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SOLVD Health, AvertD
Clinical Chemistry and Toxicology Panel Meeting
October 20, 2022

FDA Presentation

K. Melodi Gussow, Ph.D.
FDA/CDRH/OPEQ/OHT7/DCTD

Presentation Agenda

- Overview of device, disease, and regulatory review process
- Indications for Use
- Device Description
- Regulatory History
- Clinical Study

Topic of Panel Meeting

De Novo application for novel device:

Genetic risk prediction of Opioid Use Disorder (OUD) in patients receiving prescription for oral opioids for the treatment of acute pain for first time

FDA's Benefit/Risk Analysis

During our review of a De Novo, FDA:

- Assesses whether the probable benefits of the device outweigh the probable risks
- Takes into account risk mitigations
- Considers clinical and/or non-clinical testing

Opioid Use Disorder

Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)

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:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major obligations at work, school or home.
6. Continued opioid use despite having persistent or recurring social or interpersonal problems caused by or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurring opioid use in situations in which it is physically hazardous.
9. 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.
10. Tolerance, as defined by either of the following:
    a) A need for markedly increased amounts or opioids to achieve intoxication or desired effect
    b) A markedly diminished effect with continued use of the same amount of an opioid
11. Withdrawal, as manifested by either of the following:
    a) The characteristic opioid withdrawal syndrome.
    b) Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

Genetic Testing to Identify Increased Risk of OUD

- Many factors may contribute to OUD risk
- A test demonstrating the probable benefits outweigh probable risks could have significant public health benefits
- Should also consider potential implications of false negative and false positive results
- Emotional ramifications and stigmas associated with genetic testing

Proposed Indications 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. The 15 detected genetic polymorphisms are involved in the brain reward pathways that are associated with opioid use disorder (OUD) and identify subjects who may be at increased genetic risk for OUD. Information from AvertD provides subjects 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 subject.

For prescription use only.

Device Description

A multiplex, genotyping (hybridization capture microarray gene expression analysis) assay intended for use in testing human DNA collected from buccal swab specimens. DNA from buccal samples is isolated, amplified, and purified prior to detection of the 15 SNPs on a microarray. The 15 genotype test results are fed into a machine-learning algorithm that yields a qualitative output of either "YES", "NO", or "N/A".

Collect buccal samples, ship to lab, and store for up to 60 days

DNA extraction, amplification, and purification prior to microarray SNP detection

15 SNPs detected

Allelic Variants	rs Number
5-HTR2A C>T	rs7997012
COMT G>A	rs4680
DRD1 A>G	rs4532
DRD2 G>A	rsl800497
DRD4 T>C	rs3758653
DAT1 A>G	rs6347
DBH C>T	rsl611115
MTHFR C>T	rsl801133
OPRKI G>T	rsl051660
GABA C>A	rs211014
OPRM1 A>G	rsl799971
MUOR G>A	rs9479757
GAL T>C	rs948854
DOR G>A	rs2236861
ABCB1 C>T	rs1045642

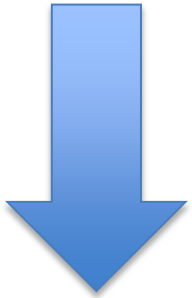
SNP information used to formulate the predict value (0-1)

If value >0.33, the set value is 1, which indicates high genetic risk for OUD.

Reports "YES", "NO", or "N/A" when genetic risk cannot be determined.

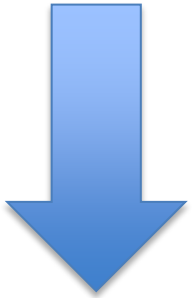
Regulatory History of OUD Prediction Devices

Cleared or approved devices



No cleared or approved devices indicated for identifying patients at genetic risk of developing OUD

The AvertD Test (15 SNPs)



- Granted Breakthrough Designation in 2018 (11 SNPs)
- Initial De Novo (15 SNPs) request declined, and decision upheld on appeal
- New De Novo request, with additional information, currently under review

Topics of Discussion at Panel Meeting

- Whether the results of the clinical study adequately represent performance in the intended use population and setting

- Whether the probable benefits to health from use of the AvertD test outweigh the probable risks for the proposed indications

Device Performance

Analytical (non-clinical) testing: We will not be seeking panel input on these studies in this meeting

