SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Next generation sequencing oncology panel, somatic or germline variant detection system

Device Trade Name: Oncomine™ Dx Target Test

Device Procode: PQP

Applicant's Name and Address: Life Technologies Corporation
5781 Van Allen Way
Carlsbad, CA 92008

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P160045/S028

Date of FDA Notice of Approval: August 25, 2021

The original PMA (P160045) for the Oncomine Dx Target Test (ODxT Test) was approved on June 22, 2017 for the detection of specific genetic alterations in tumor specimens from patients with non-small cell lung cancer (NSCLC) to determine who may benefit from any of three targeted therapeutic indications (gefitinib, crizotinib, and dabrafenib in combination with mekinist). On September 4, 2020, a panel-track supplement (P160045/S019) was approved for detecting RET fusions in tumors from NSCLC patients for a fourth therapeutic indication. The SSEDs for the previously approved indications are available on the CDRH website.

The current panel-track supplement was submitted to expand the indications for use of the ODxT Test to include a companion diagnostic indication for the identification of *IDH1* single nucleotide variants (SNVs) in cholangiocarcinoma (CC) patients who may benefit from the targeted drug therapy, TIBSOVO® (ivosidenib).

II. INDICATIONS FOR USE

The Oncomine™ Dx Target Test is a qualitative in vitro diagnostic test that uses targeted high throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs) and deletions in 23 genes from DNA and fusions in *ROS1* and *RET* from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC), and *IDH1* SNVs from FFPE tumor

tissue samples from patients with cholangiocarcinoma (CC) using the Ion PGM™ Dx System.

The test is indicated as a companion diagnostic to aid in selecting NSCLC and CC patients for treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1: List of variants for therapeutic use

Tissue type	Gene	Variant	Targeted therapy
Non-small cell lung cancer (NSCLC)	*BRAF*	*BRAF* V600E mutations	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
	EGFR	*EGFR* L858R mutation, *EGFR* Exon 19 deletions	IRESSA® (gefitinib)
	RET	*RET* Fusions	GAVRETO™ (pralsetinib)
	ROS1	*ROS1* Fusions	XALKORI® (crizotinib)
Cholangiocarcinoma (CC)	*IDH1*	*IDH1* R132C, *IDH1* R132G, *IDH1* R132L, *IDH1* R132S, and *IDH1* R132H mutations	TIBSOVO® (ivosidenib)

Safe and effective use has not been established for selecting therapies using this device for variants and tissue types other than those listed in Table 1.

Results other than those listed in Table 1 are indicated for use only in patients who have already been considered for all appropriate therapies (including those listed in Table 1). Analytical performance using NSCLC specimens has been established for the variants listed in Table 2.

Table 2: List of variants with established analytical performance only

Gene	Variant ID	Nucleotide Change
KRAS	COSM512	c.34_35delGGinsTT
KRAS	COSM516	c.34G>T
MET	COSM707	c.3029C>T
PIK3CA	COSM754	c.1035T>A

The test is not indicated to be used for standalone diagnostic purposes, screening, monitoring, risk assessment, or prognosis.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Oncomine™ Dx Target instructions for use (i.e., labeling).

V. DEVICE DESCRIPTION

The ODxT Test is an in vitro diagnostic test that provides primer panels, assay controls and interpretative software [an Assay Definition File (ADF)] designed for use with the Ion Torrent PGM Dx System and the Ion Torrent PGM Dx Reagents for detection of alterations in DNA and RNA isolated from NSCLC and CC formalin-fixed, paraffin-embedded (FFPE) tumor specimens.

