FDA Executive Summary

Prepared for the
October 20, 2022 meeting of the
Clinical Chemistry and Clinical Toxicology Devices Panel
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AvertD
SOLVD Health

I. Introduction

This document is the FDA Executive Summary for the meeting of the Clinical Chemistry and Clinical Toxicology Devices Advisory Panel meeting on the AvertD test from SOLVD Health. The sponsor has submitted an original De Novo request to obtain marketing authorization for the AvertD test. The AvertD test is a qualitative genotyping test intended to detect 15 genetic polymorphisms in genomic deoxyribonucleic acid (DNA) isolated from buccal samples. Genetic polymorphism information is fed into an algorithm which returns a result for risk of opioid use disorder (OUD) as "Yes", "No", or "N/A" (if no result determined). The test is intended to identify patients who may be at increased genetic risk for OUD prior to the first prescription of oral opioids for acute pain (see Section III. Indication for Use for the full proposed indication for use).

Table 1: List of Single Nucleotide Polymorphisms (SNPs) Detected by the AvertD Test

Allelic Variants	Gene Name	rs Number
5-HTR2A C>T	Serotonin 2A Receptor	rs7997012
COMT G>A	Catechol-O-Methyltransferase	rs4680
DRD1 A>G	Dopamine D1 Receptor	rs4532
DRD2 G>A	Dopamine D2 Receptor	rsl800497
DRD4 T>C	Dopamine D4 Receptor	rs3758653
DAT1 A>G	Dopamine Transporter	rs6347
DBH C>T	Dopamine Beta Hydroxylase	rsl611115
MTHFR C>T	Methylene Tetrahydrofolate Reductase	rsl801133
OPRKI G>T	Kappa Opioid Receptor	rsl051660
GABA C>A	Gamma-Aminobutyric Acid (GABA)	rs211014
OPRM1 A>G	Mu Opioid Receptor	rsl799971
MUOR G>A	Mu Opioid Receptor	rs9479757
GAL T>C	Galanin	rs948854
DOR G>A	Delta Opioid Receptor	rs2236861
ABCB1 C>T	ATP Binding Cassette Transporter I (ABCB1)	rs1045642

Results of the test are intended to be used in combination with clinical evaluation and assessment of the patient. The De Novo submission is under review by the Division of Chemistry and Toxicology Devices (DCTD), Office of Health Technology 7: Office of In Vitro Diagnostics (OHT7), Office of Product Evaluation and Quality (OPEQ), within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA). This document will provide background on OUD, describe the evidence, including clinical study data, SOLVD Health has submitted in support of this new device, and summarize the areas for which FDA seeks expert input from the Panel. In particular, FDA seeks input on whether the clinical study data demonstrates that the probable benefits of the device outweigh its probable risks in people 18 years of age and older that are prescribed oral opioids for the first time to treat acute pain.

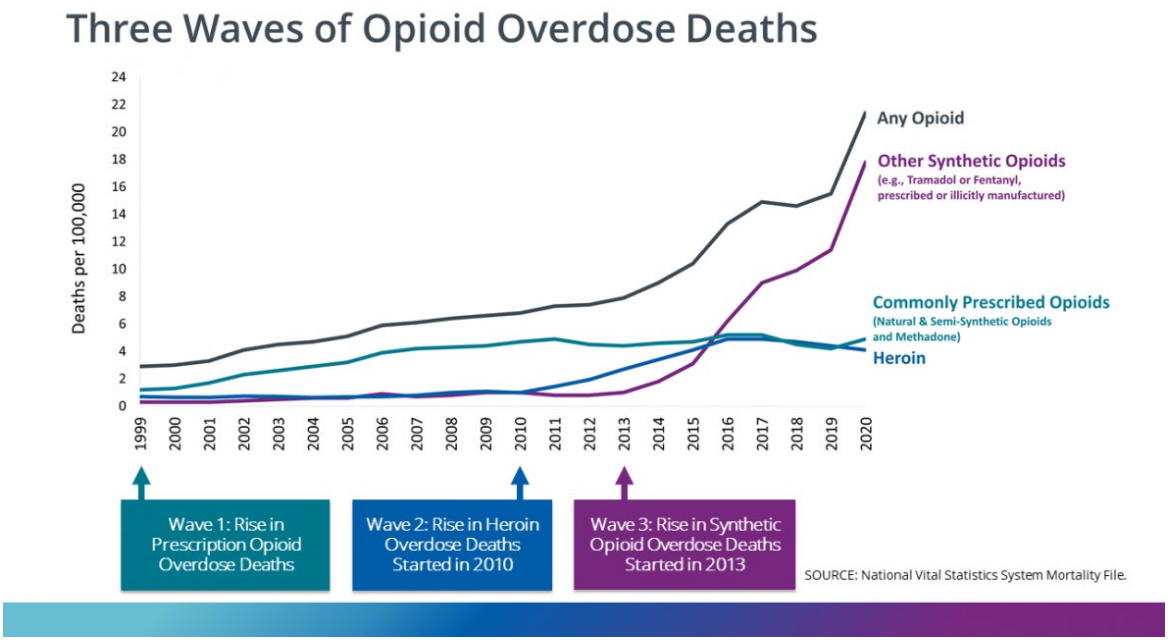
Table of Contents

II. Background

A. Brief History

Opioids are a class of drugs that interact with opioid receptors on nerve cells in the body and brain, thereby blocking pain signals, resulting in pain relief. Opioids have been used for the treatment of pain for millennia (Norn, et al. 2005) but became popular in the United States in 1860s as a way to treat wounded soldiers (Bandyopadhyay 2019). OxyContin was introduced to the market in 1996, following which prescriptions for oral opioids began to increase. An increase in prescription overdose deaths due to opioids began to rise around this time (1990s) in what is described as the Wave 1 of opioid overdose deaths (CDC, Annual Surveillance Report of Drug-Related Risks and Outcomes 2019) (CDC, Vital signs: overdoses of prescription opioid pain relievers - United States, 1999 - 2008. 2011). Later, in 2010 there was an increase in deaths in which the illicit opioid, heroin, was involved, which is described as Wave 2 (Rudd, et al. 2014). Deaths involving other opioids, including other synthetic opioids, continued to increase around 2013 (Wave 3) (Gladden, P and P. 2018) (O'Donnell, RM and P. 2017) (O'Donnell, J, et al. 2017) resulting in the declaration of a public health emergency due to the opioid epidemic in October 2017 (HHS and Hargan 2017). According to the Center for Disease Control and Prevention (CDC) there were 80,816 overdose deaths involving opioids in 2021 in the United States[1].

Figure 1: Trend lines of the 3 Waves of Opioid Overdose Deaths since 1999



[1] Information taken from https://www.cdc.gov/nchs/pressroom/nchs_press_releases/2022/202205.htm#:~:text=Provisional%20data%20from%20CDC's%20National,93%2C655%20deaths%20estimated%20in%202020

B. Opioid Use Disorder (OUD) Diagnosis

Opioids can have great benefit in the treatment of acute and chronic pain when used as prescribed. However even when used as prescribed by a doctor, opioid use can lead to dependence, misuse, and addiction (i.e., opioid use disorder), and can lead to overdose and deaths.

Opioid use disorder (OUD) is a chronic disorder, with serious potential consequences including disability, relapses, and death. The Diagnostic and Statistical Manual of Mental Disorders, 5th Edition[2] (DSM-5 2013) describes OUD as a problematic pattern of opioid use leading to clinically significant impairment or distress, as manifested by at least two of the following occurring within a 12-month period:

- Opioids are often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in a failure to fulfill major obligations at work, school or home.
- Continued opioid use despite having persistent or recurring social or interpersonal problems caused by or exacerbated by the effects of opioids.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- Recurring opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurring physical or psychological problem likely to have been caused or exacerbated by the substance.
- Tolerance, as defined by either of the following:
    - A need for markedly increased amounts or opioids to achieve intoxication or desired effect
    - A markedly diminished effect with continued use of the same amount of an opioid
- Withdrawal, as manifested by either of the following:
    - The characteristic opioid withdrawal syndrome[3].
    - Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

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[2] The Diagnostic and Statistical Manual of Mental Disorders (DSM) is the handbook used by healthcare professionals in the United States and much of the world as the authoritative guide to the diagnosis of mental disorders. DSM contains descriptions, symptoms and other criteria for diagnosing mental disorders. It provides a common language for clinicians to communicate about their patients and establishes consistent and reliable diagnoses that can be used in research on mental disorders. It also provides a common language for researchers to study the criteria for potential future revisions and to aid in the development of medications and other interventions. The DSM-5 is the Fifth Edition, the most recent version.

[3] Withdrawal syndrome is outlined in the DSM-5 as A) either of the following: 1) Cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer), or 2) administration of an opioid antagonist after a period of opioid use and B) Three (or more) of the following, developing within minutes to several days after Criterion A: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; or insomnia.

A diagnosis of OUD is generally made by clinical assessment, either via psychiatric evaluation or by using a structured or semi-structured interview administered by a trained administrator in a clinical research setting.

C. Risk Factors and OUD Risk Assessment Tools

Anyone can develop OUD, but several factors have been associated with higher risk. These include personal or family history of any substance use disorder (SUD), mental health diagnoses, and socioeconomic and environmental contributors such as high stress or high-risk environments. Research has also indicated that there may be genetic factors that contribute to risk of developing OUD (Crist, et al., 2019). However, the genetic associations of individual candidate genes identified so far explain only a small portion of OUD risk. Furthermore, many individuals with present risk factors may never develop the disease. While non-genetic tools for assessment of OUD risk in the chronic pain population exist[4], to date, there are no genetic-based risk assessment tools cleared or approved by the FDA for use in identifying patients at risk for developing OUD in individuals that could be prescribed opioids for management of acute pain.

D. Potential Benefits and Risks

Given the ongoing opioid epidemic and concerning trends in opioid overdoses and deaths, the development of risk stratification tools that could help limit higher risk opioid exposures while maintaining availability for patients who need it could have a significant public health benefit. Devices and tools that are capable of providing information that is helpful in identifying patients at risk of developing OUD can be of great utility in limiting undue exposure. Genetic testing offers the possibility that information, applicable for the lifetime of the patient, can be provided about risk for OUD development. However, there are also risks to genetic testing. Unlike qualitative risk assessment tools for chronic pain that include routine screening (i.e., questionnaires about patient history and urine drug testing), genetic tests may have different emotional ramifications and stigmas associated with them (Prince 2017). The risks associated with false positive and false negative results should also be carefully considered. Specifically, patients erroneously identified as being at high genetic risk of developing OUD could be deprived of needed pain treatment (specifically treatment with oral opioids), while patients erroneously identified as low genetic risk, or not at risk, could be exposed to opioids without appropriate precautions.

In summary, a device that detects genetic variants that may be associated with OUD could be potentially beneficial in combating the opioid epidemic. However, it's important to acknowledge

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[4] Several non-genetic screening procedures/tools (i.e., questionnaires) have been developed to assess risk of OUD in the chronic pain population (for example the Opioid Risk Tool (ORT), Drugs of Abuse Screening and Assessment Tools Chart, and the Substance Abuse and Mental Health Services Administration's guide book for screening for substance use disorders). Many of these qualitative risk assessment tools have been evaluated for specificity and sensitivity in a clinical setting and are currently in use in clinical practice. [5] Section 520(m)(6)(E)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)5 defines "pediatric patients" as persons aged 21 or younger at the time of their diagnosis or treatment (i.e., from birth through the 21st year of life, up to but not including the 22nd birthday). However, in the sponsor's indication for use statement, the term "adult" refers to subjects 18 years or older.

that research into associations with OUD indicate that there are many factors that may contribute to individual patient risk – and genetic risk may not be the biggest factor (Crist, Reiner and Berrettini 2019). Other modes of assessing OUD risk, such as patient and family histories, may be stronger predictors. A genetic device may introduce new risks (such as emotional ramifications and stigmas, described above) to patients that are not present with other risk assessment tools such as questionnaires (which are used in chronic pain patients). In order to determine whether the probable benefits of use of a genetic device to detect risk of developing OUD outweigh the probable risks, careful consideration of the device and its performance is needed.