The focus of today's discussion is clinical testing to support the claims

Clinical testing: A clinical study was conducted to assess performance of the device to support its intended use

Overview of Clinical Study

- Prospective observational study with one retrospective element
- Study enrolled subjects with an index exposure at least 12 months prior to enrollment
- Self-reported index exposure to prescription oral opioids
- Additional information collected from medical records after initial study completion in response to FDA questions
- Enrichment strategy due to low prevalence of OUD in United States (U.S.) population
- Buccal samples collected from subjects at 10 U.S. sites
- 385 subjects included in final clinical study population
- Results of the AvertD were compared to the OUD-status determined by clinical evaluation during enrollment
- Clinical study primary endpoint calculations:
  - Sensitivity = 82.76% (95% CI: 76.31, 88.05);
  - Specificity = 79.23% (95% CI: 73.06, 84.54)

Study Sites

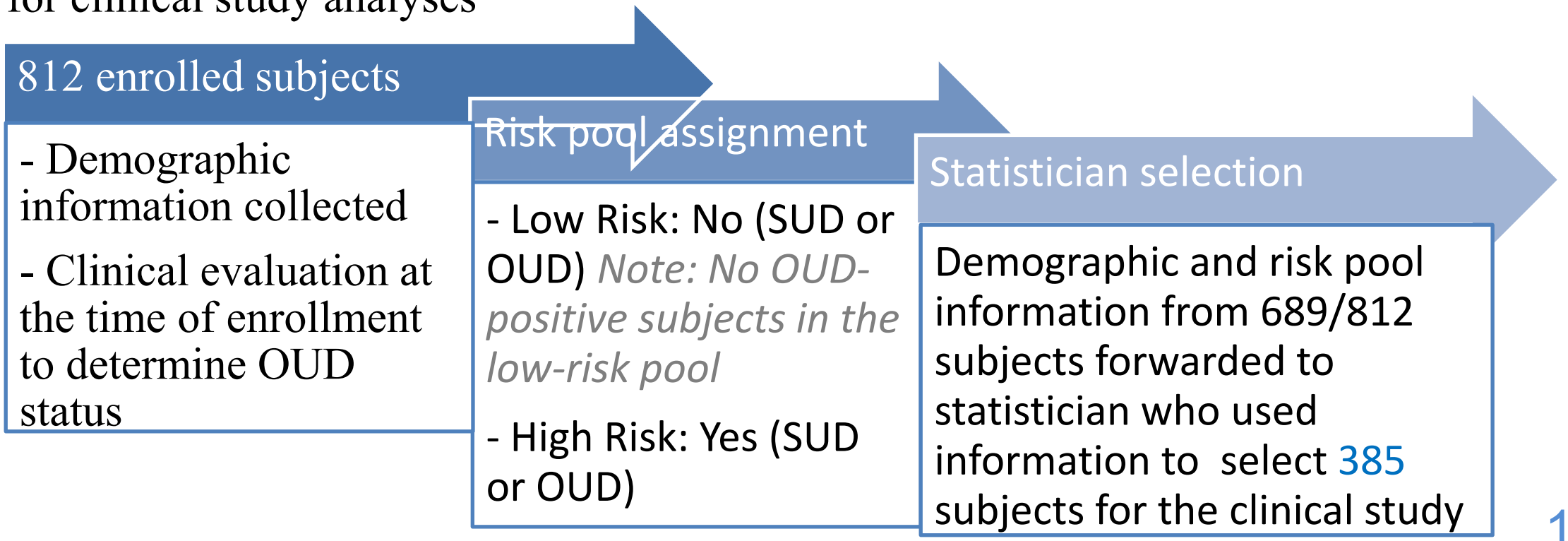
- Two (2) sites are Opioid Treatment Program sites, Site 10 and Site 11. These sites had at least one healthcare provider that held a waiver to prescribe buprenorphine.
- One (1) additional site had at least one healthcare provider that held a waiver to prescribe buprenorphine, Site 2.