The ODxT Test consists of the following:

Oncomine™ Dx Target Test Controls and Diluent Kit:

- Oncomine™ Dx Target Test DNA and RNA Panel Kit
- Oncomine™ Dx Target Control Kit DNA
- Oncomine™ Dx Target Control Kit RNA
- Ion Torrent™ Dx No Template Control Kit
- Oncomine™ Dx Target Test RNA Control Diluent Kit

Ion Torrent™ Dx FFPE Sample Preparation Kit:

- Ion Torrent™ Dx Total Nucleic Acid Isolation Kit
- Ion Torrent™ Dx cDNA Synthesis Kit
- Ion Torrent™ Dx DNA Quantification Kit
- Ion Torrent™ Dx RNA Quantification Kit
- Ion Torrent™ Dx Dilution Buffer Kit

Ion Torrent™ PGM™ Dx Reagents / Chips:

- Ion PGM™ Dx Library Kit
- Ion OneTouch™ Dx Template Kit
- Ion PGM™ Dx Sequencing Kit
- Ion 318™ Dx Chip Kit

Instrumentation and Software:

- The assay is run on the Ion Torrent™ PGM™ Dx System:
    - Ion OneTouch™ Dx System:
        - Ion OneTouch™ Dx Instrument
        - Ion OneTouch™ ES Dx Instrument
    - Ion PGM™ Dx Sequencer
    - Ion PGM™ Dx Chip Minifuge
    - Ion Torrent™ Server
    - Torrent Suite™ Dx Software
    - Other accessories:
        - Ion PGM™ Wireless Scanner
        - DynaMag™ Dx 16 2mL Magnet
        - DynaMag™ Dx 96 Side-Well Magnet

The system also utilizes specified accessories. The assay's definition files are provided on a USB memory device along with the ODxT Test User Guides:

- Oncomine™ Dx Target Assay Definition File (includes interpretive software)
- Oncomine™ Dx Target Test User Guide
- Veriti™ Dx Thermal Cycler Settings
- Electronic Document Instructions (provided to users both as a paper copy and a PDF document on the USB drive)

Nucleic Acid Extraction:
DNA and RNA extraction is performed using the proprietary Ion Torrent™ Dx FFPE Sample Preparation Kit. The deparaffinized sample is first subjected to protein digestion with Proteinase K at an elevated temperature in a guanidinium thiocyanate solution to facilitate release and protection of RNA and DNA by inhibiting nuclease activity. After a heating step to inactive the Proteinase K enzyme, the digested sample is transferred into a spin column containing a silica-based filter membrane.

The RNA is selectively eluted and separated from DNA which is retained on the filter. The eluted RNA is mixed with ethanol and captured onto a second spin column containing a silica-based membrane filter. The RNA is retained, and cellular impurities are removed by a series of washes. The bound RNA is treated with DNase to reduce contaminating DNA. Following a series of washes to remove residual DNase and DNA degradation products, the purified RNA is eluted from the filter.

The DNA retained on the first filter is similarly subjected to a series of washes to remove cellular impurities and then purified DNA is eluted from the filter. The Elution Solution provided with the kit is a low ionic strength Tris-buffered solution containing EDTA that facilitates elution of nucleic acids from the silica filter. The solution provides appropriate pH for stability of RNA and DNA and inhibits nucleases by binding metal cofactors.

Quantification:
RNA and DNA quantification is performed using a fluorescence dye-binding assay and a qualified fluorometer/fluorescence reader capable of operating at the specific excitation and emission wavelengths. First, working solutions consisting of buffer and proprietary fluorophores are prepared for both DNA and RNA samples, as well as the DNA and RNA standards supplied at different concentrations in the kit (0 ng/µL to 10 ng/µL). Second, the DNA and RNA samples are incubated with their respective solutions at room temperature where the fluorophores bind to the target DNA and RNA molecules. When bound to the DNA and RNA, the fluorophores exhibit fluorescence enhancement at a specific excitation wavelength. The emitted fluorescent signals are captured and converted into signal fluorescence units. Third, the concentration (in ng/µL) of the DNA and RNA samples are determined by performing a linear regression with the values obtained from the DNA and RNA standards.

Sample Dilution Buffer is provided in the kit to dilute the DNA and RNA samples to a specific concentration required for cDNA synthesis and library preparation.

RT Step (RNA only):

RNA is enzymatically converted to cDNA using the Ion Torrent™ Dx cDNA Synthesis Kit. Ten nanograms (ng) of RNA is enzymatically converted to cDNA using an enzyme mix containing a proprietary engineered version of M-MLV reverse transcriptase (Superscript III RT), an RNase inhibitor, a proprietary helper protein, and a buffer containing random primers, dNTPs, and $MgCl_2$.

