety[9, 10]								
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.7 (0.3, 1.4)	**0.6 (0.3, 1.0)**	*	0.6 (0.1, 3.6)	1.1 (0.5, 2.4)	0.5 (0.2, 1.4)	*	*
Hydrocodone	0.7 (0.3, 1.3)	**0.6 (0.4, 0.9)**	1.2 (0.7, 1.9)	1.0 (0.8, 1.4)	*	**0.4 (0.2, 1.0)**	2.4 (0.9, 6.4)	0.9 (0.4, 1.9)
Fentanyl	0.7 (0.3, 1.9)	1.1 (0.4, 2.7)	*	*	*	**3.1 (1.8, 5.3)**	*	*
Methadone	0.7 (0.3, 1.6)	0.8 (0.3, 1.9)	*	*	*	*	*	*
Oxymorphone	*	*	*	*	*	*	*	*
Hydromorphone	*	1.4 (0.7, 2.6)	*	*	*	*	*	*
Tramadol	0.6 (0.2, 1.8)	0.4 (0.2, 1.1)	1.8 (0.3, 11.5)	1.1 (0.3, 4.0)	*	*	*	*
Buprenorphine	*	0.5 (0.3, 1.1)	*	*	*	*	*	*
Codeine	**2.9 (1.4, 6.2)**	**0.4 (0.2, 0.6)**	*	*	*	*	*	*
Tapentadol	*	*	*	*	*	*	*	*
Meperidine	*	*	*	*	*	*	*	*
Butorphanol	*	*	*	*	*	*	*	*
Other[11]	0.9 (0.3, 2.9)	0.3 (0.1, 1.5)	0.6 (0.2, 2.4)	0.7 (0.2, 2.9)	0.2 (0.0, 1.6)	0.4 (0.1, 1.3)	**0.2 (0.0, 0.7)**	0.6 (0.1, 2.9)
Use of an ADF OA[9] (any vs. none)	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I
Duration of Schedule II OA therapy during baseline period[9]								
Per 7-day increase	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	**1.1 (1.0, 1.1)**	N/I	N/I	1.0 (1.0, 1.1)	N/I	N/I

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**
SUD history								
Past-year nonopioid, non-nicotine SUD (yes vs. no)	**1.5 (1.0, 2.1)**	1.4 (0.9, 2.1)	1.1 (0.5, 2.2)	0.8 (0.5, 1.5)	N/I	**4.0 (1.3, 11.9)**	2.4 (0.5, 11.2)	2.0 (0.5, 7.3)
Nonopioid, non-nicotine SUD, prior to the past year (yes vs. no)	1.6 (0.8, 3.2)	**1.6 (1.4, 1.9)**	**2.1 (1.2, 3.5)**	1.2 (1.0, 1.6)	N/I	1.5 (0.8, 2.7)	**9.8 (3.1, 30.8)**	**2.4 (1.3, 4.5)**
POMAQ-classified opioid misuse (yes vs. no)	**2.5 (1.2, 5.2)**	**2.2 (1.4, 3.6)**	**2.7 (1.1, 6.2)**	1.2 (0.9, 1.6)	3.4 (0.7, 16.8)	2.3 (1.0, 5.4)	1.9 (0.6, 5.8)	**2.2 (1.1, 4.6)**
POMAQ-classified opioid abuse (yes vs. no)	1.2 (0.6, 2.4)	1.3 (0.6, 2.7)	1.9 (0.7, 5.4)	**1.8 (1.2, 2.8)**	N/I	N/I	**5.4 (2.3, 12.9)**	1.5 (0.7, 3.4)
OUD-H, past year (yes vs. no)	N/I	N/I	N/I	N/I	not applicable	N/I	not applicable	N/I
OUD-P,[12] past year (yes vs. no)	N/I	1.9 (0.8, 4.3)	N/I	N/I	not applicable	N/I	not applicable	N/I
OUD-H, prior to the past year (yes vs. no)	N/I	N/I	1.2 (0.3, 4.4)	N/I	N/I	N/I	N/I	N/I
OUD-P,[12] prior to the past year (yes vs. no)	**2.6 (1.1, 6.3)**	N/I	**3.2 (1.6, 6.5)**	**2.3 (1.4, 3.7)**	N/I	0.7 (0.2, 2.9)	**9.0 (2.6, 31.0)**	**4.4 (1.7, 11.7)**
Health- and pain-related factors								
ED visits								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1-2	N/I	N/I	0.7 (0.3, 1.5)	1.4 (0.9, 2.0)	N/I	N/I	**0.0 (0.0, 0.1)**	0.5 (0.2, 1.4)
≥3	N/I	N/I	**2.8 (1.5, 5.0)**	**2.1 (1.3, 3.4)**	N/I	N/I	2.2 (0.5, 9.8)	**2.9 (1.6, 5.3)**
Inpatient stays								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	0.9 (0.6, 1.4)	N/I	N/I	**0.7 (0.5, 1.0)**	N/I	**0.1 (0.0, 0.3)**	N/I	N/I
≥2	**0.4 (0.2, 0.7)**	N/I	N/I	1.2 (0.7, 2.2)	N/I	**0.1 (0.0, 0.4)**	N/I	N/I

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**
Other medication use[13] (any vs. none)								
Antidepressants	N/I	1.1 (0.7, 1.6)	N/I	N/I	N/I	1.1 (0.5, 2.1)	**2.3 (1.3, 4.1)**	1.5 (0.5, 3.9)
Antipsychotics	N/I	1.2 (0.6, 2.1)	1.7 (0.8, 3.6)	1.2 (0.6, 2.4)	N/I	N/I	N/I	2.1 (0.9, 5.2)
Gabapentinoids	**2.0 (1.5, 2.5)**	**1.5 (1.1, 2.1)**	1.2 (0.8, 1.9)	1.3 (1.0, 1.7)	**5.0 (2.1, 11.9)**	**2.8 (1.9, 4.3)**	N/I	1.3 (0.5, 3.5)
Muscle relaxers	N/I	N/I	N/I	N/I	1.8 (0.5, 6.1)	N/I	N/I	1.3 (0.7, 2.5)
Naloxone	N/I	N/I	N/I	1.4 (0.9, 2.2)	N/I	N/I	**9.0 (2.8, 28.4)**	N/I
Sedative hypnotics	N/I	N/I	N/I	N/I	N/I	N/I	1.1 (0.5, 2.5)	N/I
Stimulants	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I
Number of pain conditions recorded in EHR								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1-2	N/I	N/I	0.4 (0.1, 1.9)	N/I	N/I	N/I	N/I	0.3 (0.1, 1.0)
≥3	N/I	N/I	0.4 (0.1, 2.0)	N/I	N/I	N/I	N/I	0.3 (0.1, 1.8)
ECI score								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
1	N/I	N/I	N/I	N/I	**0.2 (0.1, 0.3)**	N/I	N/I	2.2 (0.7, 7.4)
≥2	N/I	N/I	N/I	N/I	**0.1 (0.0, 0.6)**	N/I	N/I	1.3 (0.5, 3.6)
Fibromyalgia from patient-reported symptoms								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	N/I	1.5 (0.9, 2.4)	N/I	N/I	N/I	N/I	N/I	N/I
BMI (kg/m^2)								
Underweight/ normal	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I
Obese	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I
Missing	N/I	N/I	N/I	N/I	N/I	N/I	N/I	N/I
Mental health conditions and social factors								
MDD, past year (yes vs. no)	1.0 (0.5, 2.4)	1.5 (0.9, 2.5)	0.5 (0.1, 1.7)	0.8 (0.5, 1.3)	2.6 (1.0, 6.8)	**3.1 (1.4, 6.6)**	N/I	N/I
MDD, prior to the past year (yes vs. no)	N/I	0.8 (0.5, 1.2)	1.4 (0.6, 3.0)	1.3 (0.7, 2.4)	N/I	0.9 (0.4, 2.1)	N/I	0.8 (0.4, 1.7)
ADHD (yes vs. no)	N/I	0.9 (0.4, 1.7)	0.8 (0.3, 1.9)	1.1 (0.7, 1.9)	N/I	**2.4 (1.1, 5.3)**	1.8 (0.5, 6.4)	0.8 (0.1, 5.0)
Borderline personality disorder (yes vs. no)	1.1 (0.5, 2.1)	1.4 (0.7, 2.7)	1.0 (0.4, 2.5)	1.5 (0.7, 3.1)	N/I	1.5 (0.5, 4.1)	0.6 (0.1, 3.3)	1.3 (0.4, 4.0)

	ER/LA Cohort[1]		LtOT Cohort[2]		ER/LA Cohort[1]		LtOT Cohort[2]	
	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Any Pain-Adjusted DSM-5-OUD[3]	Any DSM-5-OUD[4]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]	Moderate-to-Severe Pain-Adjusted DSM-5-OUD[5]	Moderate-to-Severe DSM-5-OUD[6]
Risk Factor	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**	**Fully Adjusted[7] OR (95% CI)**
GAD (yes vs. no)	1.3 (0.7, 2.4)	1.1 (0.8, 1.4)	1.3 (0.5, 3.5)	1.5 (1.0, 2.2)	N/I	0.9 (0.5, 1.6)	1.2 (0.3, 5.0)	**2.5 (1.4, 4.6)**
PTSD (yes vs. no)	N/I	0.7 (0.3, 1.7)	0.8 (0.2, 2.7)	1.1 (0.6, 2.1)	**1.4 (1.0, 2.0)**	0.9 (0.3, 3.2)	1.4 (0.3, 7.0)	1.0 (0.3, 3.3)
ACE								
0	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Re
1	**5.3 (2.9, 9.9)**	**2.5 (1.7, 3.9)**	**0.3 (0.1, 0.8)**	1.3 (0.8, 2.0)	4.8 (1.0, 23.9)	**4.2 (2.4, 7.3)**	N/I	0.8 (0.1, 5.0)
2	2.4 (0.7, 8.2)	**2.5 (1.5, 4.3)**	0.3 (0.0, 2.4)	**2.4 (1.4, 4.1)**	1.3 (0.1,	2.0 (1.0, 4.2)	N/I	**0.2 (0.1, 0.4)**
3	1.8 (0.6, 5.2)	**2.4 (1.5, 3.9)**	0.9 (0.3, 2.6)	1.9 (0.9, 4.0)	14.6)[14]	2.5 (0.5, 12.7)	N/I	1.0 (0.2, 4.8)
4+	**2.6 (1.1, 6.1)**	**1.7 (1.2, 2.3)**	1.1 (0.5, 2.2)	**1.7 (1.2, 2.5)**	1.3 (0.1, 21.2)	2.5 (0.8, 8.5)	N/I	1.2 (0.3, 5.7)
History of parental substance use								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	1.3 (0.9, 1.7)	1.3 (0.9, 2.0)	1.1 (0.6, 1.9)	N/I	N/I	N/I	N/I	N/I
Poor sleep quality								
No	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Yes	N/I	N/I	1.7 (0.5, 5.2)	1.1 (0.6, 2.0)	N/I	0.6 (0.3, 1.2)	N/I	N/I
Other patient-reported measures (per 1-unit change worse)								
Pain severity	1.1 (1.0, 1.1)	1.0 (1.0, 1.1)	1.1 (0.9, 1.2)	0.9 (0.9, 1.0)	1.1 (0.9, 1.3)	1.0 (0.9, 1.1)	N/I	1.2 (1.0, 1.4)
Pain interference	1.1 (1.0, 1.3)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)	N/I	**1.3 (1.1, 1.5)**	1.2 (1.0, 1.4)	1.0 (0.8, 1.1)
Stress	1.0 (0.9, 1.0)	1.0 (1.0, 1.1)	1.0 (1.0, 1.1)	1.0 (1.0, 1.0)	N/I	1.0 (0.9, 1.0)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)
Social support	N/I	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	N/I	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)
SF-12 physical score	N/I	N/I	N/I	N/I	N/I	1.0 (1.0, 1.1)	N/I	N/I
SF-12 mental score	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	1.0 (1.0, 1.0)	**1.0 (1.0, 1.0)**	N/I	1.0 (1.0, 1.0)	1.0 (0.9, 1.0)	1.0 (1.0, 1.0)

Source: FDA-generated table adapted from data provided in Appendix 1 Q5 Table F REV and Q5 Table I REV, FDA IR Response dated June 04, 2024.

Note: For nonreference variables denoted "N/I", the variable did not reach statistical significance at p<0.10 in univariate analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Includes patients who initiated an ER/LA OA that included at least 28 days' supply of an ER/LA OA within a 60-day window followed by a subsequent ER/LA OA prescription within a 7-day period, all within a 90-day period prior to the patient's baseline interview. Patients could not have used an ER/LA OA in the 6 months before the initial 28 days' supply of an ER/LA OA, but patients on IR/SA OAs during the same 6 months were still eligible for this cohort.

[2] Includes patients who initiated of either an ER/LA OA or a Schedule II IR/SA OA for at least 70 of the past 90 days. Patients could not have used an ER/LA OA or a Schedule II IR/SA OA in the 6 months before the initial ER/LA OA or Schedule II IR/SA OA prescription contributing to at least 70 days of use, but other prescription OA therapy would not exclude them (e.g., tramadol use).

[3] Any pain-adjusted DSM-5-OUD was defined as having two or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] Any DSM-5-OUD was defined as having two or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[5] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[6]Moderate-to-severe DSM-5-OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[7] Fully adjusted models were adjusted for all risk factors for with ORs and 95% CIs are presented in the corresponding column of this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses ($p<0.10$), plus age, sex, race, and ethnicity.

[8] There were no Black participants with the moderate-to-severe pain-adjusted DMS-5-OUD outcome in the ER/LA cohort. To achieve model convergence, Black race was combined with other/mixed race for this outcome.