Site #	Name of Site	Opioid Treatment Program Site?	At least one prescriber who held a waiver to prescribe buprenorphine?
1	Healthstar Physicians	No	No
2	Clinical Research Associates	No	Yes
3	Continental Research Network	No	No
4	Florida Research Center	No	No
5	Vista Health Research	No	No
6	Vital Pharma Research	No	No
7	Medical Research Networx LLC	No	No
9*	Community Clinical Research Center	No	No
10	Caron Pennsylvania Treatment Center	Yes	Yes
11	Seven Hills Hospital (Acadia)	Yes	Yes

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

Subject Selection for Clinical Study

- All enrolled subjects were given a clinical evaluation to determine whether they met the DSM-5 criteria for OUD (OUD-positive or OUD-negative)
- Subjects were grouped into a "high-risk" pool or a "low-risk" pool based on the presence of absence of OUD or another substance use disorder (SUD)
- Information from 689/812 subjects were forwarded to a statistician who selected 385 for clinical study analyses



Subject Enrollment

- Subjects were enrolled using 4 different case report forms (CRFs)
  - Differences exist between the 4, and only the 4th version (CRF Version 4) included a complete, albeit different, list of inclusion and exclusion criteria

CRF Version	# Subjects analyzed	Inclusion and exclusion criteria included on the CRF	Same as clinical study protocol?
1	61	Subject has been prescribed opioid(s) for a minimum of **5** consecutive days (No other inclusion of exclusion criteria and no questions about comorbidities) **company stated that index exposure identified by "records associated with this study"*	No
2	1	Subject has been prescribed opioid(s) for a minimum of **4** consecutive days (No other inclusion of exclusion criteria and no questions about comorbidities) **company stated that index exposure identified by "records associated with this study"*	No
3	41	Subject has been prescribed opioid(s) for a minimum of 4 consecutive days **and a maximum of 30 consecutive days** **Month and year of first opioid prescription** (No other inclusion of exclusion criteria and no questions about comorbidities)	No
4	282	(next slide)	No

Inclusion/Exclusion Criteria

- Sites were trained prior to enrolling subjects using the study protocol and a training deck
- The clinical study protocol, training deck, and CRFs included different inclusion criteria. Specifically:

Inclusion Criteria		
Criteria listed in Clinical Study Protocol	**Criteria listed in Training Deck**	**Criteria listed in CRF Version 4**
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	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 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
Exclusion Criteria		
Criteria listed in Clinical Study Protocol	**Criteria listed in Training Deck**	**Criteria listed in CRF Version 4**
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	None	Subject has ever received medical care that included taking prescription oral opioids for more than 30 consecutive days

Additional Information

After the clinical study was completed, additional information about the clinical study subjects was collected from the medical records and medical histories available at the enrollment sites using 3 forms

Medical records and medical histories is defined by the company as: "*Information that includes but is not limited to the 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*."

Additional Information – 3 Forms

Form 1: Inclusion/Exclusion Criteria

FORM 1

To collect information to support that clinical study subjects met the inclusion and exclusion criteria as they were written in the clinical study protocol.

SOLVD concluded that, based on the additional information collection, all subjects met the inclusion and exclusion criteria, as listed and as intended in the clinical study protocol (100.00%, 385/385, with 4 not included in analyses because they lacked a test result)

Site Sub-Group Sensitivity and Specificity

- Sub-analyses:
  - By opioid-treatment site
  - By site with at least one healthcare provider who held a waiver to prescribe buprenorphine

Site #	Name of Site	Opioid Treatment Program Site?	At least one prescriber who held a waiver to prescribe buprenorphine?
1	Healthstar Physicians	No	No
2	Clinical Research Associates	No	Yes
3	Continental Research Network	No	No
4	Florida Research Center	No	No
5	Vista Health Research	No	No
6	Vital Pharma Research	No	No
7	Medical Research Networx LLC	No	No
9*	Community Clinical Research Center	No	No
10	Caron Pennsylvania Treatment Center	Yes	Yes
11	Seven Hills Hospital (Acadia)	Yes	Yes

Site Sub-Group Sensitivity and Specificity

- Sub-analyses:
  - By opioid-treatment site

Opioid Treatment Program Site	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Yes (Sites 10/11)	86.47% (79.62%, 91.27%)	80.00% (49.02%, 94.34%)
No (Sites 01/02/03/04/05/06/07/09)	70.73% (55.52%, 82.39%)	79.19% (72.99%, 84.27%
Total	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)

Note: 76.44% (133/174) of OUD-positive subjects were enrolled at sites 10 and 11

Site Sub-Group Sensitivity and Specificity

- Sub-analyses:
  - By site with at least one healthcare provider who held a waiver to prescribe buprenorphine