Library Preparation workflow:
The process begins with polymerase chain reaction (PCR) and uses the ODxT Test DNA and RNA Panel and the Ion PGM™ Dx Library Kit to specifically amplify target regions of interest from cDNA (including cDNA from the RNA control) and DNA (including the DNA Control) and the No Template Control).. For the detection of RNA fusions, the current device has optimization of the RNA workflow and has changes to the primer concentrations and the denaturation temperature used in PCR.

Two different libraries are generated and pooled for each sample; one for DNA targets and one for RNA targets. During library preparation for each sample, one of the 16 oligonucleotide barcodes in the Library Kit is used for the DNA-derived library and another oligonucleotide barcode is used for the RNA-derived library. This ensures the correct identification of each respective portion of the assay (DNA and RNA) from each patient sample. After library preparation, the DNA and RNA libraries for all samples and controls may be blended for the templating reaction.

Data Analysis:
This process is executed by the Torrent Suite™ Dx software, v. 5.12.5, which runs on the Ion Torrent™ Server. Together, these manage the complete end-to-end workflow from sample to variant call. The DNA reads are 'mapped' to the reference human genome (hg19) followed by detection of single nucleotide variants (SNV) and deletions (del) using a reference hotspot file. The RNA reads are ‘mapped’ to a reference containing control sequences and candidate gene fusion sequences. Gene fusions are detected as present if they map to these reference sequences and pass certain filtering criteria provided by the ODxT Test ADF.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no FDA-approved companion diagnostic (CDx) alternatives for the detection of *IDH1* SNVs for the identification of CC patients eligible for treatment with TIBSOVO® (ivosidenib).

Table 3 provides a list of FDA approved alternative CDx assays for indications listed in Table 1.

Table 3: List of FDA Approved CDx Assays for Genes Targeted by ODxT Test

Gene	Variant	Device	Company	Technology	Therapy
BRAF	*BRAF* V600E	FoundationOne CDx	Foundation Medicine, Inc.	NGS	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
EGFR	L858R, Exon 19 deletions	therascreen EGFR RGQ PCR Kit	Qiagen Manchester, Ltd.	PCR	IRESSA® (gefitinib)
		cobas EGFR Mutation Test v2	Roche Molecular Systems, Inc	PCR	
		FoundationOne CDx	Foundation Medicine, Inc.	NGS	

Abbreviations: PCR=Polymerase chain reaction; NGS=Next Generation Sequencing

Each alternative has its own advantages and disadvantages. A patient should fully discuss any alternative with his/her physician to select the most appropriate method. For additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/media/119249/download.

VII. MARKETING HISTORY

The ODxT Test was introduced into interstate commerce in the United States on June 22, 2017 and is commercially available in the US, 12 countries in Europe (Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, UK, Scotland, Italy, Netherlands, Poland), Japan, Korea, and Israel. The ODxT Test has not been withdrawn from the market for reasons related to safety and effectiveness.

The changes to the ODxT Test described above in Section II have not been previously marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device in CC patients.

- Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect ODxT Test results and subsequently improper patient management decisions in treatment.
- Patients with false positive results may undergo treatment with the therapy listed in the intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy.
- There is also a risk of delayed results, which may lead to delay of treatment with the appropriate targeted therapy.

No adverse events were reported in connection with the use of the ODxT Test in the clinical studies used to support this panel track PMA supplement as the studies were performed retrospectively using banked samples.

For the specific adverse events that occurred in the clinical studies, refer to the drug label (i.e., FDA approved package insert) available at Drugs@FDA.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The evidence in support of the performance of the ODxT Test in detecting SNVs in *IDH1* was from the data presented using intended use specimens and sample blends across all validation studies. Studies evaluating analytical accuracy/concordance, precision studies near the limit of detection (LoD), interferents, tissue input, and stability were conducted to support the indication for *IDH1* SNVs.

i. Analytical Accuracy/Concordance

To evaluate the ability of the ODxT Test DNA panel to identify somatic *IDH1* variants in human specimens, 349 FFPE tumor samples from the clinical study were analyzed using the ODxT Test to demonstrate positive percent agreement (PPA) and negative percent agreement (NPA) concordance with a validated reference detection method (Sanger sequencing assay). Of note, samples were enrolled based on the clinical trial assay (CTA) and not the reference Sanger assay.