[9] Baseline opioid exposure is measured from 6 months before the index date to the index date (inclusive of the index date). Note, there could be a gap between the 90-day period to determine a patient's eligibility for the study based on their OA use and their baseline interview due to the rolling recruitment process used in the study. As a result, a patient's duration of OA therapy by the time they entered the ER/LA or LtOT cohorts could be longer than 90 days. Predominance is based on greatest total days supply or most prescriptions if there was a tie.

[10] The following opioid moieties were not prescribed in the ER/LA initiators cohort and are therefore not included in the table: dihydrocodeine, levorphanol, pentazocine, and propoxyphene.

[11] When an opioid moiety contained ≤2 events of a given outcome, it was collapsed into the "other" category. Opioid moieties included in the "other" category for a given outcome are indicated by *.

[12]Pain-adjusted.

[13] Medication use defined as two or more dispensings in the prior year except naloxone where use was defined as one or more dispensings or one or more procedure codes.

[14] There were no participants with three ACEs with the moderate-to-severe pain-adjusted DSM-5-OUD outcome in the ER/LA cohort. To achieve model convergence, participants who had two ACEs and three ACEs were combined for this outcome.

Abbreviations: ACE, adverse childhood experiences; ADF, abuse-deterrent formulation; ADHD, attention-deficit/hyperactivity disorder; BMI, body mass index; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ECI, Elixhauser Comorbidity Index; ED, emergency department; EHR, electronic health record; ER/LA, extended-release/long-acting; FDA, Food and Drug Administration; GAD, generalized anxiety disorder; IR, information request; IR/SA, immediate-release/short-acting; LtOT, long-term opioid therapy; MDD, major depressive disorder; MME, morphine milligram equivalent; N/I, not included; OA, opioid analgesic; OR, odds ratio; OUD, opioid use disorder; OUD-H, opioid use disorder due to heroin use; OUD-P, opioid use disorder due to prescription opioid use; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, post-traumatic stress disorder; Ref, reference; SF-12, 12-item Short Form Health Survey; SUD, substance use disorder

6.6 Cross-Sectional PMR 3033-1 Study Tables

Table 34. Associations Between Risk Factors and Past-3-Month Opioid Misuse[1] in Unadjusted, Demographically Adjusted, and Fully Adjusted Models in the PMR 3033-1 Cross-Sectional Study

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,059)	
Factor	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
POMAQ modality						
Telephone	Ref	Ref	Ref	Ref	Ref	Ref
Web	0.9	0.6153	0.9	(0.7, 1.1)	N/I	N/I
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	0.9	0.7390	0.9	(0.5, 1.8)	1.0	(0.5, 2.3)
50-59	0.7	0.2163	0.7	(0.4, 1.2)	0.8	(0.3, 1.7)
≥60	**0.6**	**0.0474**	0.6	(0.4, 0.9)	1.0	(0.5, 1.9)
Sex (male vs. female)	**1.6**	**<0.0001**	**1.7**	**(1.3, 2.1)**	**1.5**	**(1.0, 2.3)**
Race[5]						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	0.7	0.3094	0.7	(0.4, 1.3)	0.9	(0.5, 1.5)
Other/Mixed	1.2	0.4654	1.2	(0.6, 2.3)	1.7	(0.9, 3.3)
Ethnicity (Hispanic vs. non-Hispanic)[5]	1.3	0.1324	1.2	(0.8, 1.9)	0.9	(0.5, 1.6)
Annual household income						
$25,000 or less	Ref	Ref	Ref	Ref	Ref	Ref
$25,001-$50,000	1.1	0.4346	1.1	(0.8, 1.5)	1.4	(0.9, 2.1)
$50,001-$75,000	**1.9**	**0.0100**	**1.8**	**(1.1, 3.1)**	**2.2**	**(1.0, 4.8)**
$75,001-$100,000	1.0	0.9842	1.0	(0.5, 1.9)	0.9	(0.3, 2.8)
$100,001-$150,000	1.3	0.3920	1.2	(0.6, 2.2)	1.6	(0.7, 3.8)
Greater than $150,000	**1.5**	**0.0363**	1.3	(0.9, 1.9)	**1.7**	**(1.1, 2.7)**
Prefer not to report	0.9	0.7961	0.9	(0.5, 1.7)	1.3	(0.8, 2.0)
Education						
<High school degree	0.9	0.8194	1.0	(0.6, 1.4)	N/I	N/I
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	1.0	0.7292	1.1	(0.9, 1.3)	N/I	N/I
Any graduate school	0.7	0.2203	0.7	(0.4, 1.4)	N/I	N/I
Medicaid (yes vs. no)	1.0	0.9193	1.0	(0.7, 1.4)	N/I	N/I
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	**1.3**	**0.0549**	**1.4**	**(1.1, 1.9)**	**1.4**	**(1.0, 1.9)**
Network or fee-for-service providers	1.1	0.8407	1.0	(0.6, 1.6)	1.0	(0.5, 1.7)
OA-related factors						
Predominant opioid formulation[6]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	**0.6**	**0.0008**	**0.6**	**(0.4, 0.7)**	**0.5**	**(0.4, 0.7)**

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,059)	
Factor	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Predominant opioid moiety[6]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.8	0.1661	0.7	(0.5, 1.1)	0.8	(0.4, 1.5)
Hydrocodone	**0.8**	**0.0824**	0.8	(0.6, 1.1)	0.6	(0.3, 1.2)
Fentanyl	**0.5**	**0.0885**	0.5	(0.2, 1.2)	0.5	(0.1, 1.5)
Methadone	0.9	0.6137	0.8	(0.5, 1.2)	1.1	(0.4, 2.7)
Other[7]	1.1	0.7602	1.1	(0.7, 1.7)	0.9	(0.4, 2.2)
Abuse-deterrent opioid exposure (yes vs. no)	**0.7**	**0.0008**	**0.7**	**(0.5, 0.9)**	**0.5**	**(0.3, 0.8)**
Average daily dose of opioids						
<50 MME	Ref	Ref	Ref	Ref	Ref	Ref
50-89 MME	0.8	0.2129	0.8	(0.6, 1.1)	N/I	N/I
90-119 MME	0.9	0.5469	0.9	(0.7, 1.2)	N/I	N/I
≥120 MME	0.8	0.2142	0.7	(0.5, 1.1)	N/I	N/I
Substance use disorder history (yes vs. no)						
Nonopioid and non-nicotine substance use disorder, past year	**5.1**	**<0.0001**	**4.7**	**(3.3, 6.8)**	**4.3**	**(2.4, 7.6)**
Nonopioid and non-nicotine substance use disorder, prior to past year	**2.3**	**0.0003**	**2.2**	**(1.3, 3.5)**	1.4	(0.8, 2.5)
Hallucinogen use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Hallucinogen use disorder, prior to past year	1.9	0.1162	1.6	(0.7, 3.9)	N/I	N/I
Sedative use disorder, past year	5.8	0.2144	5.4	(0.3, 112.2)	N/I	N/I
Sedative use disorder, prior to past year	1.0	0.9713	0.9	(0.3, 3.1)	N/I	N/I
Cocaine use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Cocaine use disorder, prior to past year	**2.1**	**<0.0001**	**2.1**	**(1.4, 3.0)**	N/I	N/I
Stimulant use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Stimulant use disorder, prior to past year	1.6	0.3479	1.4	(0.5, 4.1)	N/I	N/I
Alcohol use disorder, past year	**5.0**	**0.0020**	**4.7**	**(1.8, 12.2)**	N/I	N/I
Alcohol use disorder, prior to past year	**1.8**	**0.0362**	1.7	(0.9, 3.1)	N/I	N/I
Cannabis use disorder, past year	**4.1**	**<0.0001**	**3.8**	**(1.9, 7.4)**	N/I	N/I
Cannabis use disorder, prior to past year	**2.7**	**<0.0001**	**2.5**	**(1.6, 4.1)**	N/I	N/I
Other drug use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Other drug use disorder, prior to past year	**11.7**	**0.0012**	**7.8**	**(1.7, 35.0)**	N/I	N/I
Nicotine use disorder, past year	**2.0**	**<0.0001**	**2.1**	**(1.5, 2.9)**	N/I	N/I

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,059)	
Factor	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Nicotine use disorder, prior to past year	**1.4**	**0.0555**	1.3	(1.0, 1.8)	N/I	N/I
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	0.8	0.1710	0.8	(0.6, 1.1)	0.6	(0.4, 0.9)
3+	**1.5**	**0.0081**	**1.4**	**(1.0, 2.0)**	1.0	(0.6, 1.7)
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.0	0.9563	1.1	(0.8, 1.4)	N/I	N/I
2+	1.0	0.8920	1.0	(0.7, 1.4)	N/I	N/I
Other medication use (any vs. none)[9]						
Antidepressants	1.0	0.8298	1.0	(0.7, 1.5)	N/I	N/I
Antipsychotics	1.6	0.1382	1.6	(0.9, 2.8)	N/I	N/I
Gabapentinoids	**1.2**	**0.0586**	**1.2**	**(1.0, 1.5)**	1.2	(0.9, 1.6)
Muscle relaxers	**1.3**	**0.0230**	**1.3**	**(1.0, 1.7)**	1.3	(0.9, 1.9)
Naloxone	**1.4**	**0.0362**	**1.4**	**(1.0, 1.9)**	**1.5**	**(1.0, 2.1)**
Sedative hypnotics	1.2	0.1984	1.2	(0.9, 1.7)	N/I	N/I
Stimulants	1.6	0.2089	1.4	(0.7, 3.0)	N/I	N/I
Number of pain conditions from EHR						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	0.7	0.2940	0.8	(0.4, 1.4)	N/I	N/I
3+	0.9	0.5681	1.0	(0.6, 1.6)	N/I	N/I
Elixhauser comorbidity score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.0	0.8429	0.9	(0.7, 1.3)	N/I	N/I
2+	0.9	0.5840	1.0	(0.8, 1.2)	N/I	N/I
Body mass index						
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	0.7	0.2383	0.7	(0.4, 1.2)	N/I	N/I
Obese	0.7	0.1400	0.7	(0.4, 1.1)	N/I	N/I
Missing	0.8	0.1374	0.7	(0.5, 1.0)	N/I	N/I
Fibromyalgia from patient-reported symptoms (yes vs. no)	**2.3**	**<0.0001**	**2.3**	**(1.6, 3.4)**	**2.5**	**(1.6, 3.9)**
Mental health conditions and social factors						
Major depressive disorder, past year (yes vs. no)	**2.0**	**0.0021**	**2.0**	**(1.3, 3.1)**	**1.6**	**(1.1, 2.4)**
Major depressive disorder, prior to past year (yes vs. no)	**1.4**	**0.0611**	1.5	(1.0, 2.2)	0.9	(0.6, 1.2)
ADHD (yes vs. no)	**1.6**	**0.0165**	**1.5**	**(1.0, 2.2)**	0.8	(0.5, 1.3)
Borderline personality disorder (yes vs. no)	**1.9**	**0.0037**	**1.8**	**(1.2, 2.7)**	1.0	(0.7, 1.5)
GAD (yes vs. no)	**2.2**	**0.0011**	**2.2**	**(1.4, 3.4)**	**1.4**	**(1.1, 1.9)**
PTSD (yes vs. no)	**1.7**	**0.0152**	**1.6**	**(1.0, 2.6)**	0.8	(0.5, 1.2)
History of parental substance use (yes vs. no)	**1.7**	**<0.0001**	**1.7**	**(1.4, 2.1)**	1.4	(1.0, 2.0)

Factor	Unadjusted (N=1,207) OR	Unadjusted (N=1,207) p[4]	Demographically Adjusted[2] (N=1,207) OR	Demographically Adjusted[2] (N=1,207) 95% CI	Fully Adjusted[3] (N=1,059) OR	Fully Adjusted[3] (N=1,059) 95% CI
ACE score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.1	0.8751	1.1	(0.6, 2.1)	1.0	(0.5, 1.9)
2	1.5	0.1846	1.6	(0.9, 2.9)	1.2	(0.6, 2.2)
3	1.1	0.8366	1.1	(0.6, 2.0)	0.6	(0.3, 1.3)
≥4	**2.0**	**<0.0001**	**2.1**	**(1.5, 2.9)**	1.5	(0.9, 2.3)
Poor sleep quality (yes vs. no)	**1.4**	**0.0002**	**1.4**	**(1.2, 1.8)**	0.9	(0.7, 1.3)
Other patient-reported measures (per 1-unit change in score worse)						
Pain severity score	1.0	0.4106	1.0	(0.9, 1.2)	N/I	N/I
Pain interference score	**1.1**	**0.0113**	**1.1**	**(1.0, 1.2)**	1.0	(0.9, 1.1)
Stress score	**1.0**	**<0.0001**	**1.0**	**(1.0, 1.1)**	1.0	(1.0, 1.1)
Social support score	**1.0**	**0.0027**	**1.0**	**(1.0, 1.0)**	1.0	(1.0, 1.0)
SF-12 physical score	**1.0**	**<0.0001**	**1.0**	**(1.0, 1.0)**	**1.0**	**(0.9, 1.0)**
SF-12 mental score	**1.0**	**0.0002**	**1.0**	**(1.0, 1.1)**	1.0	(1.0, 1.0)
Gene-specific burden scores[10]						
OPRM1 burden score	0.9	0.3023	0.9	(0.8, 1.1)	N/I	N/I
Cytochrome P450 2D6 burden score	0.9	0.4379	0.9	(0.8, 1.1)	N/I	N/I
Cytochrome P450 3A4 burden score	1.0	0.7445	0.9	(0.7, 1.2)	N/I	N/I

Source: FDA-adapted table based on information provided in PMR 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, as well as final data submitted by the OPC on June 4, 2024, in "Response to Clarifying Questions for the PMR 3033-1 Cross-Sectional and Prospective Studies, May 3, 2024," Appendix 1, Q5 Table A, Q5 Table B, and Q5 Table C REV.

Note: For nonreference variables denoted "N/I", the variable was not statistically significantly associated with the outcome at p<0.10 in unadjusted analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Opioid misuse was measured using the POMAQ, with a 3-month lookback period.