Site with at least one prescriber who held a waiver to prescribe buprenorphine	Sensitivity Exact 95% CI	Specificity Exact 95% CI
Yes (Sites 02/10/11)	82.72% (76.00%, 88.20%)	89.47% (75.20%, 97.06%)
No (Sites 01/03/04/05/06/07/09)	83.33% (51.59%, 97.91%)	76.92% (69.83%, 83.05%)
Total	82.76% (76.31%, 88.05%)	79.23% (73.06%, 84.54%)

Note: 93.10% (162/174) of OUD-positive subjects were enrolled at sites 2, 10, and 11

Analysis of OUD-Severity in Clinical Study Population

- The DSM-5 provides guidelines for determining OUD severity based on the list of symptoms for diagnosing OUD:
  - Mild = 2-3 symptoms
  - Moderate = 4-5 symptoms
  - Severe = 6 or more symptoms
- Although prevalence estimates vary, one study (in a chronic pain population) found that the prevalence of mild OUD to be higher than that of moderate OUD, which was higher than that of severe OUD*

Mild OUD > Moderate OUD > Severe OUD

* Boscarino et. al., 2015

Analysis of OUD-Severity in Clinical Study Population

- Opioid treatment program sites:
  - 76.44% (133/174) of all OUD-positive subjects were enrolled at these sites
  - 132/133 subjects have information on severity
  - 126 were severe (94.73%, 126/133), 2 were moderate (1.5%, 2/133), 4 were mild (3.0%, 4/133).
  - Therefore, the majority (94.73%) of OUD-positive subjects enrolled at opioid treatment program sites had severe OUD.

- Sites with at least one healthcare provider who held a waiver to prescribe buprenorphine:
  - 93.10% (162/174) of all OUD-positive subjects were enrolled at these sites
  - 160/162 subjects have information on severity
  - 129 were severe (79.63%, 129/162), 27 were moderate (16.67%, 27/162), 4 were mild (2.47%, 4/143)
  - Therefore, the majority (79.63%) of OUD-positive subjects enrolled at sites with at least one waiver had severe OUD

- In total, the majority of OUD-positive subjects (74.13%, 129/174) had severe OUD

Increased rate of OUD-positive Subjects as Time Since Self-Reported Index Exposure Increases

- Self-reported index exposure dates ranged from 1 – 51 years prior to the date of enrollment
- Percent of OUD-positive subjects increased as time since self-reported index exposure increased

Time Since Exposure (years)	# of Subjects in This Time Bin who were OUD-positive	Percent of OUD-positive Subjects in This Time Bin
1-3	24/84	28.57%
4-7	34/97	35.05%
8-10	27/66	40.91%
11-13	21/34	61.76%
14-16	19/31	61.29%
17-24	28/41	68.29%
25+ (25-51 years)	21/28	75.00%
Total	174/381	45.67%

Form 2: Information to Support Self-Reported Index Exposure Dates

To collect information to support the self-reported index exposure dates (i.e., record of a procedure or event related to a potential opioid prescription (Tier 2), documentation that a prescription was provided with or without the actual record (Tier 3), or actual prescription records (Tier 4))

Form 2: Information to Support Self-Reported Index Exposure Dates – All Tiers

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

Tier 1: All subjects who meet the inclusion and exclusion criteria

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 subject 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 and Tier 6

Form 2: Tier 4

- 35.06% (133/381) of subjects had a prescription documentation for oral opioids (Tier 4)

	# Subjects	
Years Since Self-Reported Index At Time of Enrollment	**All**	**Subjects with prescription documentation**
1-2	61	31 (50.82%)
3-4	59	19 (32.20%)
5-6	46	20 (43.48%)
7-8	37	3 (8.11%)
9-10	46	11 (23.91%)
> 10	136	51 (37.50%)
Total # Subjects	385	135
% of Total # Subjects	100%	35.06%

- Tier 4 overall performance:
  - Sensitivity = 70.73% (54.46%, 83.87%) [Overall = 82.76%]
  - Specificity = 84.78% (75.79%, 91.42%) [Overall = 79.23%]