III. Indication for use

AvertD is a prescription, qualitative genotyping test used to detect and identify 15 clinically relevant genetic polymorphisms in genomic DNA isolated from buccal samples collected from adults.[5] The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD) and identify patients who may be at increased genetic risk for OUD. Information from AvertD provides patients 18 years of age or older and healthcare providers with objective information to be used for informed decision-making prior to the first prescription of oral opioids for acute pain. The information from AvertD is intended to be used in combination with a clinical evaluation and assessment of the patient.

IV. Device Description

A. Device Summary

The AvertD is a multiplex, genotyping (hybridization capture microarray gene expression analysis) assay intended for use in testing human DNA collected from buccal swab specimens. The AvertD detects the presence or absence of 15 SNPs. It is designed to distinguish between two groups: patients at increased genetic risk of OUD and patients who are not at increased genetic risk of OUD and intended to be used in combination with a clinical evaluation and assessment of the patient.

The test is comprised of the INFINITI Buccal Sample Collection Kit (FDA clearance pending), an amplification mix, reagent pack, microarray, and assay specific software. The test is to be run on the INFINITI® PLUS Analyzer, which was previously cleared. DNA is isolated from buccal swabs collected using the sample collection kit, amplified, and purified prior to SNP detection on the analyzer. Presence or absence of a SNP, as determined on the analyzer, is processed by the algorithm, which was developed using data from patients known to have OUD and patients known to not have OUD. The algorithm was developed using machine learning and uses the 15 genotype test results to formulate the predict value (0.000000000-1.000000000). A score above 0.33 indicates increased genetic risk for OUD. The AvertD test report includes the genotype calls

[5] Section 520(m)(6)(E)(i) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)5 defines "pediatric patients" as persons aged 21 or younger at the time of their diagnosis or treatment (i.e., from birth through the 21st year of life, up to but not including the 22nd birthday). However, in the sponsor's indication for use statement, the term "adult" refers to subjects 18 years or older.

(allelic variants) and describes the genetic risk for developing OUD following short term exposure to oral opioids (taking opioids for 4-30 days per a valid prescription for acute pain) as "YES", "NO", or "N/A" when genetic risk cannot be determined.

The device and the principle of the test are described in detail in Sections 4.1 and 4.2 of the sponsor's Executive Summary (pages 32-34).

B. SNPs Detected by the Device

Research studies have indicated that the 15 SNPs detected by the AvertD may be associated with OUD. Research studies have also indicated that the 15 SNPs are not specific to OUD and may be associated with several other disorders of addiction and mood (Ding, et al. 2013) (Pan, Yao and Wang 2014) (Slavich, et al. 2015). OUD and other substance use disorders (SUDs) are considered to derive in part from changes in the brain reward circuit function, which is also implicated in comorbid mental illnesses such as depression, bipolar disorder, and schizophrenia (Levis, Mahler and Baram 2021). People with OUD often experience comorbid conditions (Y. a. Pan 2022) and it is possible that any genetic associations with OUD are not specific to OUD, but rather to a set of disorders that have been linked to the brain reward pathway.

V. Regulatory History

There are currently no FDA-cleared or approved devices indicated for identification of genetic polymorphisms to evaluate genetic risk for developing OUD.

- A version of the subject device, which included 11 of the 15 SNPs now included in the finalized device, was granted Breakthrough Device Designation[6] in March 2018.
- An initial De Novo[7] request for this device was declined in August 2021 and the decision was upheld on appeal in January 2022.
- The sponsor resubmitted the De Novo request in June 2022 after collecting additional information about the subjects in the clinical study to respond to the Agency's concerns.
- FDA is seeking Advisory Committee input before rendering a final decision on the submission.

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[6] The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products. Devices are eligible for breakthrough device designation if both of the following criteria are met: (1) the device provides for more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions; and (2) the device also meets at least one of the following: (a) Represents breakthrough technology, (b) No approved or cleared alternatives exist, (c) Offers significant advantages over existing approved or cleared alternatives or (d) Device availability is in the best interest of patients. The guidance is available here: https://www.fda.gov/media/108135/download.

[7] The De Novo classification request provides a marketing pathway to classify novel medical devices for which general controls alone, or general and special controls, provide reasonable assurance of safety and effectiveness for the intended use, but for which there is no legally marketed predicate device. De Novo classification is a risk-based classification process. Devices that are classified into class I or class II through a De Novo classification request (De Novo request) may be marketed and used as predicates for future premarket notification [510(k)] submissions, when applicable. The guidance is available here: https://www.fda.gov/media/72674/download.

VI. Clinical Study

A. Background

a. Summary Study Design

A prospective clinical study, with one retrospective element, was conducted using buccal samples collected from subjects enrolled at 10 sites across the United States of America between February 2, 2019 and February 19, 2020. All study specimens were collected by a healthcare provider and were stored at ambient temperature prior to testing using the AvertD test by a central laboratory that was masked to the subject information. Buccal samples were stored between 24 to 393 days at ambient temperature prior to testing[8].

A total of 812 subjects were enrolled into the clinical study. Information from 689 of the subjects were forwarded to a statistician who used a predefined sampling plan to select 385 subjects for inclusion in the clinical study (see Section VI.B. Statistical Analysis Plan). The clinical study evaluated subjects who had experienced a 4-30 day exposure to prescription oral opioids 1-51 years prior to study enrollment (the retrospective element) to determine risk of developing OUD following such opioid exposure. The OUD status of each subject was determined by clinical evaluation during enrollment. Sensitivity and specificity estimates were calculated by comparing the OUD status (determined by clinical evaluation during enrollment) to the results of the AvertD test.

b. Subject Enrollment

Subjects were sequentially enrolled at 10 sites using an enrollment log which was used to document the date and time of enrollment. Enrollers at each site approached potentially eligible patients and, after the patient agreed to participate in the study and signed the informed consent document, the patient was enrolled using one of 4 different case report forms (see Section VI.A.b.i.2. Case Report Forms). No study-specific recruitment materials were used and there was no master list of potential subjects at the site used to screen prior to subjects being enrolled in the study. Patients were enrolled as part of a routine visit to the sites (see Section VI.A.b.ii. Study Sites). Most of the subjects enrolled in the clinical study were identified by practitioners that were familiar with the clinical history of the patients, and presumably had a relationship with the patient.

Subjects were required to meet a set of inclusion and exclusion criteria in order to be enrolled into the clinical study (see Section VI.A.b.i.1. Site Training and Section VI.A.b.i.2. Case Report

[8] Buccal samples were collected using a collection device that has not yet been cleared and were stored in a stabilization solution. Stability testing supports storage of the samples for up to 60 days in the stabilization solution. The AvertD product labeling also states that samples that have been collected within ≤60 days are appropriate for use with the AvertD. Most (81.56%, 314/385) samples were stored for >60 days. We are not seeking specific Panel input on the suitability of samples stored longer than the 60 days in the clinical study.

Forms for discussion of differences in the inclusion and exclusion criteria used during enrollment versus those listed in the clinical study protocol). Therefore, all 812 subjects in the clinical study met the inclusion and exclusion criteria used at the time of enrollment. None of the 812 subjects withdrew and no subject was lost to follow-up.

i. Inclusion/Exclusion Criteria and Additional Information Collection

Section Summary: This section describes the inclusion and exclusion criteria listed in the clinical study protocol and the sponsor's intention for the criteria. The criteria include self-reported index exposure of at least 1 year prior to enrollment and were intended to exclude the chronic pain population and subjects whose index exposure to oral opioids may have been illicit. This section also describes the differences between the criteria in the clinical study protocol, the criteria in the training material used to train the enrollment sites, and the 4 different case report forms used to enroll subjects in the clinical study. After the clinical study was completed and in an effort to address FDA feedback, the sponsor collected additional information from medical records and medical histories available at the enrollment sites 1) to support that all subjects met the inclusion and exclusion criteria listed in the clinical study protocol (in light of the differences in the case report forms), 2) to support the accuracy of the self-reported index exposure, and 3) to document the presence of comorbidities at the time of index exposure and at the time of enrollment. We are seeking input from the Panel on whether a) the inclusion and exclusion criteria capture a study population that is representative of the intended use population, b) the uncertainty due to differences in the inclusion and exclusion criteria in the training material and the case report forms impact the interpretability of the clinical study and results, and c) the additional information collected after clinical study completion supports that all subjects were enrolled according to the inclusion and exclusion criteria in the clinical study protocol and that self-reported index exposure is accurate.

The clinical study protocol lists the inclusion criteria as follows:

1. Subject is at least 18 years old
2. Subject or legal representative has consented to participate in the study
3. Subject has provided consent for DNA testing (either by signing the informed consent for this study or by past consent). In the latter case, the DNA sample collected in a prior study must meet all requirements for this study
4. Subject has consented to buccal sample collection in accordance with this study protocol or subject has a DNA sample that meets the DNA requirements of the study as documented by signing the study-specific informed consent
5. Subject was exposed to prescription oral opioids for a duration of 4-30 consecutive days or a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria
6. The index exposure to prescription oral opioids began at least 1 year prior to enrollment in this study

The clinical study protocol lists the exclusion criteria as follows:

1. Subject has never received medical care that included taking oral opioids for more than 30 consecutive days unless a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria
2. Subject or legal representative is not able to provide informed consent to participate in the study

Subjects enrolled in the study were to have had a minimum exposure of 4 consecutive days to oral opioids because this duration has been shown to precede persistent opioid use and is consistent with clinical prescribing patterns in the U.S. (Shah, et al., 2017) (Shah, et al., 2017). Subjects were to have had a maximum exposure of 30 consecutive days to be consistent with acute use of prescription oral opioids rather than chronic use (i.e., treatment for chronic pain). The criteria was set for all enrolled subjects unless the subject had a known Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnosis of OUD, in which case it is possible that these subjects have a history of exceeding 30 consecutive days of prescription oral opioids (e.g., treatment with buprenorphine to treat OUD) under the direction of a qualified healthcare provider following an acute exposure of 4-30 consecutive days (which would qualify them for the study). A minimum follow up period of 1 year after oral opioid exposure was specified to allow sufficient time to transition from first opioid exposure to developing OUD.

The exclusion criteria were designed with the intention of excluding subjects being treated for chronic pain. Treatment with oral opioids for more than 30 consecutive days (unless being treated for OUD) is consistent with treatment for chronic pain, hence an upper limit of 30 consecutive days of treatment was incorporated into the exclusion criteria.

The inclusion and exclusion criteria listed in the clinical study protocol were not exactly the same as those listed on the training material used to train enrollers or the case report forms (CRFs) used to enroll subjects. Differences are summarized in Section VI.A.b.i.1 and VI.A.b.i.2, below.

1. Site Training

Each site was trained individually using the study protocol and a training deck (slide presentation) prior to beginning enrollment. The training included an overview of good clinical practice (GCP), review of sponsor and investigator responsibilities, review of the clinical study protocol, as well as a summary of how to collect, store, and ship samples collected during enrollment. The training deck summarized inclusion criteria for enrollment in a manner that was different compared to the clinical study protocol (see Table 2 below). The training deck did not include exclusion criteria for enrollment. Clarifications on how the inclusion and exclusion criteria should be applied, per the clinical study protocol, were described orally during individual site training as part of the protocol review but were not presented in the training deck.

Table 2: Comparison of Inclusion and Exclusion Criteria Listed in Training Material Versus the Clinical Study Protocol

Inclusion Criteria		
Criteria listed in *Training Deck*	**Criteria listed in *Clinical Study Protocol***	**Comparison**
Males and females, age ≥ 18 year	Subject is at least 18 years old	Same
• A minimum exposure of 4 consecutive days to prescription oral opioids • **Never received medical care that included taking prescribed oral opioids for more than 30 consecutive days**	Subject was exposed to prescription oral opioids for a duration of 4-30 consecutive days **or a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria**	Different
This exposure to oral opioids was at least 12 months ago	The index exposure to prescription oral opioids began at least 1 year prior to enrollment in this study	Same
Consent	• Subject or legal representative has consented to participate in the study • Subject has provided consent for DNA testing (either by signing the informed consent for this study or by past consent). In the latter case, the DNA sample collected in a prior study must meet all requirements for this study • Subject has consented to buccal sample collection in accordance with this study protocol or subject has a DNA sample that meets the DNA requirements of the study as documented by signing the study-specific informed consent	Same
Exclusion Criteria		
Criteria listed in *Training Deck*	**Criteria listed in *Clinical Study Protocol***	**Comparison**
None	Subject has never received medical care that included taking oral opioids for more than 30 consecutive days unless a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria	Different
None	Subject or legal representative is not able to provide informed consent to participate in the study	Different

After training was completed, each person who received training was provided a form to sign to document involvement in the training session. Study staff at all 10 sites attended the training session. Of the 10 sites, the principal investigators at 7 sites signed this form indicating that they were trained to enroll subjects into the clinical study. Principal investigators at 3 sites, sites 1, 7, and 9 (see Table 4 below), did not complete this form and confirmed that they did not attend the training session but did receive the protocol and the training materials. Two of the 3 principal investigators, who did not attend training, confirmed that they reviewed the training materials with their staff, who did attend the training prior to initiating the study. One of the 3 principal investigators did not confirm that training materials were reviewed with staff who attended the training prior to initiating the study. Each of the principal investigators, including those who did not attend the training session, enrolled subjects in the clinical study.