[2] Demographically adjusted models were adjusted for age, sex, race, and ethnicity.

[3] Fully adjusted models were adjusted for all risk factors for which fully adjusted ORs and 95% CIs are shown in this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.01), plus age, sex, race, and ethnicity.

[4] P-values, rather than 95% CIs, are presented for the unadjusted analysis, because 95% CIs were not presented in the report submitted by the OPC. For the unadjusted analysis, bolding indicates p<0.1000.

[5] Race and ethnicity are from self-reported questionnaire data. Five patients were missing self-reported race.

[6] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[7] The "other" category for active pharmaceutical ingredient combines all ingredients where there were ≤2 eventsfor a given outcome. In this analysis, this included oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, butorphanol, and others not listed here.

[8] For cells denoted "not estimable," ORs were not estimable due to a lack of model convergence arising from the small number of participants with the specified outcome.

[9] Medication use defined as two or more dispensings in the prior year, except for buprenorphine and naloxone where use defined as one or more dispensing or one or more procedure code.

[10] Genetic analyses include the subset of eligible patients who provided evaluable genetic samples: 822 for OPRM1, 829 for cytochrome P450 2D6, and 821 for cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experience; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; EHR, electronic health records; ER/LA, extended-release/long-acting; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; N/I, not included; OA, opioid analgesic; OPC, Opioid PMR Consortium; OR, odds ratio; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PTSD, posttraumatic stress disorder; MME, morphine milligram equivalent; Ref, reference; SF-12, 12-Item Short Form Health Survey, SUD, substance use disorder

Table 35. Associations Between Risk Factors and Past-3-Month Opioid Abuse[1] From Unadjusted, Demographically Adjusted, and Fully Adjusted Models in the PMR 3033-1 Cross-Sectional Study

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,078)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
POMAQ modality						
Telephone	Ref	Ref	Ref	Ref	Ref	Ref
Web	**0.7**	**0.0095**	**0.7**	**(0.6, 0.9)**	0.5	(0.3, 1.1)
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	0.9	0.7984	0.7	(0.3, 1.8)	0.9	(0.3, 2.4)
50-59	1.7	0.1455	1.7	(0.8, 3.6)	1.9	(0.5, 6.4)
≥60	1.4	0.3613	1.4	(0.6, 3.1)	2.0	(0.6, 6.8)
Sex (male vs. female)	**2.3**	**0.0009**	**2.3**	**(1.4, 3.7)**	**2.2**	**(1.1, 4.5)**
Race[5]						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	**0.5**	**0.0354**	0.6	(0.4, 1.1)	0.9	(0.5, 1.6)
Other/mixed	0.8	0.6075	0.9	(0.5, 1.8)	1.5	(0.5, 4.3)
Ethnicity (Hispanic vs. non-Hispanic)[5]	1.3	0.3917	1.2	(0.6, 2.2)	0.8	(0.2, 3.2)
Annual household income						
$25,000 or less	Ref	Ref	Ref	Ref	Ref	Ref
$25,001-$50,000	1.0	0.9003	0.9	(0.5, 1.6)	1.4	(0.7, 2.8)
$50,001-$75,000	**1.4**	**0.0372**	1.2	(0.8, 1.7)	**2.4**	**(1.4, 4.1)**
$75,001-$100,000	0.3	0.1783	0.2	(0.0, 1.7)	0.3	(0.0, 3.0)
$100,001-$150,000	1.1	0.8661	1.0	(0.5, 2.1)	2.1	(0.6, 6.8)
Greater than $150,000	0.9	0.8700	0.9	(0.4, 2.3)	2.0	(0.7, 6.0)
Prefer not to report	**0.2**	**0.0026**	0.1	(0.0, 0.4)	0.2	(0.1, 0.5)
Education						
<High school degree	**0.5**	**0.0155**	**0.5**	**(0.3, 0.9)**	**0.3**	**(0.1, 0.8)**
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	**0.6**	**0.0041**	**0.7**	**(0.4, 1.0)**	0.7	(0.4, 1.1)
Any graduate school	**0.2**	**0.0741**	0.2	(0.0, 1.2)	0.3	(0.1, 1.1)
Medicaid (yes vs. no)	1.5	0.1046	**1.6**	**(1.0, 2.5)**	N/I	N/I
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	1.0	0.9593	1.2	(0.7, 2.0)	N/I	N/I
Network or fee-for-service providers	1.2	0.5235	1.3	(0.8, 2.2)	N/I	N/I
OA-related factors						
Predominant opioid formulation[6]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	0.9	0.3319	0.8	(0.6, 1.0)	N/I	N/I
Predominant opioid moiety[6]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	1.1	0.7085	1.0	(0.6, 1.9)	0.7	(0.3, 1.9)
Hydrocodone	**1.8**	**0.0111**	**2.1**	**(1.4, 3.2)**	1.5	(0.7, 3.4)
Fentanyl	**1.6**	**0.0746**	1.8	(1.0, 3.2)	0.9	(0.5, 1.6)
Methadone	1.1	0.8016	0.9	(0.5, 1.8)	0.6	(0.3, 1.2)
Other[7]	1.1	0.8535	1.3	(0.5, 3.2)	1.0	(0.3, 3.4)
Abuse-deterrent opioid exposure (yes vs. no)	**0.5**	**0.0393**	**0.5**	**(0.2, 1.0)**	**0.4**	**(0.3, 0.6)**

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,078)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Average daily dose of opioids						
<50 MME	Ref	Ref	Ref	Ref	Ref	Ref
50-89 MME	1.1	0.6760	1.0	(0.5, 1.8)	N/I	N/I
90-119 MME	0.8	0.4159	0.7	(0.4, 1.3)	N/I	N/I
≥120 MME	1.2	0.6139	1.1	(0.6, 2.0)	N/I	N/I
Substance use disorder history (yes vs. no)						
Nonopioid and non-nicotine substance use disorder, past year	**7.5**	**<0.0001**	8.5	(5.0, 14.5)	5.9	(2.9, 11.9)
Nonopioid and non-nicotine substance use disorder, prior to past year	**3.9**	**<0.0001**	3.6	(2.6, 4.9)	2.1	(1.3, 3.4)
Hallucinogen use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Hallucinogen use disorder, prior to past year	3.7	0.1189	3.0	(0.5, 16.5)	N/I	N/I
Sedative use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Sedative use disorder, prior to past year	1.2	0.8403	1.1	(0.2, 7.2)	N/I	N/I
Cocaine use disorder, past year	**32.2**	**0.0072**	**22.6**	**(1.8, 284.7)**	N/I	N/I
Cocaine use disorder, prior to past year	**3.6**	**<0.0001**	**3.2**	**(2.1, 4.9)**	N/I	N/I
Stimulant use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Stimulant use disorder, prior to past year	**2.7**	**0.0005**	**2.3**	**(1.3, 4.3)**	N/I	N/I
Alcohol use disorder, past year	**5.5**	**0.0001**	**5.5**	**(2.1, 14.3)**	N/I	N/I
Alcohol use disorder, prior to past year	**2.0**	**0.0059**	**1.7**	**(1.0, 2.8)**	N/I	N/I
Cannabis use disorder, past year	**8.2**	**<0.0001**	**10.2**	**(4.3, 24.2)**	N/I	N/I
Cannabis use disorder, prior to past year	**6.2**	**<0.0001**	**5.8**	**(3.3, 10.0)**	N/I	N/I
Other drug use disorder, past year	Not estimable[8]	Not estimable[8]	Not estimable[8]	Not estimable[8]	N/I	N/I
Other drug use disorder, prior to past year	**7.9**	**0.0026**	**7.7**	**(2.6, 23.0)**	N/I	N/I
Nicotine use disorder, past year	**2.2**	**0.0204**	**2.4**	**(1.2, 4.9)**	N/I	N/I
Nicotine use disorder, prior to past year	**2.1**	**<0.0001**	**2.1**	**(1.7, 2.5)**	N/I	N/I
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	1.2	0.5658	1.4	(0.8, 2.5)	N/I	N/I
3+	1.2	0.6144	1.4	(0.7, 2.9)	N/I	N/I
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.1	0.7094	1.2	(0.7, 2.0)	N/I	N/I
2+	0.7	0.4539	0.7	(0.3, 1.9)	N/I	N/I
Other medication use (any vs. none)[9]						
Antidepressants	0.9	0.5282	0.8	(0.6, 1.2)	N/I	N/I
Antipsychotics	**2.3**	**0.0178**	**2.9**	**(1.4, 5.8)**	**2.5**	**(1.1, 5.3)**
Gabapentinoids	0.8	0.2824	0.8	(0.6, 1.2)	N/I	N/I
Muscle relaxers	**0.7**	**0.0361**	0.7	(0.5, 1.1)	0.8	(0.5, 1.3)
Naloxone	0.9	0.8299	1.0	(0.4, 2.1)	N/I	N/I
Sedative hypnotics	1.2	0.3310	1.3	(0.9, 1.9)	N/I	N/I
Stimulants	1.1	0.9058	1.1	(0.4, 3.1)	N/I	N/I

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,078)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Number of pain conditions from EHR						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	0.7	0.5837	0.8	(0.3, 2.1)	N/I	N/I
3+	0.7	0.4073	0.9	(0.5, 1.6)	N/I	N/I
Elixhauser comorbidity score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	0.7	0.3732	0.6	(0.3, 1.4)	N/I	N/I
2+	1.0	0.8931	1.0	(0.7, 1.4)	N/I	N/I
Body mass index						
Underweight/normal	Ref	Ref	Ref	Ref	N/I	N/I
Overweight	0.8	0.3565	0.7	(0.4, 1.3)	N/I	N/I
Obese	0.8	0.5252	0.8	(0.5, 1.3)	N/I	N/I
Missing	1.0	0.9715	0.9	(0.6, 1.5)	N/I	N/I
Fibromyalgia from patient-reported symptoms (yes vs. no)	0.8	0.4433	0.7	(0.4, 1.4)	N/I	N/I
Mental health conditions and social factors						
Major depressive disorder, past year (yes vs. no)	**2.3**	**<0.0001**	**2.7**	**(1.9, 3.8)**	1.6	(0.7, 3.6)
Major depressive disorder, prior to past year (yes vs. no)	1.2	0.3889	1.4	(1.0, 2.1)	N/I	N/I
ADHD (yes vs. no)	**1.9**	**0.0431**	1.8	(0.8, 3.8)	1.0	(0.4, 2.4)
Borderline personality disorder (yes vs. no)	**2.2**	**0.0007**	**2.7**	**(1.6, 4.4)**	0.8	(0.4, 1.5)
GAD (yes vs. no)	**3.0**	**<0.0001**	**3.1**	**(1.8, 5.1)**	1.8	(0.7, 4.5)
PTSD (yes vs. no)	**2.6**	**0.0003**	**2.7**	**(1.4, 5.2)**	1.1	(0.4, 3.2)
History of parental substance use (yes vs. no)	**2.2**	**<0.0001**	**2.5**	**(1.8, 3.4)**	**1.7**	**(1.1, 2.6)**
ACE score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.5	0.3059	1.8	(0.8, 4.0)	1.1	(0.4, 2.8)
2	**2.3**	**0.0211**	**2.2**	**(1.1, 4.5)**	1.4	(0.6, 3.2)
3	1.8	0.1178	**2.3**	**(1.1, 4.8)**	1.0	(0.4, 2.6)
≥4	**2.9**	**0.0007**	**3.7**	**(1.8, 7.4)**	1.5	(0.6, 3.7)
Poor sleep quality (yes vs. no)	**2.8**	**0.0466**	2.7	(1.0, 7.9)	1.5	(0.4, 5.4)
Other patient-reported measures (per 1-unit change in score for the worse)						
Pain severity score	1.0	0.6101	1.0	(0.9, 1.1)	N/I	N/I
Pain interference score	**1.1**	**0.0518**	1.1	(1.0, 1.2)	0.9	(0.8, 1.0)
Stress score	**1.1**	**<0.0001**	**1.1**	**(1.0, 1.1)**	1.0	(0.9, 1.0)
Social support score	**1.0**	**<0.0001**	**1.0**	**(1.0, 1.0)**	1.0	(1.0, 1.0)
SF-12 physical score	1.0	0.2007	1.0	(1.0, 1.0)	N/I	N/I
SF-12 mental score	**1.0**	**<0.0001**	**1.0**	**(1.0, 1.1)**	1.0	(1.0, 1.1)
Gene-specific burden scores[10]						
OPRM1 burden score	1.0	0.6131	1.0	(0.9, 1.2)	N/I	N/I
Cytochrome P450 2D6 burden score	0.9	0.5085	0.9	(0.8, 1.2)	N/I	N/I
Cytochrome P450 3A4 burden score	1.0	0.8566	1.1	(0.8, 1.4)	N/I	N/I

Source: FDA-adapted table based on information provided in PMR 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, as well as final data submitted by the OPC on June 4, 2024, in "Response to Clarifying Questions for the PMR 3033-1 Cross-Sectional and Prospective Studies, May 3, 2024," Appendix 1, Q5 Table A, Q5 Table B, and Q5 Table C REV.

Note: For nonreference variables denoted "N/I", the variable was not statistically significantly associated with the outcome at p<0.10 in unadjusted analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Opioid misuse was measured using the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), with a 3-month lookback period.

[2] Demographically adjusted models were adjusted for age, sex, race, and ethnicity.

[3] Fully adjusted models were adjusted for all risk factors for which fully adjusted ORs and 95% CIs are shown in this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.01), plus age, sex, race, and ethnicity.

[4] p-values, rather than 95% CIs, are presented for the unadjusted analysis, because 95% CIs were not presented in the report submitted by the OPC.

[5] Race and ethnicity are from self-reported questionnaire data. Five patients were missing self-reported race.

[6] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[7] The "other" category for active pharmaceutical ingredient combines all ingredients where there were ≤2 events for a given outcome. In this analysis, this included oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, butorphanol, and others not listed here.