One hundred and sixty-eight (168) specimens from patients that tested positive using the Sanger assay were analyzed using the ODxT Test. In addition, 181 specimens that tested negative using the Sanger assay were analyzed using the ODxT Test. Of the *IDH1*-positive samples, 165 generated valid results from the ODxT Test. Two samples had ODxT Test invalid results due to failed control or library QC metrics for the sequencing runs. Of the *IDH1*-negative samples, 170 generated valid results from the ODxT Test.

The PPA was defined as the proportion of *IDH1*-positive specimens as called by the Sanger assay that were also *IDH1*-positive as called by the ODxT Test, and the NPA was defined as the proportion of *IDH1*-negative specimens as called by the Sanger assay that were also *IDH1*-negative as called by the ODxT Test. A sensitivity analyses was performed to evaluate the impact of invalid and no call ODxT Test results on the concordance between the reference Sanger method and the ODxT Test results.The unadjusted concordances with and without invalids/no calls are shown in Table 4.

Table 4: *IDH1*—Unadjusted Concordance results

Agreement measure	Excluding invalids and no calls		Including invalids and no calls	
	Percent agreement	95% CI	Percent agreement	95% CI
PPA	99.4% (163/164)	(96.7%, 100.0%)	97.0% (163/168)	(93.2%, 99.0%)
NPA	96.5% (164/170)	(92.5%, 98.7%)	90.6% (164/181)	(85.4%, 94.4%)

[1]Seven samples were found to be discordant in this analysis, where one was called a false negative and six were called false positives with the ODxT Test.

The PPA and NPA was then adjusted for the enriched enrollment selection by the CTA. Using a 31.8% prevalence of the CTA in the intent to treat population, the PPA estimate in reference to the Sanger Assay would be 98.6% (CI 95.8%-100%) and the NPA estimate in reference to the Sanger Assay would be 98.4% (CI 97.0%-99.5%) after adjusting for enrichment.

ii. Analytical Sensitivity

1. Limit of Detection (LoD)

   The LoD was evaluated for all 5 *IDH1* R132 variants that are detected by the ODxT Test and are listed in Table 5. The LoD is the lowest allelic frequency (AF) of the *IDH1* R132 variants that can be detected at least 95% of the time. DNA from variant-containing samples or cell lines were blended with DNA from wild type (WT) FFPE cholangiocarcinoma samples at multiple levels and used as input DNA for the test.

   A minimum of 120 data points were generated for each *IDH1* R132 variant by testing 6 AF levels, 2 reagent lots, and 10 replicates (per level per lot).

   The LoD of the 5 *IDH1* R132 variants ranged from 4.5–5.7% AF.