2. Case Report Forms

Case report forms (CRFs) were used to document the subject enrollment (see Attachment 1 for copies of the original forms used to enroll subjects). Four different CRFs were used to enroll subjects. Each form documented subject ID, consent information, gender, age (birthday), ethnicity, race, DSM-5 classification of OUD if subject was OUD-positive (as severe, moderate, or mild), and date of enrollment. The differences between the versions used to enroll subjects are summarized below:

a. CRF Version 1:
    i. Of the 385 subjects evaluated in the clinical study, 61 were enrolled using CRF Version 1.
    ii. In addition to the information listed above (i.e., subject ID, consent information, etc.), this version asked about history of opioid prescription as follows: "*Subject has been* [sic] *prescibed Opiod(s) for a minimum of **5** consecutive days: Yes/No*"
    iii. No other inclusion or exclusion criteria were included.
b. CRF Version 2:
    i. Of the 385 subjects evaluated in the clinical study, 1 was enrolled using CRF Version 2.
    ii. In addition to the information listed above, this form also:
        1. Documented additional demographic information, as follows.
            a. marital status
            b. tobacco use
            c. state of residence
        2. Asked about history of opioid prescription as follows: "*Subject has been* [sic] *prescibed Opiod(s) for a minimum of **4** consecutive days Yes/No:"*. Note that the minimum consecutive days of prescription changed from 5 days (version 1) to 4 days (version 2).
    iii. No other inclusion or exclusion criteria were included.

c. CRF Version 3:
    i. Of the 385 subjects evaluated in the clinical study, 41 were enrolled using CRF Version 3.
    ii. In addition to the information listed above, this form also:
        1. Included an upper limit on the number of consecutive days a subject was prescribed opioids, as follows: "*Subject has been prescribed Opioid(s) for a minimum of 4 consecutive days* ***and a maximum of 30 consecutive days****: Yes/No"*
        2. Asked for the month and year of the prescription, as follows: "*Month and year of first opioid prescription (MMM_YYYY)*"
    iii. No other inclusion or exclusion criteria were included
d. CRF Version 4:
    i. Of the 385 subjects evaluated in the clinical study, 282 were enrolled using CRF Version 4
    ii. In addition to the information listed above, this form also included a list of inclusion and exclusion criteria (see Table 4 below for comparison to criteria listed in the clinical study protocol) which could be answered yes or no.

Table 3: Comparison of Inclusion and Exclusion Criteria Listed on CFR Version 4 Versus the Clinical Study Protocol

Inclusion Criteria		
Criteria listed in *CRF Version 4*	**Criteria listed in *Clinical Study Protocol***	**Comparison**
Subject is at least 18 years old	Subject is at least 18 years old	Same
- Subject is able to provide informed consent to participate in the study (Note: a legal representative may NOT provide consent on behalf of the subject.) - Subject has consented to participate in the study	Subject or legal representative has consented to participate in the study	Same Note: No legal representative consented on behalf of any subjects
Subject has consented to DNA testing either by signing the informed consent for this study or by past consent	Subject has provided consent for DNA testing (either by signing the informed consent for this study or by past consent). In the latter case, the DNA sample collected in a prior study must meet all requirements for this study	Same
Subject has consented to buccal sample collection in accordance with this study protocol or subject has a DNA sample that meets the DNA requirements of the study as	Subject has consented to buccal sample collection in accordance with this study protocol or subject has a DNA sample that meets the DNA requirements of the study as	Same

documented by signing the study-specific informed consent	documented by signing the study-specific informed consent	
- Subject **has taken** prescription oral opioids for at least 4 consecutive days and not more than 30 consecutive days - Date subject first took prescription oral opioids for at least 4 consecutive days and not more than 30 consecutive days	Subject **was exposed** to prescription oral opioids for a duration of 4-30 consecutive days **or a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria**	Different
Date when the subject first took prescription oral opioids for at least 4 consecutive day and not more than 30 consecutive days occurred at least one year ago	The index exposure to prescription oral opioids began at least 1 year prior to enrollment in this study	Same
Exclusion Criteria		
Criteria listed in *CRF Version 4*	**Criteria listed in *Clinical /study Protocol***	**Comparison**
Subject has **EVER** received medical care that included taking **prescription** oral opioids for more than 30 consecutive days	Subject has **never** received medical care that included taking oral opioids for more than 30 consecutive days **unless a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria**	Different
None	Subject or legal representative is not able to provide informed consent to participate in the study	Different Note: Although no exclusion consent criterion was provided in CRF Version 4, all enrolled subjects gave consent.

CRF Version 1 is inconsistent with versions 2-4 as it states that the minimum number of days for prescription of oral opioids is 5 days, in contrast to 4 days listed on Version 2-4. CRF Versions 1 and 2 differ from Versions 3 and 4 because they do not include the maximum number of days for prescription of oral opioids (30 days). Inclusion and exclusion criteria were not listed on CRF Versions 1-3 and therefore, at the time of enrollment, it was not recorded that each subject enrolled using versions 1-3 met the enrollment criteria. The only version that includes inclusion and exclusion criteria, CRF Version 4, lists slightly different criteria from those in the clinical study protocol, as shown in Table 4, above. Namely:

- One inclusion criterion in CRF Version 4 states: '*Subject **has taken** prescription oral opioids for at least 4 consecutive days and not more than 30 consecutive days.*" However, the corresponding inclusion criterion in the clinical protocol states: "*Subject **was exposed to** prescription oral opioids for a duration of 4-30 consecutive days **or a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria.**"* The former portion of the criterion is intended to capture subjects being treated for acute pain with prescription oral opioids (at the exclusion of subjects being treated for chronic pain). The latter portion of this criterion is intended to capture subjects who may be undergoing treatment for OUD, which can include prescription of buprenorphine for longer than 30 days.

- One exclusion criterion in CRF Version 4 states: "*Subject has **EVER** received medical care that included taking **prescription** oral opioids for more than 30 consecutive days.*" The corresponding exclusion criterion in the clinical study protocol states: "*Subject has **never** received medical care that included taking oral opioids for more than 30 consecutive days **unless a psychiatrist has diagnosed the subject as having OUD according to DSM-5 criteria.**"* Similar to the inclusion criterion described above, the criterion is intended to exclude subjects treated with oral opioids for longer than 30 days (i.e., the chronic pain population) unless they have been diagnosed with OUD and may be receiving treatment with buprenorphine for longer than 30 days.

The proposed intended use population is subjects 18 years and older who may be prescribed oral opioids for the first time for the treatment of acute pain (see Section III. Intended Use). The criteria in the CRFs (as well as in the Training Deck) do not explicitly exclude the chronic pain population. The criteria in the CRFs (as well as in the Training Deck) also do not explicitly exclude other mechanisms of prescription opioid exposure, such as illicit oral opioid use.

3. Additional Information Collection

In an effort to address the questions raised by FDA during initial submission review, the sponsor conducted additional information collection following initial study completion. The additional information collection described below queried the medical records and medical histories available at the enrollment sites to complete 3 forms, each with different objectives:

1. Form 1: Identify information to support that clinical study subjects met the inclusion and exclusion criteria as they were written in the clinical study protocol.
2. Form 2: Identify information to support the self-reported index exposure dates.
3. Form 3: Identify records of comorbidities at the time of index exposure and at the time of enrollment to better understand the study population and its applicability to the intended use population.

Objective 1 (Form 1)

After the clinical study and data analyses were completed, an additional inquiry was made to the individual enrollment sites (hereafter called "additional information collection") to identify medical records that could support that all subjects met the inclusion and exclusion criteria, as it was written in the clinical study protocol. Each site was requested to review medical records and medical history[9] available at the site. The subjects were not contacted for the additional information collection, and only the information available at the enrollment site was used (i.e., previous medical records and histories from other clinical sites the subject may have visited were not included in the data collection).

The additional information to assess if subjects met the inclusion and exclusion criteria was documented on a new form (not any of the 4 versions used to enroll subjects into the clinical study), named *Form 1: Protocol Inclusion and Exclusion Case Report Form* (see Attachment 2), which listed the exact inclusion criteria as the clinical study protocol.

The following are among the instructions provided to the sites to complete Form 1:

- To complete this form, review all medical history and medical records for the subject available at the site.
- For the inclusion criteria, Question 5a and Question 5b must both be answered.
  Note: Questions 5a and 5b are provided below for reference:
    - *5a. Exposed to prescription oral opioids for a duration of 4-30 consecutive days (Yes/No)*
    - *5b. A psychiatrist diagnosed the subject as having OUD according to DSM-5 criteria (Yes/No)*
- For inclusion criterion Question 5a, it must be the subject's first exposure and the prescription oral opioid was prescribed to the subject who took the oral opioid for 4-30 days.
- For Question 5b, if the subject was prescribed oral opioids for longer than 30 days, it was for treatment of OUD which was diagnosed according to the DSM-5 criteria.
- For Questions 5a and 6a, the original study documentation* should be used to complete these fields. If the month of index exposure is unknown, enter 999 for the month. If the year is unknown, enter 9999 for the year.
  Note: question 6a is provided below for reference:
    - *The index exposure to prescription oral opioids began at least 1 year prior to enrollment in this study.*
      6a. Insert date of index exposure: MMM/YYY

  Note: "Original study documentation" refers to the original CRFs Versions 1-4 used to enroll subjects into the clinical study (Attachment 1). The original CRFs were only referenced to answer questions 5a. and 6a. and all other information on Form 1 was completed using information identified in medical records and history.

[9] Medical record and medical history refer to documentation regarding subject care/treatment at the enrolling site. Medical histories may be generated during patient intake and may be based on subject memory.

- For Exclusion Criterion 1, the intent for the "unless a psychiatrist had diagnosed the subject as having OUD according to DSM-5 criteria" was to allow subjects who are being actively treated for OUD (e.g., buprenorphine or methadone) to qualify for the study.

Based on the additional information collection, the sponsor concluded that 100.00% (385/385) of the clinical study subjects met the inclusion and exclusion criteria written in the clinical study protocol.

Objective 2 (Form 2)

For all enrolled subjects, information on whether the subject was exposed to prescription oral opioids and the dates of the initial (index) exposure were self-reported (i.e., based on subject recall). In other words, subjects were asked by the enroller at the time of enrollment to recall the date of their first prescription oral opioid exposure. The additional information collection sought to identify information in the medical records and medical histories to support the self-reported index exposure dates recalled by subjects at enrollment. Each site was requested to review medical records and medical history available at the site for each subject within 1 calendar year of the self-reported date of index exposure. First, the records were reviewed for any procedure or event that may have resulted in an oral opioid prescription (such as a surgery) and then for a description of the prescription for the event, and then for documentation of the prescription (e.g., physical copy). This information was documented on a new form, named *Form 2: Exposure Data to Prescription Oral Opioids Case Report Form* (see Attachment 2).

The following are among the instructions provided to the sites to complete Form 2:

- To complete this form, review all available medical history and medical records at your site for the subject in the time period pre-printed on the form. This time period will vary for each subject.
  Note: The time period was plus or minus one year of the self-reported index exposure date.
- For question 3, if a medical history or medical record is available that may correlate to the self-reported exposure, but no clear date is available in the medical record or history, please mark possibly.
- Examine the records and medical history for events or procedures where oral opioids may be prescribed for acute pain as part of medical care, such as (this is not an exhaustive list):
  - Surgical procedures include, but are not limited to, knee surgery or any orthopedic surgery, caesarean-section, laparoscopic surgery, appendicitis, cosmetic surgery
  - Dental procedures including wisdom tooth extraction, dental implants, root canal, periodontal disease
  - Accidents or injuries, such as motor vehicle accidents, fractures, burns
- For the medical records, be sure to review all available sections for each encounter, include without limitation: reason for visit (chief complaint), past surgical history, past medical history, prescription history, review of systems, procedure and operative notes, radiology reports, consults, current medications, and summary of findings.