[8] For cells denoted "not estimable," ORs could not be estimated due to a lack of model convergence arising from the small number of participants with the specified outcome.

[9] Medication use defined as two or more dispensings in the prior year, except for buprenorphine and naloxone where use defined as one or more dispensing or one or more procedure code.

[10] Genetic analyses include the subset of eligible patients who provided evaluable genetic samples: 822 for OPRM1, 829 for cytochrome P450 2D6, and 821 for cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experience; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; EHR, electronic health records; ER/LA, extended-release/long-acting; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; N/E, not estimated; OA, opioid analgesic; OPC: Opioid PMR Consortium; OR, odds ratio; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PTSD, posttraumatic stress disorder; MME, morphine milligram equivalent; SF-12, 12-Item Short Form Health Survey; SUD, substance use disorder

Table 36. Associations Between Risk Factors and Moderate-to-Severe Pain-Adjusted DSM-5-OUD[1] From Unadjusted, Demographically Adjusted, and Fully Adjusted Models in the PMR 3033-1 Cross-Sectional Study

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,133)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
PRISM-5-Op modality						
Telephone	Ref	Ref	Ref	Ref	Ref	Ref
In person	**2.2**	**0.0629**	1.5	(0.9, 2.5)	1.0	(0.6, 1.6)
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	1.0	0.9845	0.9	(0.2, 3.3)	0.7	(0.2, 3.0)
50-59	0.5	0.1790	0.5	(0.1, 1.7)	**0.4**	**(0.2, 0.8)**
≥60	**0.3**	**0.0219**	0.3	(0.1, 1.1)	0.6	(0.2, 2.3)
Sex (male vs. female)	**2.7**	**0.0109**	**2.7**	**(1.2, 6.0)**	**4.1**	**(1.6, 10.9)**
Race[5]						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	2.5	0.1346	2.0	(0.6, 6.5)	**3.4**	**(1.0, 11.2)**
Other/mixed	0.6	0.5805	0.3	(0.1, 1.9)	**0.2**	**(0.0, 1.0)**

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,133)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Ethnicity (Hispanic vs. non-Hispanic)[5]	**4.3**	**0.0119**	**4.3**	**(1.5, 11.7)**	**4.1**	**(1.3, 13.3)**
Annual household income						
$25,000 or less	Ref	Ref	Ref	Ref	Ref	Ref
$25,001-$50,000	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
$50,001-$75,000	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
$75,001-$100,000	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
$100,001-$150,000	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Greater than $150,000	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Prefer not to report	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Education						
<High school degree	2.1	0.1061	1.6	(0.6, 4.3)	N/I	N/I
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	1.1	0.7291	1.3	(0.7, 2.2)	N/I	N/I
Any graduate school	0.4	0.2855	0.5	(0.1, 2.0)	N/I	N/I
Medicaid (yes vs. no)	**3.8**	**0.0001**	**3.7**	**(1.9, 7.2)**	**2.5**	**(1.0, 6.5)**
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	**2.8**	**0.0024**	**2.1**	**(1.1, 4.0)**	1.0	(0.4, 2.5)
Network or fee-for-service providers	2.7	0.2048	2.4	(0.6, 9.8)	1.5	(0.3, 8.4)
OA-related factors						
Predominant opioid formulation[7]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	0.8	0.4891	0.7	(0.3, 1.5)	N/I	N/I
Predominant opioid moiety[7]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	**0.5**	**0.0054**	**0.4**	**(0.2, 0.7)**	0.3	(0.1, 1.0)
Methadone	**0.5**	**0.0986**	**0.3**	**(0.1, 1.0)**	0.1	(0.0, 1.0)
Other[8]	**0.3**	**0.0037**	**0.3**	**(0.1, 0.9)**	**0.3**	**(0.1, 1.0)**
Abuse-deterrent opioid exposure (yes vs. no)	1.2	0.7120	1.2	(0.4, 3.4)	N/I	N/I
Average daily dose of opioids						
<50 MME	Ref	Ref	Ref	Ref	Ref	Ref
50-89 MME	0.6	0.3692	0.6	(0.2, 1.5)	0.6	(0.2, 1.5)
90-119 MME	1.0	0.9804	1.0	(0.4, 2.2)	0.5	(0.2, 1.6)
≥120 MME	**2.3**	**0.0968**	1.9	(0.8, 4.2)	1.2	(0.4, 3.6)
Substance use disorder history (yes vs. no)						
Nonopioid and non-nicotine substance use disorder, past year	**6.0**	**<0.0001**	**4.4**	**(2.3, 8.6)**	2.7	(0.9, 7.6)
Nonopioid and non-nicotine substance use disorder, prior to past year	**3.7**	**0.0001**	**3.8**	**(1.9, 7.6)**	2.3	(1.0, 5.4)
Hallucinogen use disorder, past year	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,133)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Hallucinogen use disorder, prior to past year	**5.3**	**0.0001**	**5.0**	**(2.0, 12.2)**	N/I	N/I
Sedative use disorder, past year	**36.4**	**0.0061**	**52.5**	**(5.5, 504.4)**	N/I	N/I
Sedative use disorder, prior to past year	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Cocaine use disorder, past year	**17.8**	**0.0199**	**11.8**	**(1.1, 131.9)**	N/I	N/I
Cocaine use disorder, prior to past year	**2.2**	**0.0161**	**2.3**	**(1.2, 4.4)**	N/I	N/I
Stimulant use disorder, past year	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Stimulant use disorder, prior to past year	0.9	0.8888	0.8	(0.1, 6.7)	N/I	N/I
Alcohol use disorder, past year	4.1	0.1103	3.4	(0.7, 16.8)	N/I	N/I
Alcohol use disorder, prior to past year	**3.4**	**<0.0001**	**3.7**	**(1.9, 7.4)**	N/I	N/I
Cannabis use disorder, past year	**5.0**	**<0.0001**	**3.5**	**(1.8, 6.6)**	N/I	N/I
Cannabis use disorder, prior to past year	**3.0**	**0.0007**	**2.8**	**(1.4, 5.8)**	N/I	N/I
Other drug use disorder, past year	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Other drug use disorder, prior to past year	Not estimable[6]	Not estimable[6]	Not estimable[6]	Not estimable[6]	N/I	N/I
Nicotine use disorder, past year	**2.1**	**0.0136**	**2.3**	**(1.2, 4.2)**	N/I	N/I
Nicotine use disorder, prior to past year	**3.1**	**<0.0001**	**4.1**	**(2.2, 7.6)**	N/I	N/I
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	1.5	0.1640	1.3	(0.8, 2.4)	1.3	(0.7, 2.5)
3+	**3.5**	**<0.0001**	**2.4**	**(1.3, 4.3)**	1.1	(0.4, 3.0)
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	**1.9**	**0.0743**	2.0	(1.0, 3.9)	1.7	(0.8, 3.6)
2+	**2.4**	**0.0480**	2.2	(0.9, 5.4)	**2.6**	**(1.0, 6.5)**
Other medication use (any vs. none)[9]						
Antidepressants	1.3	0.1222	**2.2**	**(1.4, 3.5)**	N/I	N/I
Antipsychotics	0.7	0.5986	0.6	(0.1, 2.8)	N/I	N/I
Gabapentinoids	1.5	0.1379	1.5	(0.7, 3.0)	N/I	N/I
Muscle relaxers	0.9	0.8258	1.0	(0.5, 1.8)	N/I	N/I
Naloxone	**1.8**	**0.0790**	1.7	(0.9, 3.2)	1.4	(0.5, 3.7)
Sedative hypnotics	**1.6**	**0.0975**	1.8	(0.8, 3.9)	1.3	(0.7, 2.4)
Stimulants	0.8	0.7940	0.7	(0.1, 5.8)	N/I	N/I
Number of pain conditions from EHR						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	2.5	0.4174	2.2	(0.2, 20.8)	N/I	N/I
3+	1.4	0.7498	1.4	(0.2, 13.5)	N/I	N/I
Elixhauser comorbidity score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.2	0.7454	1.0	(0.3, 3.2)	N/I	N/I
2+	1.4	0.5138	1.4	(0.5, 3.6)	N/I	N/I
Body mass index						
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	0.5	0.1265	0.5	(0.2, 1.3)	**0.2**	**(0.1, 0.9)**
Obese	**0.3**	**0.0001**	**0.3**	**(0.2, 0.5)**	**0.3**	**(0.2, 0.5)**
Missing	**0.2**	**<0.0001**	**0.3**	**(0.2, 0.6)**	**0.2**	**(0.1, 0.4)**

	Unadjusted (N=1,207)		Demographically Adjusted[2] (N=1,207)		Fully Adjusted[3] (N=1,133)	
Variable	**OR**	**p[4]**	**OR**	**95% CI**	**OR**	**95% CI**
Fibromyalgia from patient-reported symptoms (yes vs. no)	**1.9**	**0.0485**	1.5	(0.7, 3.5)	0.6	(0.2, 2.0)
Mental health conditions and social factors						
Major depressive disorder, past year (yes vs. no)	**3.7**	**<0.0001**	**4.1**	**(1.8, 9.2)**	1.5	(0.5, 4.1)
Major depressive disorder, prior to past year (yes vs. no)	**2.9**	**0.0003**	**3.3**	**(1.9, 5.9)**	**3.2**	**(1.2, 9.1)**
ADHD (yes vs. no)	**3.8**	**0.0036**	**4.2**	**(1.8, 9.9)**	2.8	(1.0, 8.0)
Borderline personality disorder (yes vs. no)	**2.9**	**<0.0001**	**2.9**	**(1.8, 4.6)**	1.1	(0.4, 3.0)
GAD (yes vs. no)	**4.1**	**<0.0001**	**3.8**	**(2.0, 7.4)**	0.6	(0.2, 2.0)
PTSD (yes vs. no)	**4.2**	**<0.0001**	**3.5**	**(2.3, 5.1)**	1.3	(0.5, 3.7)
History of parental substance use (yes vs. no)	1.9	0.1018	1.9	(0.9, 4.1)	N/I	N/I
ACE score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	0.8	0.6234	0.5	(0.2, 1.8)	1.2	(0.3, 6.0)
2	0.8	0.7244	0.8	(0.2, 3.2)	0.6	(0.1, 4.8)
3	1.8	0.3454	1.6	(0.4, 5.9)	1.6	(0.1, 18.1)
≥4	**2.7**	**0.0264**	**2.8**	**(1.1, 7.1)**	2.5	(0.4, 16.6)
Poor sleep quality (yes vs. no)	3.1	0.1410	Not estimable[6]	Not estimable[6]	N/I	N/I
Other patient-reported measures (per 1-unit change in score for the worse)						
Pain severity score	**1.3**	**0.0003**	**1.3**	**(1.1, 1.5)**	1.2	(0.9, 1.6)
Pain interference score	**1.3**	**<0.0001**	**1.3**	**(1.2, 1.4)**	1.0	(0.7, 1.5)
Stress score	**1.1**	**<0.0001**	**1.1**	**(1.0, 1.1)**	1.0	(0.9, 1.0)
Social support score	1.0	0.2159	1.0	(1.0, 1.0)	N/I	N/I
SF-12 physical score	**1.0**	**0.0257**	1.0	(0.9, 1.0)	1.0	(0.9, 1.1)
SF-12 mental score	**1.1**	**<0.0001**	**1.1**	**(1.1, 1.1)**	1.1	(1.0, 1.1)
Gene-specific burden scores[10]						
OPRM1 burden score	1.0	0.9715	0.9	(0.7, 1.3)	N/I	N/I
Cytochrome P450 2D6 burden score	0.9	0.3006	0.7	(0.5, 1.0)	N/I	N/I
Cytochrome P450 3A4 burden score	1.1	0.8167	0.9	(0.5, 1.7)	N/I	N/I

Source: FDA-adapted table based on information provided in PMR 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, as well as final data submitted by the OPC on June 4, 2024, in "Response to Clarifying Questions for the PMR 3033-1 Cross-Sectional and Prospective Studies, May 3, 2024," Appendix 1, Q5 Table A, Q5 Table B, and Q5 Table C REV.

Note: For nonreference variables denoted "N/I", the variable was not statistically significantly associated with the outcome at p<0.10 in unadjusted analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Moderate-to-severe pain-adjusted DSM-5-OUD was defined as having four or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[2] Demographically adjusted models were adjusted for age, sex, race, and ethnicity.

[3] Fully adjusted models were adjusted for all risk factors for which fully adjusted ORs and 95% CIs are shown in this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.01), plus age, sex, race, and ethnicity.

[4] p-values, rather than 95% CIs, are presented for the unadjusted analysis, because 95% CIs were not presented in the report submitted by the OPC.

[5] Race and ethnicity are from self-reported questionnaire data. Five patients were missing self-reported race.

[6] For cells denoted "not estimable," ORs could not be estimated due to a lack of model convergence arising from the small number of participants with the specified outcome.

[7] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[8] The "other" category for active pharmaceutical ingredient combines all ingredients where there were ≤2 events for a given outcome. In this analysis, this included oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, butorphanol, and others not listed here.

[9] Medication use defined as two or more dispensings in the prior year, except for buprenorphine and naloxone where use defined as one or more dispensing or one or more procedure code.