Form 2: Tier 1 vs Tier 4

No prescription documentation available at sites 6, 7, 10, and 11

	All subjects (Tier 1)			Subjects with prescription documentation (Tier 4)			
Site	**Total**	**Sensitivity**	**Specificity**	**Site**	**Total**	**Sensitivity**	**Specificity**
1	75	-	84.00% (63/75)	1	17	-	94.12% (16/17)
2*	57	65.52% (19/29)	92.86% (26/28)	2*	57	65.52% (19/29)	92.86% (26/28)
3	34	87.50% (7/8)	73.08% (19/26)	3	30	87.50% (7/8)	77.27% (17/22)
4	1	-	100.00% (1/1)	4	1	-	100.00% (1/1)
5	29	75.00% (3/4)	68.00% (17/25)	5	26	75.00% (3/4)	72.73% (16/22)
6	16	-	62.5% (10/16)	6	0	-	-
7	7	-	85.71% (6/7)	7	0	-	-
9	19	-	73.68% (14/19)	9	2	-	100.00% (2/2)
10*	58	83.33% (40/48)	80.00% (8/10)	10*	0	-	-
11*	85	88.24% (75/85)	-	11*	0	-	-
Total	381	82.76% (144/174)	79.23 (164/207)	Total	133	70.73% (29/41)	84.78% (78/92)

* Site with at least 1 provider who held a waiver to prescribe buprenorphine

Form 2: Tier 3 and 2

- Tier 3:
  - 83.46% (318/381) of subjects had documentation of prescription
  - Tier 3 overall performance:
    - Sensitivity = 82.48% (75.06%, 88.44%) [Overall = 82.76%]
    - Specificity = 79.56% (72.94%, 85.18%) [Overall = 79.23%]

- Tier 2:
  - 94.75% (361/381) of subjects had documentation of a procedure or event that may be related to opioid prescription
  - Tier 2 overall performance:
    - Sensitivity = 82.72% (76.00%, 88.20%) [Overall = 82.76%]
    - Specificity = 78.89% (72.56%, 84.35%) [Overall = 79.23%]

Form 3: Records of Comorbidities

To collect information on the comorbidities of each subject (available in medical records/histories) at the time of index exposure and at the time of enrollment to assess whether the device may have detected genetic risk of comorbidities rather than genetic risk of OUD

Form 3: Records of Comorbidities

- There was comorbidity information available for 97.92% (377/385) subjects
- Medical records may not capture all comorbidities
- No clear differences in rates of comorbidities in the clinical study population compared to the US population
- No clear differences in subjects with comorbidities at the time of self-reported index exposure and at the time of enrollment

Overall Sensitivity and Specificity

		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)				

Subjects ≥18 years or Older at Time of 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.

		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)				

Summary of Clinical Study Limitations

In summary, 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.

Uncertainty: Study design	Uncertainty: Study population	Uncertainty Device design	Clinical performance
• Complex design • Enrichment strategy • Enrollment sites	• Inclusion and exclusion criteria • Index exposure to prescription oral opioids	• The 15 SNPs evaluated by the device are associated with OUD and other mental health and SUDs	• Sensitivity 82.76% [95%CI: 76.31%, 88.05%] • Specificity 79.23% [95%CI: 73.06%, 84.54%]

Conclusions

- Many factors may contribute to OUD risk
- A test demonstrating the probable benefits outweigh probable risks could have significant public health benefits
- Limitations regarding the clinical study design, study population, device design and clinical performance
- Challenges in making a benefit-risk determination

FDA is seeking expert opinions from our advisory committee

Summary of Panel Questions

Generally: Does the clinical study population adequately represent the intended use population such that the performance estimates derived from the clinical study are representative of the expected performance of the device when it is marketed and used in the intended use population?

We will have questions in the Q/A period that will touch on the following:

- The impact of factors that contribute to uncertainty (such as use of different case report forms, confidence with which certain populations were excluded, index exposures based on subject recollection, recruitment sites, risk pool assignment, demographic make-up of study population)
- Device design and association of the 15 SNPs with other SUDs/disorders
- Clinical performance (i.e., sensitivity and specificity)
- Benefits and risks of genetic testing to assess risk of developing OUD
- Clinical use of AvertD
- Labeling mitigations that may minimize risk

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Thank you!

Panel Questions

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

Panel Questions

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?

Panel Questions

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.

Panel Questions

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

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?


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