The information collected on Form 2 was captured in tiers for subgroup analyses.

- **Tier 1**: All subjects who meet the inclusion and exclusion criteria[10]
- **Tier 2**: Subjects who have documentation of a procedure (e.g., surgery) or event (e.g., accident) where oral opioids may be prescribed for acute pain as part of medical care within a calendar year before or after the self-reported index exposure
- **Tier 3**: Subjects who have a description in the medical records of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure, but may or may not have documentation of the actual prescription (e.g., a record that states "a patient was prescribed 7 days of hydrocodone for knee surgery" but the prescription may or may not be documented)
- **Tier 4**: Subjects who have documentation of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure (e.g., physical copy, electronic copy, scan, or photograph)
- **Tier 5**: Subjects for whom the available medical records indicate neither a procedure (e.g., surgery) or event (e.g., accident) where opioids may be prescribed for acute pain nor any indication in the available medical records and history that an oral opioid was prescribed.
- **Tier 6**: Subjects who have documentation of a procedure (e.g., surgery) or event (e.g., accident) where oral opioids may be prescribed for acute pain as part of medical care within a calendar year before or after the self-reported index exposure AND who have documentation of an oral opioid prescription for acute pain within a calendar year before or after the self-reported index exposure (e.g., physical copy, electronic copy, scan, or photograph).

Results from sub-analyses of the information collected on Form 2 are summarized below (see Section VI.C: Study Results for more results):

- Prescription documentation (e.g., physical copy, electronic copy, scan or photograph) was identified for 34.91% (133/381) of the subjects in the clinical study. Prescription documentation was not identified for the remaining 65.09% (248/381) of subjects in the clinical study.
- Description of a prescription was identified in the medical record for 83.46% (318/381) of the subjects in the clinical study.
- A description of an event or procedure that may have resulted in a prescription of oral opioids for acute pain was identified in the medical record or medical history for 94.75% (361/381) of the clinical study participants.

[10] Subjects may be represented in more than one tier as the tiers are not mutually exclusive. For example, a subject who met all inclusion and exclusion criteria, had an event, had a description of an oral opioid prescription for acute pain, and documentation of a physical copy of the prescription would be represented in Tier 1, Tier 2, Tier 3 and Tier 4. A subject who met all inclusion and exclusion criteria and self-reported opioid exposure but had no additional documentation or records would be represented only in Tier 1.

Objective 3 (Form 3)

The additional information collection also requested sites review the medical records and histories of the subjects enrolled in the clinical study to identify comorbidities at the time of the self-reported index exposure and the time of enrollment. The information was documented in a new form, named *Form 3: Comorbidities Case Report Form* (see Attachment 2).

The following are among the instructions provided to the sites to complete Form 3:

- To complete this form, review all medical history and medical records for the subject, available at your site.
- For the medical records, review all available sections for each encounter, including without limitation: reason for visit (chief complaint), past surgical history, past medical history, prescription history, review of systems, procedure and operative notes, radiology reports, consults, current medications, and summary of findings.
- For any "yes" response on medical history, complete the date field, using the first date the comorbidity was identified or diagnosed.
- For dates, provide the month/year (MMM/YYYY). If the month is unknown, enter "999." If the year is unknown, enter "9999."

Based on the information collected on Form 3 in the additional information collection, roughly half of the subjects (N=200) had any record of comorbidities in the medical record and there was no obvious difference in the incidence of comorbidities at the time of index exposure versus at the time of enrollment.

ii. Study Sites

Section Summary: This section describes the sites from which subjects were enrolled. Subjects were enrolled from 10 sites, 2 of which offer opioid treatment programs (sites 10 and 11) who had at least 1 healthcare provider that held a waiver to prescribe buprenorphine. The patient population at sites 10 and 11 are subjects seeking treatment for substance use disorders, including OUD, and mental health disorders. In the additional information collection, no prescription records were available to support self-reported index exposure at sites 10 and 11. One additional site (site 2) also had 1 healthcare provider that held a waiver to prescribe buprenorphine. Prescription records were available from site 2. The patient population at site 2 is unclear and the types of medical services available at this site is unknown. The other 6 sites provide clinical care as well as participate in research and 1 site that is a research only site, and it is unknown what types of medical services are available at these sites. We are seeking input from the Panel on whether, given the uncertainty surrounding the patient population at 8 of the 10 sites (subjects not enrolled at the opioid treatment program sites), the clinical study population represents the intended use population (i.e., subjects 18 years or older, receiving prescription oral opioids for the first time for the treatment of acute pain).

Subjects were enrolled at 10 sites in the United States, listed in Table 5 below. The sites included clinical practice sites who participate in research, 1 research site, and sites which offer opioid

treatment programs. Subjects at 9 of the 10 sites were enrolled as they came to the sites for their clinical care which was unrelated to the clinical study. One of the 10 sites, Medical Research Networx Diagnostics (MRNDx), does not perform clinical care (seven subjects were enrolled at this research site). MRNDx was the clinical research organization (CRO) responsible for study monitoring and data management for this study. Two of the sites, Caron Treatment Center and Seven Hills Hospital, are opioid treatment program sites listed on the Substance Abuse and Mental Health Services Administration's (SAMHSA) Opioid Treatment Program Directory (as of August 2022, https://dpt2.samhsa.gov/treatment/). The patient population at these sites includes individuals seeking treatment for substance use disorders (SUDs), including OUD, or other mental health disorders. The aforementioned sites also had at least 1 healthcare provider who held a waiver to prescribe buprenorphine (which is used to treat opioid dependency) at the time the study was performed. One other site, Clinical Research Associates, also had at least 1 healthcare provider who held a waiver to prescribe buprenorphine at the time the study was performed. None of the remaining 7 sites had a healthcare provider that held a waiver to prescribe buprenorphine. No information was provided regarding the medical services subjects were seeking when enrolled at the 8 sites that are not opioid treatment program sites, and since most (7/8) of these sites provide clinical care as well as participate in research or are research only sites, it is unknown what types of medical services are available at these sites.

In the sensitivity analyses, the 3 sites with at least 1 healthcare provider who held a waiver to prescribe buprenorphine at the time of the study (Clinical Research Associates (site 2), Caron Treatment Center (site 10), and Seven Hills Hospital (site 11)) were grouped together. The patient population at Site 2 is unclear and it is unknown whether the patient population at site 2 is the same as the patient population at sites 10 and 11 (i.e., subjects seeking treatment for SUDs, including OUD, and other mental health disorders). The remaining 7 sites were grouped together in sub-analyses. (See Section VI.C. Study Results for results of analyses.) Since the prevalence of OUD varies across different regions of the United States, subjects were recruited from sites with at least 1 provider who held a waiver to prescribe buprenorphine to increase the number of OUD-positive subjects in the clinical study.

Table 4: List of Clinical Study Sites, Site Locations, Site Grouping, Patient Population at Each Site, and Number of Subjects Enrolled at Each Site

Site #	Site Name	Site Location (City, State)	Site with at least one prescriber who holds a waiver to prescribe buprenorphine	Number of Subjects (OUD status based on clinical evaluation)	Prescription records available for some subjects at this site
1	Healthstar Physicians	Morristown, TN	No	Total = 77 OUD-positive = 0 OUD-negative = 77	Yes
2	Clinical Research Associates	Altoona, PA	Yes	Total = 57 OUD-positive = 29 OUD-negative = 2	Yes**

3	Continental Research Network	Miami, FL	No	Total =35 OUD-positive = 8 OUD-negative = 27	Yes
4	Florida Research Center	Miami, FL	No	Total = 1 OUD-positive = 0 OUD-negative = 1	Yes
5	Vista Health Research	Miami, FL	No	Total = 29 OUD-positive = 4 OUD-negative = 25	Yes
6	Vital Pharma Research	Hialeah, FL	No	Total = 16 OUD-positive = 0 OUD-negative = 16	No
7	Medical Research Networx Diagnostics	Franklin, MA	No	Total = 7 OUD-positive = 0 OUD-negative = 7	No
9*	Community Clinical Research Center	Anderson, IN	No	Total = 19 OUD-positive = 0 OUD-negative = 19	Yes
10	Caron Treatment Center	Wernersville, PA	Yes	Total = 58 OUD-positive = 48 OUD-negative = 10	No**
11	Seven Hills Hospital (Acadia)	Henderson, NV	Yes	Total = 86 OUD-positive = 86 OUD-negative = 0	No**

**Note: Site 8 did not obtain IRB approval, did not enroll any subjects, and was not included in the clinical study.*

*** Note: Documentation of the actual prescriptions (e.g., physical copy, electronic copy, scan or photograph) was not available from the 2 opioid treatment program sites but were available for the other site with at least 1 provider who held a waiver to prescribe buprenorphine (site 2).*

Due to unknown differences in patient populations at each of the sites listed above, it is possible that different patient population met the inclusion and exclusion criteria at the different sites, and that different study populations were enrolled.

c. Subject Assessment

Section Summary: The OUD status (OUD-positive or OUD-negative) of each subject in the clinical study was determined at the time of enrollment in a clinical evaluation. Subjects were grouped into "high-risk" pool or a "low-risk" pool based on whether or not they had OUD or another SUD. No OUD-positive subjects were included in the low-risk pool. We are seeking input from the Panel on whether the overall results from the clinical study, which incorporated an enrichment scheme, represent expected performance of the device in the intended use population.

i. Determination of OUD Status

At the time of enrollment, after subjects were determined to have met a set of inclusion and exclusion criteria and signed the consent form, a clinical evaluation was performed by a clinician at the site. The clinical evaluation, which included a patient interview and clinical history, assessed whether the subject met the DSM-5 criteria for OUD. Clinical history may include information from the subject indicating patterns or behaviors consistent with OUD or SUD or prior treatment for OUD or SUD.

ii. Enrichment by Risk Pool Assignment

In order to ensure a sufficient number of OUD-positive subjects were enrolled in the study, the sponsor employed an enrichment strategy. One way the study population was enriched was to recruit subjects from sites with at least 1 prescriber who held a waiver to prescribe buprenorphine (see Section VI.A.b.ii. Study Sites); patients at that site are more likely to be OUD-positive. OUD-positive subjects were also recruited from sites that offer clinical care as well as participate in research and one research only site. In order to provide the statistician with data to complete the stratified sampling, "risk" pools were incorporated.

After enrollment, subjects were assigned to a "low-risk" pool or a "high-risk" pool based on the clinical evaluation and demographic information collected on the CRFs (see Section VI.A.b.i.2. Case Report Forms). Risk pooling was conducted to create 1 pool with a lower frequency of OUD (low-risk) and another pool with a higher frequency of OUD (high-risk). To assign subjects to a risk pool, information collected during enrollment (i.e., clinical history) from each subject was reviewed for history of any substance use disorder (SUD). If a history of any SUD, including OUD, was present, the subject was classified as high-risk. If no history of any SUD, including OUD, was present, the subject was classified as low-risk. Pool assignment occurred after enrollment, was not performed by the sites, and the sites remained blinded to the risk pool to which each was assigned. The following describes how both high- and low-risk groups were enriched based on OUD and SUD status.

- Low-risk category subjects had no evidence of alcohol or drug SUD at the time of enrollment. Specifically, these subjects had no:
    - DSM-5 diagnosis of OUD documented as of the day of enrollment
    - Alcohol use disorder
    - Other drug use disorder (cocaine, cannabinoids, sedatives, stimulants, etc.)
- High-risk category subjects, on the other hand, had evidence of SUD at the time of enrollment. Specifically, these subjects had one or more of the following:
    - DSM-5 diagnosis of OUD documented as of the day of enrollment
    - Alcohol use disorder
    - Other drug use disorder

No OUD-positive subjects were included in the low-risk pool; therefore, no sensitivity analyses are available for the low risk pool (see Section VI.C. Study Results). All OUD-positive subjects were grouped in the high-risk group.