[10] Genetic analyses include the subset of eligible patients who provided evaluable genetic samples: 822 for OPRM1, 829 for cytochrome P450 2D6, and 821 for cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experience; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EHR, electronic health records; ER/LA, extended-release/long-acting; GAD, generalized anxiety disorder; IR/SA: immediate-release/short-acting; MDD, major depressive disorder; N/E, not estimated; OA, opioid analgesic; OPC: Opioid PMR Consortium; OR, odds ratio; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; MME, morphine milligram equivalent; SF-12, 12-Item Short Form Health Survey; SUD, substance use disorder

Table 37. Associations Between Risk Factors and OUD, Using Secondary Definitions of OUD, From Fully Adjusted Models in the PMR 3033-1 Cross-Sectional Study

Variable	Moderate-to-Severe DSM-5-OUD[1]		Any Pain-Adjusted DSM-5-OUD[2]		Any DSM-5-OUD[3]	
	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI
PRISM-5-Op modality						
Telephone	Ref	Ref	Ref	Ref	Ref	Ref
Web	**2.6**	**(1.2, 5.9)**	1.4	(0.8, 2.3)	**1.6**	**(1.3, 2.0)**
Sociodemographic factors						
Age group, years						
18-39	Ref	Ref	Ref	Ref	Ref	Ref
40-49	0.6	(0.2, 2.0)	1.0	(0.5, 1.9)	0.6	(0.3, 1.4)
50-59	**0.4**	**(0.2, 0.9)**	0.6	(0.3, 1.0)	**0.5**	**(0.3, 0.9)**
≥60	**0.5**	**(0.3, 1.0)**	0.9	(0.5, 1.4)	0.7	(0.4, 1.3)
Sex (male vs. female)	**3.9**	**(1.7, 9.0)**	**2.4**	**(1.5, 4.1)**	**1.4**	**(1.0, 1.9)**
Race[5]						
White	Ref	Ref	Ref	Ref	Ref	Ref
Black	1.6	(0.9, 2.6)	1.3	(0.8, 2.2)	**1.4**	**(1.0, 1.9)**
Other/mixed	0.4	(0.1, 2.1)	0.7	(0.2, 2.4)	0.8	(0.4, 1.6)
Ethnicity (Hispanic vs. non-Hispanic)[5]	**3.3**	**(1.2, 9.5)**	1.4	(0.7, 2.8)	**1.7**	**(1.2, 2.4)**
Annual household income						
$25,000 or less	Ref	Ref	Ref	Ref	Ref	Ref
$25,001-$50,000	1.0	(0.6, 1.5)	0.8	(0.6, 1.3)	1.0	(0.8, 1.3)
$50,001-$75,000	0.4	(0.1, 1.1)	0.6	(0.2, 2.2)	1.1	(0.7, 1.5)
$75,001-$100,000	2.9	(0.7, 11.0)	1.0	(0.4, 3.0)	1.2	(0.5, 2.6)
$100,001-$150,000	1.3	(0.7, 2.4)	0.5	(0.1, 2.4)	1.2	(0.7, 1.9)
Greater than $150,000	2.8	(0.4, 17.7)	1.7	(0.3, 9.2)	2.0	(0.9, 4.4)
Prefer not to report	1.0	(0.3, 3.4)	0.3	(0.1, 2.0)	0.6	(0.3, 1.1)
Education						
<High school degree	N/I	N/I	N/I	N/I	N/I	N/I
High school or General Equivalency Degree	Ref	Ref	Ref	Ref	Ref	Ref
Any college	N/I	N/I	N/I	N/I	N/I	N/I
Any graduate school	N/I	N/I	N/I	N/I	N/I	N/I
Medicaid (yes vs. no)	1.2	(0.7, 1.9)	1.6	(0.7, 3.4)	N/I	N/I

Variable	Moderate-to-Severe DSM-5-OUD[1]		Any Pain-Adjusted DSM-5-OUD[2]		Any DSM-5-OUD[3]	
	Fully Adjusted[4] OR	**95% CI**	**Fully Adjusted[4] OR**	**95% CI**	**Fully Adjusted[4] OR**	**95% CI**
Predominant place of care						
Care and insurance in an integrated delivery system	Ref	Ref	Ref	Ref	Ref	Ref
Care only in an integrated delivery system	N/I	N/I	1.0	(0.6, 1.4)	1.0	(0.8, 1.3)
Network or fee-for-service providers	N/I	N/I	1.0	(0.6, 1.7)	1.1	(0.8, 1.5)
OA-related factors						
Predominant opioid formulation[6]						
IR/SA	Ref	Ref	Ref	Ref	Ref	Ref
ER/LA	0.7	(0.3, 1.5)	N/I	N/I	N/I	N/I
Predominant opioid moiety[6]						
Oxycodone	Ref	Ref	Ref	Ref	Ref	Ref
Morphine	0.7	(0.4, 1.1)	0.5	(0.2, 1.1)	0.7	(0.5, 1.0)
Hydrocodone	0.6	(0.1, 3.0)	0.6	(0.3, 1.2)	0.9	(0.6, 1.4)
Fentanyl	1.4	(0.4, 5.0)	0.5	(0.2, 1.1)	1.0	(0.5, 2.0)
Methadone	**0.4**	**(0.2, 0.9)**	0.3	(0.1, 1.8)	1.0	(0.7, 1.5)
Other[7]	1.9	(0.6, 5.8)	1.0	(0.3, 4.0)	0.5	(0.2, 1.7)
Abuse-deterrent opioid exposure (yes vs. no)	N/I	N/I	N/I	N/I	N/I	N/I
Average daily dose of opioids						
<50 MME	Ref	Ref	Ref	Ref	Ref	Ref
50-89 MME	1.8	(0.8, 4.0)	1.3	(0.6, 2.6)	1.2	(0.6, 2.3)
90-119 MME	1.1	(0.4, 2.9)	0.7	(0.2, 1.9)	0.8	(0.4, 1.4)
≥120 MME	1.2	(0.6, 2.3)	1.5	(0.8, 3.1)	1.4	(1.0, 2.1)
Substance use disorders history (yes vs. no)						
Nonopioid and non-nicotine substance use disorder, past year	1.2	(0.3, 4.4)	1.4	(0.7, 2.5)	**3.0**	**(1.9, 4.9)**
Nonopioid and non-nicotine substance use disorder, prior to past year	**3.8**	**(1.8, 8.2)**	**2.3**	**(1.6, 3.3)**	**1.8**	**(1.5, 2.2)**
Health- and pain-related factors						
Emergency department visits						
0	Ref	Ref	Ref	Ref	Ref	Ref
1-2	**1.8**	**(1.3, 2.4)**	1.0	(0.7, 1.5)	1.0	(0.8, 1.4)
3+	2.2	(0.9, 5.2)	**1.9**	**(1.1, 3.2)**	0.9	(0.7, 1.3)
Inpatient stays						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	1.4	(0.6, 3.3)	N/I	N/I	1.4	(0.9, 2.4)
2+	1.4	(0.7, 2.8)	N/I	N/I	1.2	(0.8, 1.8)

Variable	Moderate-to-Severe DSM-5-OUD[1]		Any Pain-Adjusted DSM-5-OUD[2]		Any DSM-5-OUD[3]	
	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI
Other medication use (any vs. none)[8]						
Antidepressants	0.9	(0.5, 1.6)	1.1	(0.8, 1.5)	1.0	(0.7, 1.4)
Antipsychotics	N/I	N/I	1.2	(0.5, 2.5)	1.4	(0.7, 2.9)
Gabapentinoids	**2.2**	**(1.2, 3.7)**	N/I	N/I	1.0	(0.8, 1.4)
Muscle relaxers	1.3	(0.8, 2.1)	N/I	N/I	1.1	(0.9, 1.4)
Naloxone	N/I	N/I	N/I	N/I	**1.4**	**(1.1, 1.9)**
Sedative hypnotics	1.0	(0.5, 1.8)	0.9	(0.4, 1.7)	N/I	N/I
Stimulants	N/I	N/I	N/I	N/I	N/I	N/I
Number of pain conditions from EHR						
0	N/I	N/I	N/I	N/I	Ref	Ref
1-2	N/I	N/I	N/I	N/I	1.7	(0.9, 3.2)
3+	N/I	N/I	N/I	N/I	1.4	(0.7, 2.7)
Elixhauser comorbidity score						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	N/I	N/I	N/I	N/I	N/I	N/I
2+	N/I	N/I	N/I	N/I	N/I	N/I
Body mass index						
Underweight/normal	Ref	Ref	Ref	Ref	Ref	Ref
Overweight	**0.3**	**(0.1, 0.8)**	1.0	(0.5, 2.0)	N/I	N/I
Obese	**0.4**	**(0.2, 0.8)**	**0.6**	**(0.4, 0.9)**	N/I	N/I
Missing	**0.3**	**(0.1, 0.6)**	**0.4**	**(0.2, 0.7)**	N/I	N/I
Fibromyalgia from patient-reported symptoms (yes vs. no)	2.2	(0.8, 5.9)	1.4	(0.7, 2.8)	1.6	(0.9, 2.8)
Mental health conditions and social factors						
Major depressive disorder, past year (yes vs. no)	0.8	(0.4, 1.9)	1.4	(0.6, 3.4)	1.2	(0.8, 2.0)
Major depressive disorder, prior to past year (yes vs. no)	**3.4**	**(1.7, 6.8)**	1.0	(0.6, 1.5)	**1.5**	**(1.1, 2.1)**
ADHD (yes vs. no)	1.0	(0.5, 2.3)	1.1	(0.6, 2.2)	1.1	(0.7, 1.8)
Borderline personality disorder (yes vs. no)	0.7	(0.3, 1.5)	**2.0**	**(1.2, 3.4)**	0.9	(0.5, 1.6)
GAD (yes vs. no)	0.5	(0.2, 1.2)	0.9	(0.5, 1.8)	1.2	(0.9, 1.7)
PTSD (yes vs. no)	1.1	(0.5, 2.4)	0.6	(0.3, 1.2)	0.7	(0.5, 1.1)
History of parental substance use (yes vs. no)	0.9	(0.6, 1.3)	1.4	(0.7, 2.6)	1.1	(0.8, 1.5)
ACEs						
0	Ref	Ref	Ref	Ref	Ref	Ref
1	0.8	(0.3, 2.2)	1.5	(0.4, 5.6)	1.3	(0.8, 2.1)
2	1.5	(0.4, 5.9)	2.0	(0.6, 6.7)	**2.5**	**(1.3, 4.7)**
3	3.9	(0.7, 23.4)	1.7	(0.6, 4.8)	**1.7**	**(1.0, 2.8)**
≥4	**3.4**	**(1.8, 6.3)**	2.1	(0.9, 4.9)	**1.7**	**(1.4, 2.0)**

Variable	Moderate-to-Severe DSM-5-OUD[1]		Any Pain-Adjusted DSM-5-OUD[2]		Any DSM-5-OUD[3]	
	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI	Fully Adjusted[4] OR	95% CI
Poor sleep quality (yes vs. no)	0.5	(0.3, 1.0)	0.9	(0.3, 2.4)	1.3	(0.8, 2.2)
Other patient-reported measures (per 1-unit change in score for the worse)						
Pain severity score	1.1	(0.9, 1.4)	1.1	(0.9, 1.3)	1.0	(1.0, 1.1)
Pain interference score	1.0	(0.8, 1.3)	1.0	(0.9, 1.2)	1.0	(0.9, 1.1)
Stress score	1.0	(1.0, 1.1)	1.0	(1.0, 1.1)	1.0	(1.0, 1.0)
Social support score	1.0	(1.0, 1.0)	1.0	(1.0, 1.0)	1.0	(1.0, 1.0)
SF-12 physical score	N/I	N/I	N/I	N/I	N/I	N/I
SF-12 mental score	**1.1**	**(1.1, 1.1)**	**1.0**	**(1.0, 1.1)**	**1.0**	**(1.0, 1.0)**
Gene-specific burden scores[9]						
OPRM1 burden score	N/I	N/I	N/I	N/I	N/I	N/I
Cytochrome P450 2D6 burden score	N/I	N/I	N/I	N/I	N/I	N/I
Cytochrome P450 3A4 burden score	N/I	N/I	N/I	N/I	N/I	N/I

Source: FDA-adapted table based on information provided in PMR 3033-1 Final Report on Cross-Sectional Study Results: December 12, 2022, as well as final data submitted by the OPC on June 4, 2024, in "Response to Clarifying Questions for the PMR 3033-1 Cross-Sectional and Prospective Studies, May 3, 2024," Appendix 1, Q5 Table C REV.

Note: For nonreference variables denoted "N/I", the variable was not statistically significantly associated with the outcome at p<0.10 in unadjusted analyses and was therefore not included in the fully adjusted model for that outcome. Statistically significant values (p<0.05) are in **bold**. Some statistically significant ORs have 95% CIs that include 1.0 due to rounding.

[1] Moderate-to-severe DSM-5-OUD was defined as having four or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[2] Any pain-adjusted DSM-5-OUD was defined as having two or more pain-adjusted DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[3] Any DSM-5-OUD was defined as having two or more standard DSM-5 criteria for OUD related to prescription opioid use *or* two or more DSM-5 criteria related to heroin use, as measured by the PRISM-5-Op.

[4] Fully adjusted models were adjusted for all risk factors for which ORs and 95% CIs are shown in the corresponding column of this table, representing risk factors that were statistically significantly associated with a given outcome in unadjusted analyses (p<0.01), plus age, sex, race, and ethnicity.

[5] Race and ethnicity are from self-reported questionnaire data. Five patients were missing self-reported race.

[6] Predominant opioid moiety and predominant OA formulation were based on longest cumulative days' supply in the past 12 months or most prescriptions if there was a tie.

[7] The "other" category for active pharmaceutical ingredient combines all ingredients where there were ≤2 events for a given outcome. In this analysis, this included oxymorphone, hydromorphone, tramadol, buprenorphine, codeine, tapentadol, meperidine, butorphanol, and others not listed here.

[8] Medication use defined as two or more dispensings in the prior year, except for buprenorphine and naloxone where use defined as one or more dispensing or one or more procedure code.

[9] Genetic analyses include the subset of eligible patients who provided evaluable genetic samples: 822 for OPRM1, 829 for cytochrome P450 2D6, and 821 for cytochrome P450 3A4.