Risk pools, along with demographic information, were used by an independent statistician to determine which subjects to include in the clinical study analysis group (see Section VI.B.b. Selection of Study Analysis Population)

B. Statistical Analysis Plan

Section Summary: A detailed description of the statistical analysis plan is provided in Section 6.17 of the sponsor's Executive Summary (on page 49). A summary is provided below. Briefly, the sample size was calculated for 90.00% power and subjects were included in the clinical study to fill 32 strata.

a. Sample Size

Sample sizes were determined for a single binomial test against a constant rate for the binomial parameter. The power was computed at 90.00% because both endpoints (sensitivity and specificity) and the joint power for both is 0.9*0.9=0.81. As determined by PASS 14 software (https://www.ncss.com/software/pass/) for 90.00% power at alpha = 0.025, 154 completed OUD subjects and 159 completed non-OUD subjects were required to achieve a lower confidence limit above 0.595 for sensitivity and above 0.555 for specificity. The recruited numbers were upweighted by approximately 10.00% from the minimally required sample sizes to account for invalid test results and the fact that some subjects who were grouped in the high-risk group may ultimately be OUD-negative (see Section VI.A.C.ii. Enrichment by Risk Pool Assignment). Thus, the minimum goals for the recruited populations were set at 154/0.90=171 OUD-positive subjects and 159/0.90=177 OUD-negative subjects, for a total sample size of 348 subjects in both groups combined.

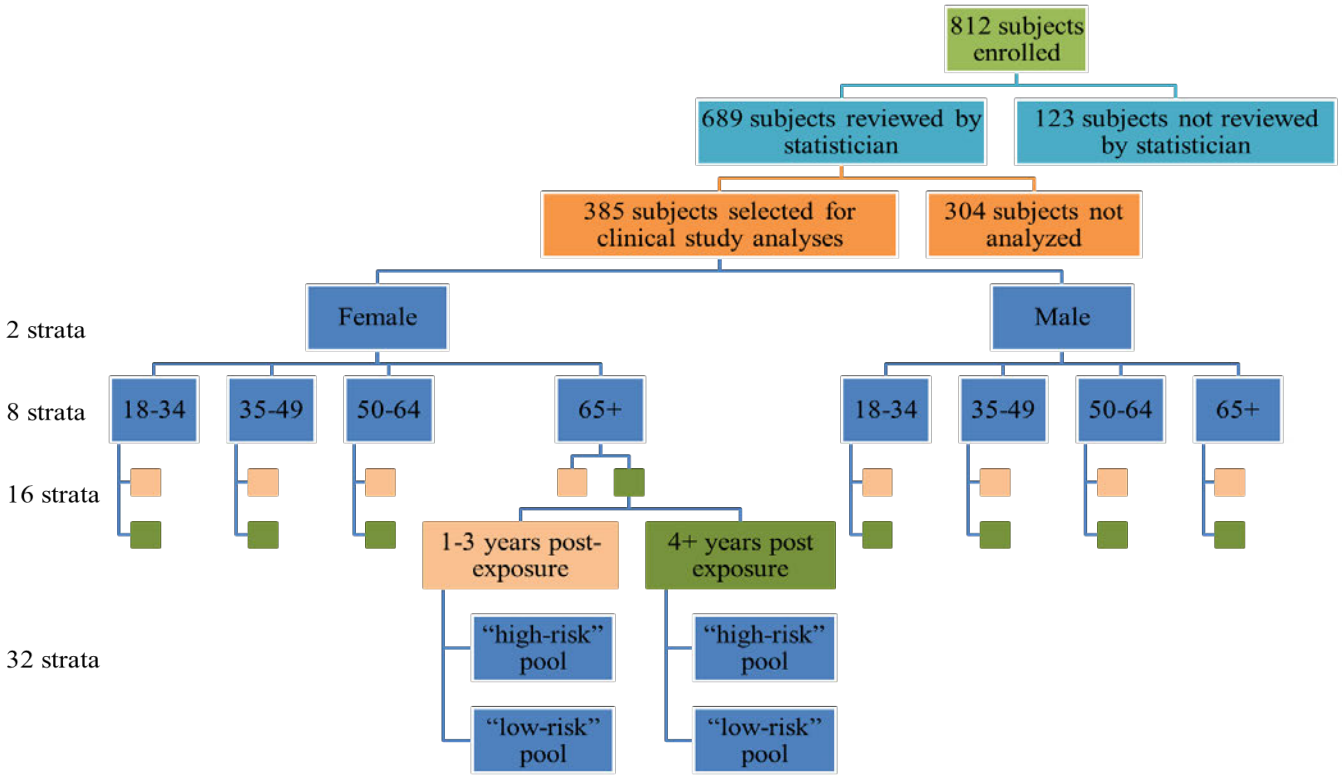
A total of 385 subjects were evaluated in the clinical study, with 210 ultimately being OUD-negative and 175 ultimately being OUD-positive.

b. Selection of Study Analysis Population

Information on enrolled subjects were forwarded to an independent statistician who determined that an adequate number of subjects had been enrolled. Of the 812 total enrolled subjects, the statistician reviewed 689 and judged that an adequate pool was available to randomly select the study analysis population. At the time of determining whether the sample size was adequate, the statistician was aware of subject demographics and risk pool assignment (see Section VI.A.C.ii. Enrichment by Risk Pool Assignment). Using subject demographics and risk pool assignment, the statistician employed a stratified sampling plan to select a subset of enrolled subjects to analyze test performance. The statistician was not provided the confirmed OUD status (determined by clinical evaluation, see Section VI.A.C.i. Determination of OUD Status) or the AvertD test result at the time of selecting the study population.

From the statistician's assessment, a study population of 385 subjects who populated 32 distinct subgroups, was analyzed. The subgroups, shown in Figure 2, below, are 2 genders (male and female), 4 age groups (18-34, 35-49, 50-64, and 65+), 2 time-since-index-exposure bins (<3 years and 4 years or more), and 2 risk pools ("high-risk" pool or "low-risk" pool).

Figure 2: Clinical Study Subject Enrollment and Subject Selection Scheme



C. Study Results

a. Overall Performance

<u>Section Summary</u>: This section summarizes the overall study results and the results of subgroup analyses. We are seeking input from the Panel on the overall benefit/risk profile of the AvertD test given the uncertainty of the clinical performance due to the study design considerations described above.

A total of 385 subjects were analyzed in the clinical study. Of the 385 subjects, 210 were OUD-negative and 175 were OUD-positive, as determined by the DSM-5 clinical evaluation. All 175 OUD-positive subjects were present in the high-risk group and 180/210 OUD-negative subjects were present in the low-risk group. Of the 385 samples (from 385 subjects), 4 resulted in invalid

test results and were not included in final analyses; therefore 381 samples were evaluated in the clinical study.

Table 5: Sensitivity and Specificity Estimates for 381 Subjects in the Clinical Study

		OUD Diagnosis (per DSM-5 clinical evaluation)		
		Positive	**Negative**	**Total**
AvertD test result	**Positive**	144	43	187
	Negative	30	164	194
	Total	174	207	381
Sensitivity = 100*(144/174) = 82.76% (95% CI: 76.31, 88.05) Specificity= 100*(164/207) = 79.23% (95% CI: 73.06, 84.54)				

CI: Confidence Interval

Table 6: Likelihood Ratios for the 381 Subjects in the Clinical Study

Statistic	**Negative Likelihood Ratio**	**Positive Likelihood Ratio**
Estimate	0.22	3.98
95% Confidence Limits	(0.17%, 0.33%)	(3.26%, 6.87%)

b. Demographic Analyses

Slightly more than half of the study population were male (N=219; 57.48%) and slightly less than half were female (N=162; 42.51%). Subjects were selected to ensure that an adequate number of subjects in each age group (18-34, 35-49, 50-64, and 65+) were represented. Device performance (sensitivity and specificity) varied slightly, but insignificantly, across most age groups and between males and females. Test specificity was noted to be significantly lower in females 65 years of age and older, although this observation may be due to the small number of subjects in this group (n=15).

Table 7: Sensitivity and Specificity by Age Group and Sex

Sex	**Age Group**	**True Negative**	**False Positive**	**False Negative**	**True Positive**	**Total**	**Sensitivity Exact 95% CI**	**Specificity Exact 95% CI**
Female	18-34	25	5	5	22	57	81.48% (61.92%, 93.70%)	83.33% (65.28%, 94.36%)
Female	35-49	22	4	3	21	50	87.50% (67.64%, 97.34%)	84.62% (65.13%, 95.64%)
Female	50-64	23	6	1	10	40	90.91% (58.72%, 99.77%)	79.31% (60.28%, 92.01%)
Female	65+	5	6	1	3	15	75.00% (19.41%, 99.37%)	45.45% (16.75%, 76.62%)

Sex	Age Group	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Female	Total	75	21	10	56	162	84.85% (73.90%, 92.49%)	78.13% (68.53%, 85.92%)
Male	18-34	26	6	8	39	79	82.98% (69.19%, 92.35%)	81.25% (63.56%, 92.79%)
Male	35-49	29	s	6	31	72	83.78% (67.99%, 93.81%)	82.86% (66.35%, 93.44%)
Male	50-64	17	5	4	10	36	71.43% (41.90%, 91.61%)	77.27% (54.63%, 92.18%)
Male	65+	17	5	2	8	32	80.00% (44.39%, 97.48%)	77.27% (54.63%, 92.18%)
Male	Total	89	22	20	88	219	81.48% (72.86%, 88.31%)	80.18% (71.54%, 87.14%)
Both Sex	18-34	51	11	13	61	136	82.43% (71.83%, 90.30%)	82.26% (70.47%, 90.80%)
Both Sex	35-49	51	10	9	52	122	85.25% (73.83%, 93.02%)	83.61% (71.91%, 91.85%)
Both Sex	50-64	40	11	5	20	76	80.00% (59.30%, 93.17%)	78.43% (64.68%, 88.71%)
Both Sex	65+	22	11	3	11	47	78.57% (49.20%, 95.34%)	66.67% (48.17%, 82.04%)
Both Sex	Grand Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)

Sensitivity across age groups within females: Two-sided exact Kruskal-Wallis test p-value 0.81. Specificity across age groups within females: Two-sided exact Kruskal-Wallis test p-value 0.048.

Sensitivity across age groups within males: Two-sided exact Kruskal-Wallis test p-value 0.77. Specificity across age groups within males: Two-sided exact Kruskal-Wallis test p-value 0.94.

Sensitivity across age groups for both sexes combined: Two-sided exact Kruskal-Wallis test p-value 0.90. Specificity across age groups for both sexes combined: Two-sided exact Kruskal-Wallis test p-value 0.24.

Sex	Age Group	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Sensitivity across females and males: Two-sided Fisher's exact test p-value 0.68. Specificity across females and males: Two-sided Fisher's exact test p-value 0.73.								

The majority of the clinical study population (92.13%, 351/381) identified their race as White and their ethnicity as non-Hispanic (74.80%, 285/381). Fourteen (14) of the total study population identified as Black/African American and 2 identified as Asian/Pacific Islander. In the table below, non-white subjects are grouped together.

Table 8: Sensitivity and Specificity by Race

Race	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
White	155	39	30	127	351	80.89% (73.86%, 86.72%)	79.90% (73.56%, 85.30%)
Non-white	9	3	0	12	24	100.00% (73.54%, 100.00%)	75.00% (42.81%, 94.51%)
No information*	0	1	0	5	6	N/A	N/A
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across race categories: Two-sided Fisher's exact test p-value 0.13. Specificity across race categories: Two-sided Fisher's exact test p-value 0.71.							

*A total of 375 subjects provided information about their race. Information was not available for 6 subjects. Of the 24 “non-white” subjects, 1 was “White/African American”, 2 were “Asian/Pacific Islander”, 14 were “Black/African American”, 1 was “East Indian”, and 6 were “other”.

Table 9: Sensitivity and Specificity by Ethnicity Completed Cases Population

Ethnicity	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Hispanic	47	19	2	22	90	91.67% (73.00%, 98.97%)	71.21% (58.75%, 81.70%)
Non-Hispanic	117	24	28	116	285	80.56% (73.14%, 86.67%)	82.98% (75.74%, 88.78%)
No information*	0	0	0	6	6	N/A	N/A
Total	164	43	30	144	381*	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across ethnicity: Two-sided Fisher's exact test p-value 0.26. Specificity across ethnicity: Two-sided Fisher's exact test p-value 0.066.							