Abbreviations: ACE, adverse childhood experience; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EHR, electronic health records; ER/LA, extended-release/long-acting; GAD, generalized anxiety disorder; IR/SA, immediate-release/short-acting; MDD, major depressive disorder; N/E, not estimated; OA, opioid analgesic; OPC: Opioid PMR Consortium; OR, odds ratio; OUD, opioid use disorder; POMAQ, Prescription Opioid Misuse and Abuse Questionnaire; PRISM-5-Op, Psychiatric Research Interview for Substance and Mental Disorders, DSM-5, Opioid Version; PTSD, posttraumatic stress disorder; MME, morphine milligram equivalent; SF-12, 12-Item Short Form Health Survey; SUD, substance use disorder

6.7 PMR 3033-2 Study Tables

Table 38. ICD-9 and ICD-10 Codes Used in the Initial (PMR 3033-6) and Updated (PMR 3033-2) OOD Algorithms

Description	ICD-9[1] Code	ICD-10 Code[2]
Poisoning by opium (alkaloids) unspecified	965	
Poisoning by heroin	965.01	
Poisoning by methadone	965.02	
Poisoning by other opiates and related narcotics	965.09	
Accidental poisoning by heroin	E850.0	
Accidental poisoning by methadone	E850.1	
Accidental poisoning by other opiates and related narcotics	E850.2	
COD: Poisoning by opiates and related narcotics[3]	965.0	
Poisoning by opium		T40.0X
Poisoning by heroin		T40.1X
Poisoning by other opioids		T40.2X
Poisoning by methadone		T40.3X
Poisoning by other synthetic narcotic		T40.4X
Unspecified narcotics[4]		T40.60
Other narcotics[4]		T40.89
COD: accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		X42
COD: intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		X62
COD: undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		Y1

Source: FDA-generated table adapted from data provided in Table 5, Amended Final Report for 3033-6, Version 5, February 28, 2019; and Supplementary Material, Whiscon Summary Report, June 21, 2021.

[1] ICD-9 codes used until October 2015.

[2] Prior to October 2015, ICD-10 codes were used for mortality only. Starting in October 2015, ICD-10 codes used for both clinical and COD coding.

[3] Used in the PMR 3033-6 algorithm only.

[4] Used in the PMR 3033-2 algorithm only.

Abbreviations: COD, cause of death; FDA, Food and Drug Administration; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement

ICD-9 Diagnosis and ICD-10 Cause-of-Death Codes Used to Sample the High-Risk-of-OOD Population in PMR 3033-6

In PMR 3033-6, the high risk of OOD sample was used for development and validation of the opioids overdose identification algorithms. The sample consists of two subsamples: (1) a sample of suspected OOD events and (2) a sample of events from at-risk individuals. The first sample consists of patients with suspected opioid overdose events that were screened and selected based on ICD-9 diagnosis and ICD-10 cause-of-death codes. The ICD-9 and ICD-10 codes to select the suspected OOD events are listed in Appendix Table 39. Because the event was defined by a patient and a point in time, individuals were allowed to contribute more than one event to the sample. The second sample consists of events from individuals at risk of OOD (but no indication of suspected overdoses) defined by ICD-9 codes for specific clinical characteristics associated with medical history and opioid use (Appendix Table 40). The final sample was drawn using stratified random sampling by ER/LA opioids status, with half of the sample having a <30-day supply of ER/LA opioids and half having a ≥30-day supply of ER/LA opioids.

Table 39. ICD-9 Diagnosis and ICD-10 Cause-of-Death Codes Used to Sample Suspected OOD in PMR 3033-6

Description	ICD-9 Diagnosis Code	ICD-10 Cause-of-Death Code
Poisoning by opium (alkaloids) unspecified	965.00	
Poisoning by heroin	965.01	
Poisoning by methadone	965.02	
Poisoning by other opiates and related narcotics	965.09	
Accidental poisoning by heroin	E850.0	
Accidental poisoning by methadone	E850.1	
Accidental poisoning by other opiates and related narcotics	E850.2	
COD: Poisoning by opiates and related narcotics	9650	
COD: Poisoning by opium		T40.0
COD: Poisoning by heroin		T40.1
COD: Poisoning by other opioids		T40.2
COD: Poisoning by methadone		T40.3
COD: Poisoning by other synthetic narcotic		T40.4
COD: Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		X42
COD: Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		X62
COD: Undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified		Y12
Adverse effects of heroin	E935.0	
Adverse effects of methadone	E935.1	
Adverse effects of other opioids and related narcotics	E935.2	
COD: Adverse effects of opioids and related analgesics		Y45.0

Source: Appendix B, PMR 3033-6 Final Study Report.

Abbreviations: COD, cause of death; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement

Table 40. ICD-9 Diagnostic Codes Used to Identify the Sample at Risk for OOD in PMR 3033-6

ICD-9 diagnostic code	Code description	Category
293.0	Delirium due to conditions classified elsewhere	Drug Use Associated
293.1	Subacute delirium	Drug Use Associated
571.40	Chronic hepatitis, unspecified	Drug Use Associated
571.49	Other chronic hepatitis	Drug Use Associated
571.5	Cirrhosis of liver without mention of alcohol	Drug Use Associated
571.8	Other chronic nonalcoholic liver disease	Drug Use Associated
571.9	Unspecified chronic liver disease without mention of alcohol	Drug Use Associated
572.8	Other sequelae of chronic liver disease	Drug Use Associated
573.0	Chronic passive congestion of liver	Drug Use Associated
573.3	Hepatitis, unspecified	Drug Use Associated
577.0	Acute pancreatitis	Drug Use Associated
577.1	Chronic pancreatitis	Drug Use Associated
681.00	Cellulitis and abscess of finger, unspecified	Drug Use Associated
681.10	Cellulitis and abscess of toe, unspecified	Drug Use Associated
681.9	Cellulitis and abscess of unspecified digit	Drug Use Associated
682.0	Cellulitis and abscess of face	Drug Use Associated
682.1	Cellulitis and abscess of neck	Drug Use Associated
682.2	Cellulitis and abscess of trunk	Drug Use Associated
682.3	Cellulitis and abscess of upper arm and forearm	Drug Use Associated
682.4	Cellulitis and abscess of hand, except fingers and thumb	Drug Use Associated
682.5	Cellulitis and abscess of buttock	Drug Use Associated
682.6	Cellulitis and abscess of leg, except foot	Drug Use Associated
682.7	Cellulitis and abscess of foot, except toes	Drug Use Associated
682.8	Cellulitis and abscess of other specified sites	Drug Use Associated
682.9	Cellulitis and abscess of unspecified sites	Drug Use Associated

ICD-9 diagnostic code	Code description	Category
V15.81	Personal history of noncompliance with medical treatment, presenting hazards to health	Drug Use Associated
293.84	Anxiety disorder in conditions classified elsewhere	Mental Health Related
294.9	Unspecified persistent mental disorders due to conditions classified elsewhere	Mental Health Related
295.00	Simple type schizophrenia, unspecified	Mental Health Related
295.20	Catatonic type schizophrenia, unspecified	Mental Health Related
295.30	Paranoid type schizophrenia, unspecified	Mental Health Related
295.32	Paranoid type schizophrenia, chronic	Mental Health Related
295.60	Schizophrenic disorders, residual type, unspecified	Mental Health Related
295.62	Schizophrenic disorders, residual type, chronic	Mental Health Related
295.70	Schizoaffective disorder, unspecified	Mental Health Related
295.74	Schizoaffective disorder, chronic with acute exacerbation	Mental Health Related
295.75	Schizoaffective disorder, in remission	Mental Health Related
295.80	Other specified types of schizophrenia, unspecified	Mental Health Related
295.90	Unspecified schizophrenia, unspecified	Mental Health Related
296.00	Bipolar I disorder, single manic episode, unspecified	Mental Health Related
296.03	Bipolar I disorder, single manic episode, severe, without mention of psychotic behavior	Mental Health Related
296.04	Bipolar I disorder, single manic episode, severe, specified as with psychotic behavior	Mental Health Related
296.10	Manic affective disorder, recurrent episode, unspecified	Mental Health Related
296.20	Major depressive affective disorder, single episode, unspecified	Mental Health Related
296.21	Major depressive affective disorder, single episode, mild	Mental Health Related
296.22	Major depressive affective disorder, single episode, moderate	Mental Health Related

ICD-9 diagnostic code	Code description	Category
296.23	Major depressive affective disorder, single episode, severe, without mention of psychotic behavior	Mental Health Related
296.24	Major depressive affective disorder, single episode, severe, specified as with psychotic behavior	Mental Health Related
296.25	Major depressive affective disorder, single episode, in partial or unspecified remission	Mental Health Related
296.26	Major depressive affective disorder, single episode, in full remission	Mental Health Related
296.30	Major depressive affective disorder, recurrent episode, unspecified	Mental Health Related
296.31	Major depressive affective disorder, recurrent episode, mild	Mental Health Related
296.32	Major depressive affective disorder, recurrent episode, moderate	Mental Health Related
296.33	Major depressive affective disorder, recurrent episode, severe, without mention of psychotic behavior	Mental Health Related
296.34	Major depressive affective disorder, recurrent episode, severe, specified as with psychotic behavior	Mental Health Related
296.35	Major depressive affective disorder, recurrent episode, in partial or unspecified remission	Mental Health Related
296.36	Major depressive affective disorder, recurrent episode, in full remission	Mental Health Related
296.40	Bipolar I disorder, most recent episode (or current) manic, unspecified	Mental Health Related
296.43	Bipolar I disorder, most recent episode (or current) manic, severe, without mention of psychotic behavior	Mental Health Related
296.44	Bipolar I disorder, most recent episode (or current) manic, severe, specified as with psychotic behavior	Mental Health Related
296.46	Bipolar I disorder, most recent episode (or current) manic, in full remission	Mental Health Related

ICD-9 diagnostic code	Code description	Category
296.50	Bipolar I disorder, most recent episode (or current) depressed, unspecified	Mental Health Related
296.51	Bipolar I disorder, most recent episode (or current) depressed, mild	Mental Health Related
296.52	Bipolar I disorder, most recent episode (or current) depressed, moderate	Mental Health Related
296.53	Bipolar I disorder, most recent episode (or current) depressed, severe, without mention of psychotic behavior	Mental Health Related
296.54	Bipolar I disorder, most recent episode (or current) depressed, severe, specified as with psychotic behavior	Mental Health Related
296.55	Bipolar I disorder, most recent episode (or current) depressed, in partial or unspecified remission	Mental Health Related
296.56	Bipolar I disorder, most recent episode (or current) depressed, in full remission	Mental Health Related
296.60	Bipolar I disorder, most recent episode (or current) mixed, unspecified	Mental Health Related
296.62	Bipolar I disorder, most recent episode (or current) mixed, moderate	Mental Health Related
296.63	Bipolar I disorder, most recent episode (or current) mixed, severe, without mention of psychotic behavior	Mental Health Related
296.64	Bipolar I disorder, most recent episode (or current) mixed, severe, specified as with psychotic behavior	Mental Health Related
296.65	Bipolar I disorder, most recent episode (or current) mixed, in partial or unspecified remission	Mental Health Related
296.7	Bipolar I disorder, most recent episode (or current) unspecified	Mental Health Related
296.80	Bipolar disorder, unspecified	Mental Health Related
296.89	Other bipolar disorders	Mental Health Related
300.00	Anxiety state, unspecified	Mental Health Related
300.01	Panic disorder without agoraphobia	Mental Health Related