*Ethnicity information was not available for 6 of the subjects.

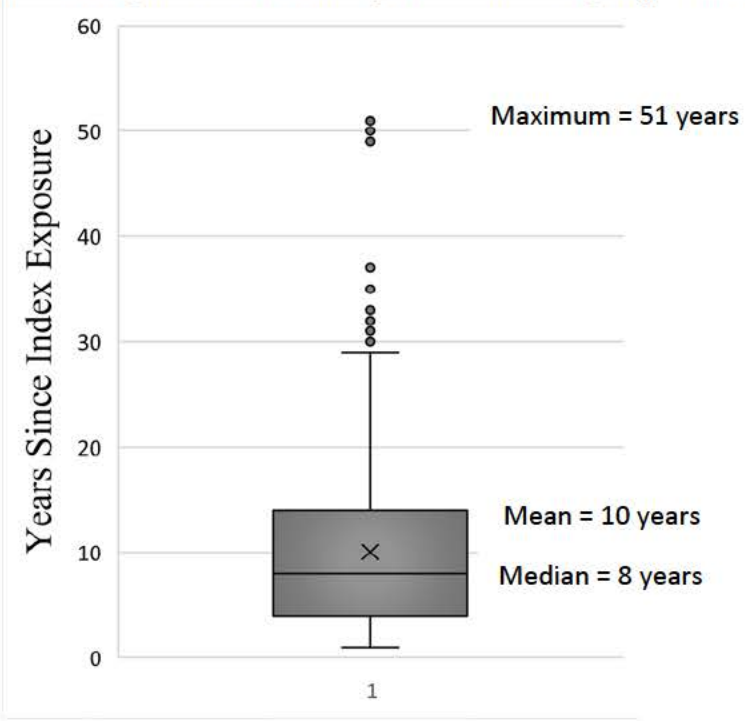
c. Time Since Index Exposure

Section Summary: Self-reported index exposure dates were collected during enrollment and were required to have been at least 12 months prior to the enrollment date. Times since exposure ranged from 1-51 years and the percentage of subjects with OUD increased as the time since index exposure increased. The sponsor collected additional information in an effort to assess the uncertainty associated with self-reported index exposure recall. We are requesting the Panel consider the information available concerning the accuracy of subject opioid exposure dates and discuss the level of uncertainty and impact on interpretation of test performance.

The device is intended to identify individuals at increased genetic risk of developing OUD. During enrollment, a minimum time of 1 year (12 months) was required to have passed between the self-reported index exposure date and enrollment for the subject to meet the inclusion and exclusion criteria. No maximum time since self-reported index exposure was implemented.

- The maximum time since self-reported index exposure was 51 years.
- The median time since self-reported index exposure was 8 years.
- The mean time since self-reported index exposure was 10 years.

Figure 3: Box and Whisker Plot of the Distribution of Years Since Self-Reported Index Exposure



When analyzed in smaller time bins, device performance fluctuates across the time-since-exposure, with no clear trend.

Table 10: Sensitivity and Specificity by Time Since Index Exposure: Smaller Time Bins

Self-reported Time Since Exposure (years)	True Negative	False Positive	False Negative	True positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
1-3	47	13	5	19	84	79.17% (59.53% - 90.76%)	78.33% (66.38% - 86.88%)
4-7	48	15	3	31	97	91.18% (77.04% - 96.95%)	76.19% (64.36% - 85.01%)
8-10	31	8	4	23	66	85.19% (67.52% - 94.09%)	79.49% (64.47% - 89.22%)
11-13	10	3	2	19	34	90.48% (71.09% - 97.35%)	76.92% (49.74% - 91.82%)
14-16	11	3	7	12	31	63.16% (41.04% - 80.85%)	91.67% (52.41% - 92.43%)
17-24	11	2	4	24	41	85.71% (68.51% - 94.30%)	84.62% (57.77% - 95.68%)
25+	6	1	5	16	28	76.19% (54.91% - 89.37%)	85.71% (48.69% - 97.44%)
				Total	381		

The percentage of subjects with OUD (per the DSM-5 clinical evaluation) increases as the time since index exposure increases.

Table 11: Percentage of subjects with OUD based on time since index exposure

Time since exposure (years)	Percent of OUD-positive Subjects
1-3	28.57%
4-7	35.05%
8-10	40.91%
11-13	61.76%
14-16	61.29%
17-24	68.29%
25+ (25-51 years)	75.00%

d. Tiered Analyses of Medical Record Information to Support Self-Reported Index Exposure Dates

Section Summary: Additional information about the enrolled study subjects was collected after the clinical study was completed. The information was divided into tiers based on what type of information was available. The tiered information was analyzed overall, by time since index exposure, and by site. We are seeking input from the Panel on whether the information provided in the tiered analysis adequately resolves the uncertainty in the clinical study data.

i. Overall Tier Analysis

After the clinical study was completed and analyses based on self-reported index exposure dates were conducted, additional information on the subjects enrolled in the clinical study was collected from the clinical sites. All information was collected from medical records or medical histories available at the enrollment site. No information from outside the enrollment site was used and the subjects were not contacted to obtain the information. The medical records and histories were queried for information within a year (plus or minus 1 year) to support the accuracy of the self-reported index exposure date. This information was collected in tiers, as described above and summarized for brevity here:

- **Tier 1**: All subjects who meet the inclusion and exclusion criteria
- **Tier 2**: Documentation of a procedure (e.g., surgery) or event (e.g., accident) where oral opioids may have been prescribed for acute pain
- **Tier 3**: Description of an oral opioid prescription for acute pain, without the actual prescription
- **Tier 4**: Documentation of an oral opioid prescription for acute pain (e.g., physical copy, electronic copy, scan or photograph)
- **Tier 5**: No documentation meeting Tiers 2, 3, or 4
- **Tier 6**: Documentation for both Tiers 2 and 4

Table 12: Summary of Number of Subjects with Information in Each Tier

Category	Observed n (%)
Tier 1	381 (100.00%)
Tier 2	361 (94.75%)
Tier 3	318 (83.46%)
Tier 4	133 (34.91%)
Tier 5	20 (5.25%)

Tier 6 is not summarized in the table above as the same subjects in Tier 4 are in Tier 6

Based on the additional information analyses and completion of Form 1, the sponsor determined that all subjects met the inclusion and exclusion criteria, as listed in the clinical study protocol. Therefore 100% of subjects are recorded in Tier 1. The breakdown of subjects with information in each tier is summarized below.

Table 13: Sensitivity and Specificity by Tier

Category	True Negative	False Positive	Total OUD-negative	False Negative	True Positive	Total OUD-positive	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Tier 1	164	43	207	30	144	174	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Tier 2	157	42	199	28	134	162	82.72% (76.00%, 88.20%)	78.89% (72.56%, 84.35%)
Tier 3	144	37	181	24	113	137	82.48% (75.06%, 88.44%)	79.56% (72.94%, 85.18%)
Tier 4	**78**	**14**	**92**	**12**	**29**	**41**	**70.73% (54.46%, 83.87%)**	**84.78% (75.79%, 91.42%)**
Tier 5	7	1	8	2	10	12	83.33% (51.59%, 97.91%)	87.50% (47.35%, 99.68%)
Tier 6	78	14	92	12	29	41	70.73% (54.46%, 83.87%)	84.78% (75.79%, 91.42%)

Sensitivity in Tier 4 (subjects with prescription records) was observed to be less than in any other tier.

ii. Tier Analysis by Time Since Index Exposure

Tier 2: The medical records and medical histories of 95% (361/381) of the subjects in the clinical study indicated that there was a procedure or an event that may correspond to subject recall of oral opioid exposure. Of the 361 subjects with information in Tier 2 the year of the procedure or event matched with the self-reported index exposure year for 92.24% (333/361). For the 28 subjects that had mismatched information, 25 did not have a year listed in the medical record, 2 were within 2 years, and 1 was within 3 years.

For subjects with information in Tier 2:

- The maximum time since self-reported index exposure was 51 years.
- The median time since self-reported index exposure was 8 years.
- The mean time since self-reported index exposure was 10 (10.2) years

Tier 3: The medical records and medical histories of 83.46% (318/381) of the subjects in the clinical study indicated that there was a prescription for oral opioids (without actual prescription records) that matched the self-reported index exposure dates. The medical records or medical histories for all but 3 (315/318) of these subjects also indicated that there was a procedure or event that may correspond to subject recall of oral opioid exposure. The year of the procedure or

event in the medical records matched with the self-reported index exposure year for 99.37% (313/315) of subjects. For the 2 subjects with mismatched information, 1 was within 2 years and 1 was within 3 years.

For subjects with information in Tier 3:

- The maximum time since self-reported index exposure was 51 years.
- The median time since self-reported index exposure was 8 years.
- The mean time since self-reported index exposure was 10 (9.7) years

Tier 4: Prescription documentation (e.g., physical copy, electronic copy, scan or photograph of the prescription) was identified for 34.91% (133/381) of the subjects in the clinical study. All of the subjects with prescription records also had documentation in the medical record or medical history indicating a procedure or event that may correspond to subject recall of oral opioid exposure (Tier 6). The year of the procedure or event in the medical records matched the self-reported index exposure year for 99.25% (132/133) of the subjects, with 1 subject having information within 2 years.

For subjects with information in Tier 4:

- The maximum time since self-reported index exposure was 50 years.
- The median time since self-reported index exposure was 6 years.
- The mean time since self-reported index exposure was 10 (10.6) years.

Table 14: Number of Subjects with Information in Each Tier by Time Since Index Exposure

	# Subjects			
Years Post-Exposure At Time of Enrollment	**All**	**Tier 2**	**Tier 3**	**Tier 4**
1-2	61	57 (93.44%)	57 (93.44%)	31 (50.82%)
3-4	59	58 (98.30%)	47 (79.66%)	19 (32.20%)
5-6	46	44 (95.65%)	44 (95.65%)	20 (43.47%)
7-8	37	34 (91.89%)	30 (81.08%)	3 (8.11%)
9-10	46	43 (93.47%)	36 (78.26%)	11 (23.91%)
> 10	136	129 (94.85%)	108 (79.41%)	51 (37.50%)
Total # Subjects	385	365	322	135
% of Total # Subjects	100%	94.81%	83.64%	35.06%
Trend by years of post-exposure: p-value by two-sided Cochran-Armitage trend test: Tier 2 (0.76), Tier 3 (0.019), Tier 4 (0.12)				

Of the subjects whose self-reported index exposure was 25 years (N=28) or longer prior to the enrollment date, prescription records for oral opioids were identified for 12/28. Seven (7/12) of these subjects were OUD-positive and 5 (5/12) were OUD-negative. Of the remaining 16 in this group, 9 had a medical record that indicated a prescription was provided and documentation of a procedure or event in a year that matches the self-reported index exposure year, and 7 had only documentation of a procedure or event. Therefore, all subjects whose self-reported index exposure was 25 years or longer prior to enrollment had medical records available at the clinical study site that indicated a prescription for oral opioids was or may have been prescribed. All but

one (N=27/28) of these subjects was recruited from a site with at least 1 provider who held a waiver to prescribe buprenorphine.

iii. Tier Analysis by Site

Information in Tier 2 (documentation of a procedure or event related to opioid prescription) and Tier 3 (description of a prescription with or without the actual prescription record) was available at all sites except site 7 (MRNDx, the research CRO which recruited 7 subjects). Information in Tier 4 (prescription records) was only available from sites 1, 2, 3, 4, 5, and 9. No prescription records were available from sites 6 and 7, one of which was a research site (site 7), or from sites 10 and 11, which offered opioid treatment programs. Prescription documentation (e.g., physical copy, electronic copy, scan or photograph) was available for 41 of the OUD-positive subjects (23.56%, 41/174) and for 92 of the OUD-negative subjects (43.80%, 92/210) in the clinical study. Of the OUD-positive subjects with prescription records available, 29 (70.73%, 29/41) were enrolled at site 2. The remaining 12/41 were enrolled at sites 3 and 5. See Attachment 3, Tables A-1 and A-2 for detailed analyses across the tiers per site.

No sensitivity analyses are available for the low-risk group because no OUD-positive subjects were included in the low-risk group.

e. Site-by-Site Analyses and Severity Analyses

Section Summary: A total of 174 OUD-positive subjects (with AvertD test results) were included in the clinical study. The majority of these OUD-positive subjects had severe OUD and were enrolled at either opioid treatment program sites (sites 10 and 11) and/or at sites with a provider with a waiver to prescribe buprenorphine (sites 2, 10 and 11). We are seeking input from the Panel on whether performance estimates derived from the clinical study population can be extrapolated to the population in which the device is intended to be used if marketed.

Subjects were enrolled at 10 sites (see Section VI.A.b.ii. Study Sites). Two of the sites are listed as opioid treatment programs (sites 10 and 11). The patient population at sites 10 and 11 are people seeking treatment for SUDs, including OUD, and other mental health disorders.

Table 15: Sensitivity and Specificity by Opioid Treatment Program Sites

Opioid Treatment Program Site	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
No (Sites 01/02/03/04/05/ 06/07/09)	156	41	12	29	238	70.73% (55.52%, 82.39%	79.19% (72.99%, 84.27%
Yes (Sites 10/11)	8	2	18	115	143	86.47% (79.62%, 91.27%)	80.00% (49.02%, 94.34%)
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across site specialization categories: Two-sided Fisher's exact test p-value 1.00. Specificity across site specialization categories: Two-sided Fisher's exact test p-value 0.12.							

The majority of OUD-positive subjects were enrolled at opioid treatment program sites (76.44%, 133/174). The remaining 23.56% (41/174) were enrolled at sites that are not opioid treatment program sites. Of the OUD-positive subjects recruited at opioid treatment program sites (sites 10 and 11) with information available regarding the severity of their OUD (132/133), 126 were severe (94.73%, 126/133), 2 were moderate (1.50%, 2/133), and 4 were mild (3.00%, 4/133).[11] Therefore, the majority (94.73%) of OUD-positive subjects enrolled at opioid treatment program sites had severe OUD.

Three of the sites have at least 1 healthcare provider who holds a waiver to prescribe buprenorphine (sites 2, 10, and 11).

[11] The DSM-5 includes diagnostic criteria to determine OUD severity (dsm-5-dx-oud-8-28-2017.pdf (asam.org)). If the subject displays 6 or more of the 11 symptoms listed, the subject is determined to have severe OUD. If the subject displays 4-5 symptoms, they are diagnosed with moderate OUD; and if the subject has 2-3 symptoms, they are diagnosed with mild OUD. For the subjects who had severity information documented in the clinical study, this information was presented on the original CRFs (CRF Versions 1-4). Severity information was not available for all subjects.

Table 16: Sensitivity and Specificity by Site with at Least One Prescriber Who Holds a Waiver to Prescribe Buprenorphine

Site with at least one prescriber who holds a waiver to prescribe buprenorphine	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
No (Sites 01/03/04/05/06/07/09)	130	39	2	10	181	83.33% (51.59%, 97.91%)	76.92% (69.83%, 83.05%)
Yes (Sites 02/10/11)	34	4	28	134	200	82.72% (76.00%, 88.20%)	89.47% (75.20%, 97.06%)
Total	164	43	30	144	381	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)
Sensitivity across site specialization categories: Two-sided Fisher's exact test p-value 1.00. Specificity across site specialization categories: Two-sided Fisher's exact test p-value 0.12.							

The majority of OUD-positive subjects were enrolled at sites with at least 1 prescriber who holds a waiver to prescribe buprenorphine (93.10%, 162/174). The remaining 6.89% (12/174) were enrolled at sites that do not have a healthcare provider with a waiver. Of the OUD-positive subjects recruited at sites with at least 1 waiver (sites 2, 10 and 11) with information available regarding the severity of their OUD (160/162), 129 were severe (79.63%, 129/162), 27 were moderate (16.67%, 27/162), and 4 were mild (2.47%, 4/143). Therefore, the majority (79.63%) of OUD-positive subjects enrolled at sites with at least 1 waiver had severe OUD.

In total, there were 174 OUD-positive subjects in the clinical study, the majority of which, 74.13% (129/174), had severe OUD and the majority of which were enrolled at specialized sites (76.44% at opioid treatment program sites or 93.10% at sites with at least 1 waiver).

f. Comorbidity analyses

Section Summary: Because subjects with OUD may have related comorbidities, there is a risk that the device detected comorbidities in the clinical study rather than OUD. Since the device is intended to be used prior to an index exposure to oral opioids for the treatment of acute pain, the risk that the device detects comorbidities in the clinical study rather than OUD was assessed by collecting information (after the clinical study was completed) about comorbidities present in the clinical study subjects at the time of index exposure from the medical records and medical histories available at the enrollment sites. Information about comorbidities at the time of enrollment (1-51 years after the self-reported index exposure) was also collected and compared to the information at index exposure to determine whether the incidence of comorbidities changed over time. Although subjects diagnosed with OUD had a higher incidence of comorbidities, which is expected, there was no apparent difference in the presence of comorbidities at the time of index exposure versus the time of enrollment.

Although comorbidity information was identified for most subjects, it is possible that comorbidity information may not have been documented at the enrollment site for some subjects and therefore some information may not be available. We are seeking input from the Panel on: a) how comorbidity information should be interpreted given the uncertainty associated with the use of medical records or medical histories to identify comorbidities and b) whether the results of testing using the AvertD are specific for detection of OUD risk versus another risk (comorbidity).

Comorbidity information available for all 385 subjects in the clinical study is reported below. The medical records and medical histories at each enrolling site for each subject were queried for any information indicating the presence of the following comorbidities: alcohol use disorder, anxiety, bipolar disorder, cannabis use disorder, depression, schizophrenia, or other SUD that is not alcohol or cannabis use disorder. Subjects were not contacted and only information available at the site was used to fill in information on Form 3 (See Section VI.A.b.i: Inclusion/Exclusion Criteria and Additional Information collection for details on how the form was filled out). It is not known how the identified comorbidities were diagnosed or where the diagnosis was made (i.e., whether the enrollment site that held the medical record or medical history was also the site where the diagnosis was made). Medical histories may include information derived from patient memory, such as medical history recorded during patient intake, and therefore comorbidity data may also be based on patient memory.

Medical records and histories were available for review of comorbidities for 97.92% (377/385) of the subjects in the clinical study. Of the 377 subjects with comorbidity information available, 200 (53.05%, 200/377) subjects had at least one of the queried comorbidities (at any time). The remaining 177 (46.95%, 177/377) did not have a record of any of the queried comorbidities. A greater percentage of subjects with OUD also had a comorbidity (67.00% versus 22.59%) at any time, which is expected.

Table 17: Number of Subjects with Comorbidities (at any time) and their OUD Status

	Subjects with comorbidities in the medical record at any time	**Subjects with no comorbidities in the medical record at any time**	**Subjects with no medical record to review for comorbidities**
Total	200 (53.05%)	177 (46.95%)	8
OUD-positive (by DSM-5 clinical evaluation)	134 (67.00%)	40 (22.59%)	1
OUD-negative (by DSM-5 clinical evaluation)	66 (33.00%)	137 (77.40%)	7

Table 18: Number of Subjects with Information on Comorbidities in the Medical Record, with or without the Year, by Specific Comorbidity

		By OUD Status	
Variable	**Statistics/ Response Category**	**OUD Negative Subjects (N=210)**	**OUD Positive Subjects (N=175)**
History of Alcohol Use Disorder	No Comorbidity	178 (84.76%)	133 (76.00%)
	Had Comorbidity: Year Known	24 (11.43%)	38 (21.71%)
	Had Comorbidity: Year Unknown	8 (3.81%)	4 (2.29%)
History of Anxiety	No Comorbidity	184 (87.62%)	116 (66.29%)
	Had Comorbidity: Year Known	20 (9.52%)	50 (28.57%)
	Had Comorbidity: Year Unknown	6 (2.86%)	9 (5.14%)
History of Bipolar Disorder	No Comorbidity	208 (99.05%)	161 (92.00%)
	Had Comorbidity: Year Known	2 (0.95%)	10 (5.1%)
	Had Comorbidity: Year Unknown	0 (0.00%)	4 (2.29%)
History of Cannabis Use Disorder	No Comorbidity	206 (98.09%)	147 (84.00%)
	Had Comorbidity: Year Known	3 (1.43%)	23 (13.22%)
	Had Comorbidity: Year Unknown	1 (0.48%)	5 (2.86%)
History of Depression	No Comorbidity	177 (84.29%)	99 (56.57%)
	Had Comorbidity: Year Known	28 (13.33%)	67 (38.29%)
	Had Comorbidity: Year Unknown	5 (2.34%)	9 (5.14%)
History of Schizophrenia	No Comorbidity	209 (99.52%)	175 (100.00%)
	Had Comorbidity: Year Known	1 (0.48%)	0 (0.00%)
	Had Comorbidity: Year Unknown	0 (0.00%)	0 (0.00%)
History of History of Substance Use Disorder Other than Opioids Alcohol or Cannabis	No Comorbidity	210 (100.00%)	117 (66.86%)
	Had Comorbidity: Year Known	0 (0.00%)	52 (29.71%)
	Had Comorbidity: Year Unknown	0 (0.00%)	6 (3.43%)

Information about comorbidities at the time of self-reported index exposure was compared to the comorbidity information at the time of enrollment. Although the number of subjects with each of the specific comorbidities evaluated is low, it does not appear that the study population had more subjects with comorbidities at the time of index exposure when compared to the time of enrollment. However, it is possible that comorbidity information may not have been documented at the enrollment site for some subjects and therefore the total number of subjects with any comorbidity may be greater than the numbers reported below.

Table 19: History of Comorbidities in Clinical Study Population at the Time of Self-Reported Index Exposure (385 subjects)

		By OUD Status	
Variable	**Response Category**	**OUD Negative Subjects (N=210)**	**OUD Positive Subjects (N=175)**
History of Alcohol Use Disorder	No	186 (88.57%)	164 (93.71%)
	Yes	17 (8.09%)	10 (5.71%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Anxiety	No	187 (89.04%)	154 (88.00%)
	Yes	16 (7.61%)	20 (11.43%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Bipolar Disorder	No	201 (95.71%)	163 (93.14%)
	Yes	2 (0.95%)	11 (6.29%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Cannabis Use Disorder	No	202 (96.19%)	168 (96.00%)
	Yes	1 (0.48%)	6 (3.43%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Depression	No	186 (88.57%)	153 (87.43%)
	Yes	17 (8.09%)	21 (12.00%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Schizophrenia	No	203 (96.67%)	174 (99.42%)
	Yes	0 (0.00%)	0 (0.00%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Substance Use Disorder Other than Opioids Alcohol or Cannabis	No	203 (96.67%)	164 (93.71%)
	Yes	0 (0.00%)	10 (5.71%)
	Data not Available	7 (3.33%)	1 (0.57%)

Table 20: History of Comorbidities in Clinical Study Population at the Time of Enrollment (385 subjects)

		By OUD Status	
Variable	**Response Category**	**OUD Negative Subjects (N=210)**	**OUD Positive Subjects (N=175)**
History of Alcohol Use Disorder	No	171 (81.42%)	132 (75.43%)
	Yes	32 (15.24%)	42 (24.00%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Anxiety	No	177 (84.29%)	115 (65.71%)
	Yes	26 (12.38%)	59 (33.71%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Bipolar Disorder	No	201 (95.71%)	160 (91.43%)
	Yes	2 (0.95%)	14 (8.00%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Cannabis Use Disorder	No	199 (94.76%)	146 (83.43%)
	Yes	4 (1.90%)	28 (16.00%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Depression	No	170 (80.95%)	98 (56.00%)
	Yes	33 (15.71%)	76 (43.43%)
	Data not Available	7 (3.33%)	1 (0.57%)
History of Schizophrenia	No	202 (96.19%)	174 (99.43%)
	Yes	1 (0.48%)	0 (0.00%)
	Data not Available	7 (3.00%)	1 (0.57%)
History of History of Substance Use Disorder Other than Opioids Alcohol or Cannabis	No	203 (96.67%)	116 (66.29%)
	Yes	0 (0.00%)	58 (33.14%)
	Data not Available	7 (3.33%)	1 (0.57%)

g. Subject ≥18 years or Older at Time of Exposure

Section Summary: Several (23.09%, 85/381) of the clinical study subjects were under the age of 18 at the time of their index exposure. We are seeking Panel input on whether, when just the population of subjects who were prescribed oral opioids at the age of 18 or older is considered, there is sufficient clinical information from the clinical study to understand device performance.