ICD-9 diagnostic code	Code description	Category
300.02	Generalized anxiety disorder	Mental Health Related
300.09	Other anxiety states	Mental Health Related
300.4	Dysthymic disorder	Mental Health Related
300.81	Somatization disorder	Mental Health Related
301.50	Histrionic personality disorder, unspecified	Mental Health Related
301.59	Other histrionic personality disorder	Mental Health Related
301.6	Dependent personality disorder	Mental Health Related
301.7	Antisocial personality disorder	Mental Health Related
301.81	Narcissistic personality disorder	Mental Health Related
301.82	Avoidant personality disorder	Mental Health Related
301.83	Borderline personality disorder	Mental Health Related
301.89	Other personality disorders	Mental Health Related
301.9	Unspecified personality disorder	Mental Health Related
308.0	Predominant disturbance of emotions	Mental Health Related
308.3	Other acute reactions to stress	Mental Health Related
308.4	Mixed disorders as reaction to stress	Mental Health Related
308.9	Unspecified acute reaction to stress	Mental Health Related
309.0	Adjustment disorder with depressed mood	Mental Health Related
309.1	Prolonged depressive reaction	Mental Health Related
309.24	Adjustment disorder with anxiety	Mental Health Related
309.28	Adjustment disorder with mixed anxiety and depressed mood	Mental Health Related
309.3	Adjustment disorder with disturbance of conduct	Mental Health Related
309.4	Adjustment disorder with mixed disturbance of emotions and conduct	Mental Health Related
309.81	Posttraumatic stress disorder	Mental Health Related
309.82	Adjustment reaction with physical symptoms	Mental Health Related
309.89	Other specified adjustment reactions	Mental Health Related
309.9	Unspecified adjustment reaction	Mental Health Related
291.0	Alcohol withdrawal delirium	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
291.1	Alcohol-induced persisting amnestic disorder	Substance Abuse Related
291.2	Alcohol-induced persisting dementia	Substance Abuse Related
291.3	Alcohol-induced psychotic disorder with hallucinations	Substance Abuse Related
291.4	Idiosyncratic alcohol intoxication	Substance Abuse Related
291.81	Alcohol withdrawal	Substance Abuse Related
291.89	Other alcohol-induced mental disorders	Substance Abuse Related
291.9	Unspecified alcohol-induced mental disorders	Substance Abuse Related
292.0	Drug withdrawal	Substance Abuse Related
292.11	Drug-induced psychotic disorder with delusions	Substance Abuse Related
292.12	Drug-induced psychotic disorder with hallucinations	Substance Abuse Related
292.2	Pathological drug intoxication	Substance Abuse Related
292.81	Drug-induced delirium	Substance Abuse Related
292.84	Drug-induced mood disorder	Substance Abuse Related
292.85	Drug induced sleep disorders	Substance Abuse Related
292.89	Other specified drug-induced mental disorders	Substance Abuse Related
292.9	Unspecified drug-induced mental disorder	Substance Abuse Related
303.00	Acute alcoholic intoxication in alcoholism, unspecified	Substance Abuse Related
303.01	Acute alcoholic intoxication in alcoholism, continuous	Substance Abuse Related
303.02	Acute alcoholic intoxication in alcoholism, episodic	Substance Abuse Related
303.03	Acute alcoholic intoxication in alcoholism, in remission	Substance Abuse Related
303.90	Other and unspecified alcohol dependence, unspecified	Substance Abuse Related
303.91	Other and unspecified alcohol dependence, continuous	Substance Abuse Related
303.92	Other and unspecified alcohol dependence, episodic	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
303.93	Other and unspecified alcohol dependence, in remission	Substance Abuse Related
304.00	Opioid type dependence, unspecified	Substance Abuse Related
304.01	Opioid type dependence, continuous	Substance Abuse Related
304.02	Opioid type dependence, episodic	Substance Abuse Related
304.03	Opioid type dependence, in remission	Substance Abuse Related
304.10	Sedative, hypnotic or anxiolytic dependence, unspecified	Substance Abuse Related
304.11	Sedative, hypnotic or anxiolytic dependence, continuous	Substance Abuse Related
304.13	Sedative, hypnotic or anxiolytic dependence, in remission	Substance Abuse Related
304.20	Cocaine dependence, unspecified	Substance Abuse Related
304.21	Cocaine dependence, continuous	Substance Abuse Related
304.22	Cocaine dependence, episodic	Substance Abuse Related
304.23	Cocaine dependence, in remission	Substance Abuse Related
304.30	Cannabis dependence, unspecified	Substance Abuse Related
304.31	Cannabis dependence, continuous	Substance Abuse Related
304.32	Cannabis dependence, episodic	Substance Abuse Related
304.33	Cannabis dependence, in remission	Substance Abuse Related
304.40	Amphetamine and other psychostimulant dependence, unspecified	Substance Abuse Related
304.41	Amphetamine and other psychostimulant dependence, continuous	Substance Abuse Related
304.42	Amphetamine and other psychostimulant dependence, episodic	Substance Abuse Related
304.43	Amphetamine and other psychostimulant dependence, in remission	Substance Abuse Related
304.50	Hallucinogen dependence, unspecified	Substance Abuse Related
304.53	Hallucinogen dependence, in remission	Substance Abuse Related
304.60	Other specified drug dependence, unspecified	Substance Abuse Related
304.63	Other specified drug dependence, in remission	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
304.70	Combinations of opioid type drug with any other drug dependence, unspecified	Substance Abuse Related
304.71	Combinations of opioid type drug with any other drug dependence, continuous	Substance Abuse Related
304.72	Combinations of opioid type drug with any other drug dependence, episodic	Substance Abuse Related
304.73	Combinations of opioid type drug with any other drug dependence, in remission	Substance Abuse Related
304.80	Combinations of drug dependence excluding opioid type drug, unspecified	Substance Abuse Related
304.81	Combinations of drug dependence excluding opioid type drug, continuous	Substance Abuse Related
304.82	Combinations of drug dependence excluding opioid type drug, episodic	Substance Abuse Related
304.83	Combinations of drug dependence excluding opioid type drug, in remission	Substance Abuse Related
304.90	Unspecified drug dependence, unspecified	Substance Abuse Related
304.91	Unspecified drug dependence, continuous	Substance Abuse Related
304.93	Unspecified drug dependence, in remission	Substance Abuse Related
305.00	Alcohol abuse, unspecified	Substance Abuse Related
305.01	Alcohol abuse, continuous	Substance Abuse Related
305.02	Alcohol abuse, episodic	Substance Abuse Related
305.03	Alcohol abuse, in remission	Substance Abuse Related
305.1	Tobacco use disorder	Substance Abuse Related
305.20	Cannabis abuse, unspecified	Substance Abuse Related
305.21	Cannabis abuse, continuous	Substance Abuse Related
305.22	Cannabis abuse, episodic	Substance Abuse Related
305.23	Cannabis abuse, in remission	Substance Abuse Related
305.30	Hallucinogen abuse, unspecified	Substance Abuse Related
305.31	Hallucinogen abuse, continuous	Substance Abuse Related
305.40	Sedative, hypnotic or anxiolytic abuse, unspecified	Substance Abuse Related
305.41	Sedative, hypnotic or anxiolytic abuse, continuous	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
305.42	Sedative, hypnotic or anxiolytic abuse, episodic	Substance Abuse Related
305.43	Sedative, hypnotic or anxiolytic abuse, in remission	Substance Abuse Related
305.50	Opioid abuse, unspecified	Substance Abuse Related
305.51	Opioid abuse, continuous	Substance Abuse Related
305.52	Opioid abuse, episodic	Substance Abuse Related
305.53	Opioid abuse, in remission	Substance Abuse Related
305.60	Cocaine abuse, unspecified	Substance Abuse Related
305.61	Cocaine abuse, continuous	Substance Abuse Related
305.63	Cocaine abuse, in remission	Substance Abuse Related
305.70	Amphetamine or related acting sympathomimetic abuse, unspecified	Substance Abuse Related
305.71	Amphetamine or related acting sympathomimetic abuse, continuous	Substance Abuse Related
305.72	Amphetamine or related acting sympathomimetic abuse, episodic	Substance Abuse Related
305.73	Amphetamine or related acting sympathomimetic abuse, in remission	Substance Abuse Related
305.80	Antidepressant type abuse, unspecified	Substance Abuse Related
305.90	Other, mixed, or unspecified drug abuse, unspecified	Substance Abuse Related
305.91	Other, mixed, or unspecified drug abuse, continuous	Substance Abuse Related
305.92	Other, mixed, or unspecified drug abuse, episodic	Substance Abuse Related
305.93	Other, mixed, or unspecified drug abuse, in remission	Substance Abuse Related
571.1	Acute alcoholic hepatitis	Substance Abuse Related
571.2	Alcoholic cirrhosis of liver	Substance Abuse Related
571.3	Alcoholic liver damage, unspecified	Substance Abuse Related
967.0	Poisoning by barbiturates	Substance Abuse Related
967.6	Poisoning by mixed sedatives, not elsewhere classified	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
967.8	Poisoning by other sedatives and hypnotics	Substance Abuse Related
967.9	Poisoning by unspecified sedative or hypnotic	Substance Abuse Related
968.0	Poisoning by central nervous system muscle-tone depressants	Substance Abuse Related
968.4	Poisoning by other and unspecified general anesthetics	Substance Abuse Related
968.9	Poisoning by other and unspecified local anesthetics	Substance Abuse Related
969.00	Poisoning by antidepressant, unspecified	Substance Abuse Related
969.02	Poisoning by selective serotonin and norepinephrine reuptake inhibitors	Substance Abuse Related
969.03	Poisoning by selective serotonin reuptake inhibitors	Substance Abuse Related
969.05	Poisoning by tricyclic antidepressants	Substance Abuse Related
969.09	Poisoning by other antidepressants	Substance Abuse Related
969.1	Poisoning by phenothiazine-based tranquilizers	Substance Abuse Related
969.2	Poisoning by butyrophenone-based tranquilizers	Substance Abuse Related
969.3	Poisoning by other antipsychotics, neuroleptics, and major tranquilizers	Substance Abuse Related
969.4	Poisoning by benzodiazepine-based tranquilizers	Substance Abuse Related
969.5	Poisoning by other tranquilizers	Substance Abuse Related
969.6	Poisoning by psychodysleptics (hallucinogens)	Substance Abuse Related
969.70	Poisoning by psychostimulant, unspecified	Substance Abuse Related
969.72	Poisoning by amphetamines	Substance Abuse Related
969.73	Poisoning by methylphenidate	Substance Abuse Related
969.79	Poisoning by other psychostimulants	Substance Abuse Related
969.8	Poisoning by other specified psychotropic agents	Substance Abuse Related
969.9	Poisoning by unspecified psychotropic agent	Substance Abuse Related
970.1	Poisoning by opiate antagonists	Substance Abuse Related
970.81	Poisoning by cocaine	Substance Abuse Related
970.9	Poisoning by unspecified central nervous system	Substance Abuse Related

ICD-9 diagnostic code	Code description	Category
	stimulant	
980.0	Toxic effect of ethyl alcohol	Substance Abuse Related
V02.62	Hepatitis C carrier	Substance Abuse Related
V11.0	Personal history of schizophrenia	Substance Abuse Related
V11.1	Personal history of affective disorders	Substance Abuse Related
V11.3	Personal history of alcoholism	Substance Abuse Related
V11.8	Personal history of other mental disorders	Substance Abuse Related
V11.9	Personal history of unspecified mental disorder	Substance Abuse Related
V65.42	Counseling on substance use and abuse	Substance Abuse Related

Source: Appendix C, PMR 3033-6 Final Study Report.

Abbreviation: ICD-9, International Classification of Diseases, Ninth Revision; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement

Table 41. Validation Results for the Updated OOD Algorithm in the PMR 3033-2 Study

Number of Reviews	Classification of OOD on Review	n	PPV (95% CI)
428[1] (algorithm-identified OOD)	Definite	343	80.1% (76.1%, 83.6%)
	Definite or suggestive	373	87.1% (83.6%, 90.0%)

Source: PMR 3033-2 Site Final Reports, Table 21.

PPV was N ÷ number of reviews; prespecified success criterion was PPV ≥80%; 95% CIs calculated per Wilson (1927) and Agresti and Coull (1998).

[1] Two-hundred records were obtained from HealthCore, and 100 records each from VUMC and KPNW. Medical records from Optum were not available, but comparisons with HealthCore indicated the two data resources were similar.

Abbreviations: CI, confidence interval; KPNW, Kaiser Permanente Northwest; N, number of OOD confirmed by chart audit; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; PPV, positive predictive value; VUMC, Vanderbilt University Medical Center

Table 42. Validation Results for the Updated Intentionality Algorithm in the PMR 3033-2 Study

Variable	Chart Audit Result – Was There Intentional Self-Harm?			
ICD-10 Classification	Clear Self-Harm (n)	Possible Self-Harm (n)	No Self-Harm (n)	Unable to Say (n)
Intentional OOD	26	10	9	0
Not intentional OOD	16	19	244	19

	Chart Audit Result – Was There Intentional Self-Harm?	
Parameter	Clear % (95% CI)	Clear or Possible % (95% CI)
Sensitivity	61.9% (46.8%, 75.0%)	50.7% (36.3%, 62.0%)
Specificity	93.7% (90.4%, 95.9%)	96.7% (93.8%, 98.2%)
PPV	57.8% (43.3%, 71.0%)	80.0% (66.2%, 89.1%)
NPV	94.6% (91.5%, 96.7%)	88.3% (84.1%, 91.4%)

Source: PMR 3033-2 Table 7-22, Whiscon Summary Report.

95% CIs were calculated as per Wilson (1927) and Agresti and Coull (1998).

Abbreviations: CI, confidence interval; ICD-10, International Classification of Diseases, Tenth Revision; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; PPV, positive predictive value; NPV, negative predictive value

Table 43. Five-Year Cumulative Incidence and Incidence Rates for All Sites, PMR 3033-2 Study

Months From Cohort Entry[1]	Cumulative Incidence, % (95% CI)				Incidence Rate, n per 1,000 PY (95% CI)			
	VUMC	KPNW	HealthCore	Optum	VUMC	KPNW	HealthCore	Optum
0	0	0	0	0	0	0	0	0
3	0.26 (0.22, 0.30)	0.11 (0.06, 0.19)	0.11 (0.09, 0.13)	0.10 (0.07, 0.12)	10.37 (8.86, 11.88)	4.44 (2.58, 7.65)	4.35 (3.47, 5.27)	3.94 (2.94, 5.18)
6	0.48 (0.43, 0.54)	0.21 (0.14, 0.31)	0.19 (0.16, 0.22)	0.17 (0.14, 0.21)	9.65 (8.61, 10.7)	4.20 (2.81, 6.26)	3.82 (3.22, 4.45)	3.51 (2.8, 4.35)
9	0.67 (0.61, 0.73)	0.32 (0.23, 0.45)	0.28 (0.24, 0.32)	0.28 (0.23, 0.33)	8.99 (8.14, 9.83)	4.32 (3.12, 5.99)	3.73 (3.23, 4.25)	3.74 (3.11, 4.46)
12	0.85 (0.78, 0.92)	0.40 (0.30, 0.54)	0.36 (0.31, 0.41)	0.37 (0.31, 0.43)	8.63 (7.9, 9.35)	4.07 (3.03, 5.47)	3.65 (3.20, 4.10)	3.75 (3.18, 4.39)
24	1.61 (1.51, 1.72)	0.68 (0.53, 0.86)	0.67 (0.60, 0.74)	0.67 (0.57, 0.76)	8.25 (7.72, 8.79)	3.47 (2.74, 4.41)	3.43 (3.10, 3.78)	3.49 (3.04, 3.99)
36	2.46 (2.32, 2.60)	1.03 (0.83, 1.26)	1.01 (0.91, 1.11)	0.96 (0.82, 1.09)	8.32 (7.86, 8.79)	3.49 (2.85, 4.28)	3.43 (3.13, 3.73)	3.4 (2.99, 3.85)
48	3.27 (3.10, 3.45)	1.28 (1.06, 1.56)	1.27 (1.15, 1.39)	1.24 (1.05, 1.43)	8.32 (7.89, 8.75)	3.34 (2.76, 4.03)	3.33 (3.06, 3.61)	3.37 (2.98, 3.79)
60	4.05 (3.85, 4.27)	1.43 (1.19, 1.73)	1.49 (1.35, 1.63)	1.54 (1.27, 1.80)	8.31 (7.91, 8.71)	3.11 (2.59, 3.74)	3.25 (2.99, 3.51)	3.34 (2.96, 3.76)

Source: FDA-generated table adapted from data provided in Site Table 8.2, Whiscon Summary Report.