Because subjects could be enrolled in the clinical study if they were 18 years of age or older at the time of study enrollment, and opioid exposure occurred prior to enrollment, not all clinical study subjects were 18 at the time of their opioid exposure. Based on the date of self-reported index exposure and the birth date information for each subject, 85 of the 381 subjects in the clinical study analyses were prescribed their first oral opioid for the treatment of acute pain prior to the age of 18. The intended use population is subjects 18 years or older who may be receiving their first oral opioid prescription. The total study population of subjects who were 18 years or older at the time of index exposure is 296. Of the 296 subjects who were 18 or older, 121 of them were OUD-positive. The number of subjects who were 18 or older who were OUD-positive

(121) is less than the number of OUD-positive subjects needed to power the study (N=171), described in Section VI.B.i. Statistical Analysis Plan, above. The total number of OUD-negative subjects in the study was 175, greater than the 159 OUD-negative subjects needed to power the study. The following table summarizes the results.

Table 21: Sensitivity and Specificity Estimates for Subjects who were 18 years or older at the time of index exposure

		OUD Diagnosis (per DSM-5 clinical evaluation)		
		Positive	**Negative**	**Total**
AvertD test result	**Positive**	102	38	138
	Negative	19	137	155
	Total	121	175	293
Sensitivity = 100*(102/121) = 84.29% (95% CI: 76.77, 89.71) Specificity= 100*(137/175) = 78.29% (95% CI: 71.61, 83.75)				

VII. Analytical Validation

Several analytical validation studies were conducted to demonstrate device performance. The studies included method comparison (accuracy), precision/reproducibility, interference, limit of detection, carry-over, traceability and stability, specimen preparation (DNA extraction method) and specimen suitability studies. We are not seeking input from the Panel on interpretation of the analytical validation studies and results. The analytical validation studies are described in greater detail in Section 4.5 of the sponsor's Executive Summary (page 37).

VIII. Summary

Given the ongoing opioid epidemic and concerning trends in opioid overdoses and deaths, the development of risk stratification tools that could help limit higher risk opioid exposures while maintaining availability for subjects who need it could have a significant public health benefit. Devices and tools that are capable of providing information that is helpful in identifying subjects at risk of developing OUD can be of great utility in limiting undue exposure.

AvertD is a prescription, qualitative genotyping test used to detect and identify 15 clinically relevant genetic polymorphisms in genomic DNA isolated from buccal samples collected from adults. The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD). The test is intended to be used to identify patients 18 years of age and older who may be at increased genetic risk for OUD.

SOLVD Health conducted a clinical study to assess the performance of the AvertD test, enrolling subjects from 10 study sites. The sponsor reports overall study results demonstrating sensitivity = 82.76% (95% CI: 76.31, 88.05) and specificity= 79.23% (95% CI: 73.06, 84.54). However, numerous factors impact the interpretation of test performance and raise uncertainty about the applicability of the observed clinical study test results to the intended use population.

FDA seeks the Panel's assistance in interpreting the data from the clinical study, assessing its applicability to the intended use population, and providing their perspective on the benefit-risk assessment. In addition, if the Panel believes the data can be adequate to support marketing authorization, FDA seeks advice on the information about clinical performance that should be included in the labeling, specifically any information on the intended use population, so that public health laboratories have access to adequate instructions for use and understand the population the device can be used in. If the Panel believes the data do not support a favorable benefit-risk determination, FDA seeks Panel input on the amount and type of data needed to support a favorable determination.

IX. Panel Questions

FDA is seeking input on the benefit-risk assessment for the AvertD Test when indicated as follows:

AvertD is a prescription, qualitative genotyping test used to detect and identify 15 clinically relevant genetic polymorphisms in genomic DNA isolated from buccal samples collected from adults. The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD) and identify patients who may be at increased genetic risk for OUD. Information from AvertD provides patients 18 years of age or older and healthcare providers with objective information to be used for informed decision-making prior to the first prescription of oral opioids for acute pain. The information from AvertD is intended to be used in combination with a clinical evaluation and assessment of the patient.

In particular, we are seeking input from the Advisory Panel to determine how the data from the clinical study and clinical performance of the AvertD Test should be interpreted.

Our over-arching question for the Advisory Panel is whether the clinical study population adequately represents the intended use population such that the performance data derived from the clinical study are representative of the expected performance of the test when it is marketed and used in the intended use population. We have the following discussion questions for the panel to address during the Advisory Committee Meeting:

1. As described in the FDA and Sponsor Executive Summaries and panel presentations, there are several factors that contribute to the uncertainty in whether the observed clinical study results accurately represent the device's performance in the intended use population for the test. For each of the following factors, please discuss its impact on: a) clinical study subject enrollment and the resulting clinical study population; b) clinical study test performance interpretation; c) applicability of the study results to the intended use population.
    a. Use of different CRF versions during the study to collect the data including completion of an additional CRF after study completion to support that subjects met the inclusion/exclusion criteria specified in the protocol;
    b. Confidence with which the study excluded subjects whose index oral opioid exposure was illicit and/or for treatment of chronic pain;
    c. Recruitment of subjects both from treatment sites and from non-treatment sites;
    d. Determination of index oral opioid exposure based on subject recollection and the additional information available in the medical records/histories at enrollment sites;
    e. Assignment to a risk pool based on SUD and OUD status, absence of OUD-positive subjects in the low-risk pool, and subsequent use of risk pools to select study participants;
    f. Demographic make-up of the study population with regard to race, ethnicity, age, and sex

2. Given the device design, in which 15 SNPs that are associated with OUD as well as other mental health and SUDs are evaluated, and the clinical study design, please discuss the following:
    a. Does the clinical study provide sufficient information to understand whether the device is detecting risk of OUD specifically or risk of OUD in addition to other comorbidities?
    b. Does the information collected following initial study completion (i.e., Form 3) clarify whether the device may be detecting comorbidities in the clinical study population?

3. The reported sensitivity and specificity of the AvertD test, when tested in the clinical study population, is 82.76% and 79.23%, respectively. The negative likelihood ratio is 0.22 and the positive likelihood ratio is 3.98.
    a. Does the reported device performance in the clinical study population represent the probable performance of the device in the intended use population?
    b. Please discuss the clinical significance of the study results, including sensitivity, specificity, positive and negative likelihood ratios.
    c. With the consideration that genetics is only one contributor to the overall risk of developing OUD, please discuss the level of sensitivity and specificity that would be clinically acceptable for a genetic risk test for helping to identify individuals at increased risk of developing OUD.

4. Please discuss the benefits and risks of genetic testing as an aid in assessing the risk of developing OUD following exposure to prescription oral opioids for acute pain.

5. Taking into consideration the current methods for assessing the risk of developing OUD after exposure to prescription oral opioids for acute pain, please discuss the clinical validity of AvertD.

6. If you believe that additional information in the labeling (e.g., warnings, limitations) would be appropriate to mitigate some risks for this test, please describe the specific risks and the labeling mitigations that should be included to minimize those risks associated with use of the device. Are there other mitigations to consider to minimize risk associated with use of the device?

Voting Question

1. Do the probable benefits to health from use of the AvertD device outweigh the probable risks for the proposed indications, taking into account the probable risks and benefits of currently available alternative forms of detecting risk of developing OUD?

X. References

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XI. Appendices

Attachment 1: CRF Versions 1-4
Attachment 2: New CRFs, Forms 1-3
Attachment 3: Tables A-1 and A-2

Attachment 3

Table A-1: Number of Subjects Enrolled at Each Site with Information in Each Tier

Tier	Site	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Tier 2	01	63	12	0	0	75	-	84.00% (73.72%, 91.45%)
Tier 2	02	26	2	10	19	57	65.52% (45.67%, 82.06%)	92.86% (76.50%, 99.12%)
Tier 2	03	19	7	1	7	34	87.50% (47.35%, 99.68%)	73.08% (52.21%, 88.43%)
Tier 2	04	1	0	0	0	1	-	100.00% (2.50%, 100.00%)
Tier 2	05	17	8	1	3	29	75.00% (19.41%, 99.37%)	68.00% (46.50%, 85.05%)
Tier 2	06	10	6	0	0	16	-	62.50% (35.43%, 84.80%)
Tier 2	07	0	0	0	0	0	-	-
Tier 2	09	14	5	0	0	19	-	73.68% (48.80%, 90.85%)
Tier 2	10	7	2	8	37	54	82.22% (67.95%, 92.00%)	77.78% (39.99%, 97.19%)
Tier 2	11	0	0	8	68	76	89.47% (80.31%, 95.34%)	-
Tier 2	Total	157	42	28	134	361	82.72% (76.00%, 88.20%)	78.89% (72.56%, 84.35%)
Tier 3	01	63	12	0	0	75	-	84.00% (73.72%, 91.45%)
Tier 3	02	25	2	10	19	56	65.52% (45.67%, 82.06%)	92.59% (75.71%, 99.09%)
Tier 3	03	19	6	1	7	33	87.50% (47.35%, 99.68%)	76.00% (54.87%, 90.64%)
Tier 3	04	1	0	0	0	1	-	100.00% (2.50%, 100.00%)

Tier 3	05	16	6	1	3	26	75.00% (19.41%, 99.37%)	72.73% (49.78%, 89.27%)
Tier 3	06	5	6	0	0	11	-	45.45% (16.75%, 76.62%)
Tier 3	07	0	0	0	0	0	-	-
Tier 3	09	14	5	0	0	19	-	73.68% (48.80%, 90.85%)
Tier 3	10	1	0	3	14	18	82.35% (56.57%, 96.20%)	100.00% (2.50%, 100.00%)
Tier 3	11	0	0	9	70	79	88.61% (79.47%, 94.66%)	-
Tier 3	Total	144	37	24	113	318	82.48% (75.06%, 88.44%)	79.56% (72.94%, 85.18%)
Tier 4	01	16	1	0	0	17	-	94.12% (71.31%, 99.85%)
Tier 4	02	26	2	10	19	57	65.52% (45.67%, 82.06%)	92.86% (76.50%, 99.12%)
Tier 4	03	17	5	1	7	30	87.50% (47.35%, 99.68%)	77.27% (54.63%, 92.18%)
Tier 4	04	1	0	0	0	1	-	100.00% (2.50%, 100.00%)
Tier 4	05	16	6	1	3	26	75.00% (19.41%, 99.37%)	72.73% (49.78%, 89.27%)
Tier 4	06	0	0	0	0	0	-	-
Tier 4	07	0	0	0	0	0	-	-
Tier 4	09	2	0	0	0	2	-	100.00% (15.81%, 100.00%)
Tier 4	10	0	0	0	0	0	-	-
Tier 4	11	0	0	0	0	0	-	-
Tier 4	Total	78	14	12	29	133	70.73% (54.46%, 83.87%)	84.78% (75.79%, 91.42%)

Table A-2: Sensitivity and Specificity Estimates per Tier by High-Risk and Low-Risk Pool

Tier	Prevalence Group	True Negative	False Positive	False Negative	True Positive	Total	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Tier 2	High	18	8	28	134	188	82.72%	69.23%

							(76.00%, 88.20%)	(48.21%, 85.67%)
Tier 2	Low	139	34	0	0	173	-	80.35% (73.63%, 85.99%)
Tier 2	Total	157	42	28	134	361	82.72% (76.00%, 88.20%)	78.89% (72.56%, 84.35%)
Tier 3	High	12	6	24	113	155	82.48% (75.06%, 88.44%)	66.67% (40.99%, 86.66%)
Tier 3	Low	132	31	0	0	163	-	80.98% (74.10%, 86.70%)
Tier 3	Total	144	37	24	113	318	82.48% (75.06%, 88.44%)	79.56% (72.94%, 85.18%)
Tier 4	High	8	4	12	29	53	70.73% (54.46%, 83.87%)	66.67% (34.89%, 90.08%)
Tier 4	Low	70	10	0	0	80	-	87.50% (78.21%, 93.84%)
Tier 4	Total	78	14	12	29	133	70.73% (54.46%, 83.87%)	84.78% (75.79%, 91.42%)