[1] The cumulative incidence at month X is the complement of most recent Kaplan-Meier OOD-free survival preceding month X. The number of events is the sum of events through month X. The number under observation is the number of persons not censored through month X.

Abbreviations: CI, confidence interval; FDA, Food and Drug Administration; KPNW, Kaiser Permanente Northwest; N, number at end of interval; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; PY, person-years; VUMC, Vanderbilt University Medical Center

Table 44. Estimated Range of the Underlying True Crude Incidence for Different Combinations of Sensitivity and PPV of the Updated OOD Algorithm in PMR 3033-2

	Sensitivity							
PPV	**60%**	**70%**	**80%**	**90%**	**95%**	**99%**	**99.9%**	**100%**
60%	1.38%	1.18%	1.03%	0.92%	0.87%	0.83%	0.83%	0.83%
70%	1.61%	1.38%	1.21%	1.07%	1.02%	0.97%	0.97%	0.96%
75%	1.72%	1.48%	**1.29%**	**1.15%**	**1.09%**	**1.04%**	1.03%	1.03%
80%	1.84%	1.57%	**1.38%**	**1.22%**	**1.16%**	**1.11%**	1.10%	1.10%
85%	1.95%	1.67%	**1.46%**	**1.30%**	**1.23%**	**1.18%**	1.17%	1.17%
90%	2.07%	1.77%	**1.55%**	**1.38%**	**1.31%**	**1.25%**	1.24%	1.24%
95%	2.18%	1.87%	1.64%	1.45%	1.38%	1.32%	1.31%	1.31%
99%	2.27%	1.95%	1.70%	1.52%	1.44%	1.38%	1.37%	1.36%
99.9%	2.29%	1.97%	1.72%	1.53%	1.45%	1.39%	1.38%	1.38%
100%	2.30%	1.97%	1.72%	1.53%	1.45%	1.39%	1.38%	1.38%

Source: FDA-generated table.

Abbreviations: FDA, Food and Drug Administration; OOD, opioid-involved overdose or opioid overdose-related death; PMR, postmarketing requirement; PPV, positive predictive value

As only the PPV was examined in the revalidation study, FDA conducted additional analyses to determine to what extent the updated OOD algorithm in PMR 3033-2 might over- or underestimate the OOD risk. As a reminder, crude incidence was defined as the total number of OOD events divided by the total number of patients available at baseline. The (true) crude incidence[55] was estimated across different levels of sensitivity, under plausible ranges of PPV estimates using PMR 3033-2 results as a basis. See the 95% CIs of PPVs in Appendix Table 41. Based on these analyses, this table shows that the true crude incidence of OOD could be between 1.04% and 1.55% (**bolded** in the table), compared to the observed crude incidence, 1.38%,[56] in PMR 3033-2. These findings lend further support to the acceptability of the overall OOD algorithm performance.

[55] Estimated crude incidence = (observed crude incidence × PPV) ÷ sensitivity

[56] Can be obtained from the numbers reported in Table 18. Total number of OOD events ÷ total number of patients × 100 = 3034 ÷ 220249 × 100 = 1.37(%).

6.8 Review of Genetics Analysis in the ER/LA PMR 3033-1 Final Study Reports

CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF TRANSLATIONAL SCIENCES

OFFICE OF CLINICAL PHARMACOLOGY

DIVISION OF TRANSLATIONAL AND PRECISION MEDICINE (DTPM)

6.8.1 DTPM Executive Summary

Purpose

The Food and Drug Administration (FDA) requires companies that are New Drug Application (NDA) holders of extended-release/long-acting (ER/LA) opioids to conduct a Post Marketing Requirement (PMR) in order to do the following: A) estimate the incidence of misuse, abuse, and addiction, and B) evaluate and quantify other risk factors for misuse, abuse and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics (PMR 3033-1). ERLA PMR 3033-1 is a post marketing required study for ERLA opioid analgesic applicants to estimate the incidence of misuse, abuse, and opioid use disorder (OUD) and evaluate and quantify other risk factors for misuse, abuse, and OUD among patients with long term use of opioids. PMR 3033-1 included a prospective study to quantify incidence of and risk factors for misuse, abuse, and OUD among patients initiating ERLA opioids, and among patients initiating long term opioid therapy, and a cross-sectional study to estimate the prevalence of misuse, abuse, and OUD among patients with greater than one year use of prescription opioids. These studies contain patient-reported data, as well as a subset of patients who provided biologic specimens for DNA sequencing.

Assessment Summary

The study included a sample of patients who were 18-79 years old at cohort entry, enrolled in a health plan (HCSRN sites) or regularly receiving care in the health system (VA and PBRNs) for at least 12 months, able and willing to provide informed consent, able to complete study measures in English and who initiated ER/LA opioid therapy or Long-term opioid therapy. The 3033-1 cross-sectional report and prospective study included information on single nucleotide polymorphisms (SNPs) obtained from sequencing in a subset of patients who provided a saliva sample. Information was obtained for the following genes: *OPRM1* (rs1799971, rs9479757, rs3778150), *CYP3A4* (rs4646440, rs2242480, rs4646438, rs4987161), and *CYP2D6* (rs5758550, rs133333). The study looked at the outcomes of interest (misuse, abuse, and OUD) by minor allele status (0, 1, 2, or missing), as well as by gene-specific burden score based on SNPs. No association between the outcomes of interest and individual's SNPs of interest. None of the three gene-specific burden scores showed significant associations with the outcomes in the unadjusted model, and therefore, models with the three genes included simultaneously were not pursued.

Recommendations

The variants rs5758550 and rs133333 are considered CYP2D6 downstream enhancers. The same two SNPs are in complete Linkage Disequilibrium (LD). Noteworthy, these SNPs could increase expression of CYP2D6, but they are also in high LD with rs16947 which is associated with reduced CYP2D6 expression. The anticipated overall effect is a normal activity of CYP2D6. Reporting results of the other SNPs without rs16947 could be potentially misleading and may not present an accurate depiction of the functional

consequences of genetic polymorphisms in CYP2D6 and might limit the interpretation of the existing analyses.

6.8.2 DTPM Background

Submission Description

The Food and Drug Administration (FDA) requires companies that are New Drug Application (NDA) holders of extended-release/long-acting (ER/LA) opioids to conduct a Post Marketing Requirement (PMR) in order to do the following: A) estimate the incidence of misuse, abuse, and addiction, and B) evaluate and quantify other risk factors for misuse, abuse and addiction associated with long-term use of opioid analgesics for management of chronic pain among patients prescribed ER/LA opioid analgesics.

Relevant Regulatory History

ERLA PMR 3033-1 is a post marketing required study for ERLA opioid analgesic applicants to estimate the incidence of misuse, abuse, and opioid use disorder (OUD) and evaluate and quantify other risk factors for misuse, abuse, and OUD among patients with long term use of opioids.

Specific Issues/Questions

Quantifying the risks of each of the primary and secondary outcomes by potential risk factors (determined *a priori* by FDA and subject matter experts) including but not limited to Opioid receptor mu 1 (OPRM1) and Cytochrome P450 (CYP3A4 and CYP2D6) enzyme status.

6.8.3 DTPM Assessment

Materials Reviewed

Data Sources

Participants were recruited from seven Health Care System Research Network (HCSRN) sites, one U.S. Department of Veterans Affairs (VA) site, and two sites participating in a Primary Care Practice-Based Research Network (PBRN).

Analysis Methods

The study has contracted the genotyping assays to Sampled SMART Labs, Piscataway, NJ, (formerly known as Rutgers University Cell and DNA Repository [RUCDR]), using TaqMan AD assay which is a multiplexed end-point assay that detects variants of a single nucleic acid sequence in the three specified genes. Gene burden scores were estimated and fitted into multivariate analysis models to ascertain the genetic association with the primary outcomes. Overall and stratified unadjusted cumulative incidence (and incidence weighted to the demographics of the targeted population) was calculated for each of the primary and secondary outcomes. Within-site correlation was accounted for using the general estimating equations (GEE) method.

Biomarker/Product Description

The sponsor investigated three SNPS (rs1799971, rs9479757, and rs3778150) in the *OPRM1* gene. Briefly, *OPRM1* gene encodes the mu receptor which is the most common therapeutic target for opioids. In addition, the sponsor investigated two SNPS (rs5758550 and rs133333) and four SNPs (rs4646440, rs2242480, rs4646438, and rs4987161) in *CYP2D6* and *CYP3A4*, respectively. Briefly, both CYP2D6 and CYP3A4 are major phase I drug-metabolizing enzymes and play a significant role in the metabolism a

great proportion of opioids. Overall, CYP2D6 and CYP3A4 are responsible for the metabolism of approximately 25% and 50% of the drugs on the market, respectively.

Evidence Analysis & Considerations

- Considering the results presented regarding genetic association in the initial report and the additional IR, the reviewer would like to provide following assessment. The reviewer agrees that the involvement of OPRM1, CY2D6, and CYP3A4 is unquestionable in the response to and metabolism of orally administered opioid drugs. However, the interrogated SNPs within the same genes remain very limited to capture the effect of genetic variabilities on opioid treatment outcomes. Additionally, the rationale for selecting SNPs lacks robustness, especially the SNPs within the *CYP2D6* gene. With the potential of gene duplication/deletion in *CYP2D6*, the authors only genotyped for two SNPs that appear to be in complete in Linkage Disequilibrium. Indeed, according to the limited evidence of the effect of rs5758550 on *CYP2D6* expression, the Association of the Molecular Pathology (AMP) Pharmacogenetics Working Group does not recommend the addition of the same SNP to the testing panel (Pratt et al. 2021). Furthermore, the rs13333 SNP is in complete Linkage Disequilibrium with rs5758550 (the presence of one SNP can predict the presence of the other SNP). This simply increases type 1 error while missing out on another allele that could have a true effect on the response to opioid therapy.
- The effect of the SNP rs2242480 remains uncertain, regarding its impact on CYP3A4 and CYP3A5 expression levels. An important aspect of choosing a SNP is allele frequency within the population. The SNPs rs4646438 and rs4987161 are considered rare variants and are too rare to be included in the tier 1 or 2 recommendations for routine clinical testing by the AMP Pharmacogenetic Working Group.
- Though it is the most widely used therapeutic target for opioid, targeting only the mu receptor gene for analysis may shift the overall effect towards the null. For example, butorphanol is a kappa receptor agonist and partial mu receptor agonist. Regarding opioid efficacy, other genes that have been also implicated in the response to opioid therapy such as COMT. Collectively, the reviewer believes that the lack of a systematic approach to choosing the genes or SNPs of interest confounds the overall interpretation on the lack of effect of genetic polymorphisms on the primary outcomes of this PMR. In addition to CYP2D6 and CYP3A4, there are other drug-metabolizing enzymes that could influence the response to ER/LA opioids (see appendix). With *CYP3A4* being one of the most conserved drug metabolizing genes, genetic polymorphisms in *CYP3A4* are unlikely to result in a large clinical effect size. On the other hand, genetic polymorphisms in *CYP3A5* are well established and disproportionately prevalent in Blacks and African Americans. *CYP2D6* is highly polymorphic gene, with more than 130 variants reported. Also, the genetic architecture of *CYP2D6* is complex and requires a thorough investigation of the haplotype blocks to ensure accurate genotype to phenotype prediction.
- Overall, the reviewer believes that the study findings support that the interrogated SNPs do not appear to be associated with opioid misuse or abuse. However, a more robust approach is needed for selecting the SNPs, considering existing guidelines and population allele frequencies, in order to provide a more comprehensive assessment of the role of genetic polymorphisms in opioid misuse or abuse.

6.8.4 DTPM Recommendations

Summary

This analysis identified that the most consistently associated factor with increased risk of more than one primary outcome (i.e., misuse, abuse, OUD) in both cohorts was having a nonopioid and non-nicotine substance use disorder in the past year. However, the same analysis did not find an association between selected genetic polymorphisms and the primary outcomes. Though the study fulfilled the PMR from DTPM's perspective, there were significant limitations to the genetic assessment approach of this study and a more thorough assessment would be needed to make conclusive statements about role of genetics in opioid misuse or abuse.

Labeling

Given the genetic association results of this study, no labeling changes are suggested based on this PMR.

6.8.5 DTPM Appendix

Table 45. Major Routes of Metabolism for Several Opioid Medications

Drug	Major CYP450 Metabolizing Enzymes
Oxycodone	Metabolized in liver by CYP3A mediated N-demethylation to noroxycodone is the primary metabolic pathway of oxycodone with a lower contribution from CYP2D6 mediated O-demethylation to oxymorphone
Morphine	Significantly metabolized in liver via UGT2B7 and with CYP3A4 involvement
Hydrocodone	Metabolites: CYP3A4 mediated N-demethylation to norhydrocodone is the primary metabolic pathway; CYP2D6 to hydromorphone (active metabolite with higher binding capacity to mu opioid receptor)
Fentanyl	Metabolism: CYP3A4 (Predominantly)
Methadone	CYP2B6 is the major drug metabolizing enzyme based on drug-drug interaction studies in healthy volunteers
Oxymorphone	Metabolized via UGT2B7, CYP3A and CYP2D6
Hydromorphone	CYP2C9, CYP2D6 and CYP3A
Tramadol	Extensively metabolized via CYP2D6 and CYP3A4, as well as by conjugation of parent and metabolites
Buprenorphine	CYP3A4 and other glucuronidation enzymes
Codeine	Mainly metabolized by CYP2D6
Tapentadol	Metabolized via sulfation
Meperidine	Mainly hydrolysis (CES1), CYP2B6, CYP3A4, CYP2C19, and glucuronidation
Butorphanol	Metabolites: hydroxybutorphanol; N-dealkylation & conjugation of butorphanol & its metabolites.

Source: Reviewer generated from literature and drug labeling.