Table 5: LoD of clinical *IDH1* variants

Variant	ID	Sample type	AF	# of Positive Calls (A)	# of Total Calls (B)	Hit Rate + 95% C.I. (A/B)	Estimated LoD (AF)
R132C	COSM28747	Clinical sample	10.2%	20	20	100% (83.2%, 100%)	4.5%
			8.1%	20	20	100% (83.2%, 100%)	
			6.3%	20	20	100% (83.2%, 100%)	
			4.5%	19	20	95% (75.1%, 99.9%)	
			3.4%	8	20	40% (19.1%, 63.9%)	
			2.4%	2	20	10% (1.2%, 31.7%)	
R132G	COSM28749	Clinical sample	11.9%	20	20	100% (83.2%, 100%)	5.7%
			9.6%	20	20	100% (83.2%, 100%)	
			7.4%	20	20	100% (83.2%, 100%)	
			5.7%	19	20	95% (75.1%, 99.9%)	
			2.4%	1	20	5% (0.1%, 24.9%)	
			2.6%	3	20	15% (3.2%, 37.9%)	
R132H	COSM28746	Cell line	9.7%	20	20	100% (83.2%, 100%)	4.9%
			8.0%	20	20	100% (83.2%, 100%)	
			6.1%	20	20	100% (83.2%, 100%)	
			4.9%	20	20	100% (83.2%, 100%)	
			3.9%	16	20	80% (56.3%, 94.2%)	
			2.6%	2	20	10% (1.2%, 31.7%)	
R132L	COSM28750	Cell line	10.6%	20	20	100% (83.2%, 100%)	5.1%
			7.8%	20	20	100% (83.2%, 100%)	
			6.6%	20	20	100% (83.2%, 100%)	
			5.1%	20	20	100% (83.2%, 100%)	
			3.3%	7	20	35% (15.4%, 59.2%)	
			1.9%	0	20	0% (0%, 16.8%)	
R132S	COSM28748	Cell line	11.0%	20	20	100% (83.2%, 100%)	5.3%
			8.6%	20	20	100% (83.2%, 100%)	
			7.1%	20	20	100% (83.2%, 100%)	
			5.3%	20	20	100% (83.2%, 100%)	
			3.6%	13	20	65% (40.8%, 84.6%)	
			1.8%	0	20	0% (0%, 16.8%)	

2. Tissue Input

   Fifteen slide-mounted FFPE samples were analyzed to determine if samples extracted using the Ion Torrent Dx Total Nucleic Acid Isolation Kit yield DNA and RNA at the concentrations that are required by the ODxT Test when tissue input requirements are met. The test requires DNA at a concentration of ≥0.83 ng/µL and RNA at a concentration of ≥1.43 ng/µL.

   Five resection samples with ≥20% (30-100%) tumor content were prepared without macrodissection, 5 resection samples with <20% to ≥10% tumor cell content were macrodissected, and 5 samples were collected by core needle biopsy (CNB). For the resection samples with ≥100 mm^2 surface area, 1 × 5 µm section was used per extraction. For resection samples with <100 mm^2, 4 x 5 µm sections were used per extraction. For CNBs, all of which had a surface area <30 mm^2, 9 × 5 µm sections were used per

extraction. DNA and RNA concentrations were determined using the Ion Torrent Dx DNA and RNA Quantification Kits, respectively.

iii. Interference

Studies were performed to evaluate the potential for sources of interference to affect test results. Hemoglobin and bile acids were identified as two potentially interfering substances that may be found in CC FFPE tissue samples. These interferents were evaluated using the ODxT Test on the Ion PGM™ Dx System as indicated in Table 6.

Table 6: Interfering substances and amounts

Variant Detected Cosmic ID	Condition	AF Average (%)	AF Difference between Test and Control	% Difference
COSM28749 (R132G)	Control	23.4	N/A	NA
	Bile Salt[1]	23.9	0.5	2.10%
	Hemoglobin[1]	23.1	-0.3	-1.30%
COSM28747 (R132C)	Control	21.3	N/A	NA
	Bile Salt[1]	20.9	-0.3	1.40%
	Hemoglobin[1]	20.5	-0.8	-3.80%
COSM28747 (R132C)	Control	17.1	N/A	NA
	Bile Salt[1]	17.5	0.4	2.30%
	Hemoglobin[1]	19.4	2.3	13.50%

[1]After deparaffinization, biles salts (30 nmol/mL) or hemoglobin (4 mg/mL) were added to the digestion buffer used to pre-wet the tissue section.

Three *IDH1* (1 R132G and 2 R132C) variant positive and 1 WT FFPE CC clinical samples (2 replicates each) were extracted in the presence and absence of the endogenous substance and processed through the entire assay workflow. The concordance between variant calls and the changes in AF in samples with and without interfering substances was calculated for each substance under investigation.

With no calls excluded, the results of testing with hemoglobin and bile acids showed 100% concordance with the control condition for both the *IDH1* R132 variant-positive and WT FFPE CC samples and no significant changes in AF were observed. Additional stability studies will be completed as conditions of approval (see Section XIII).

iv. Precision

1. Single Site Sample Processing Reproducibility

   The reproducibility and repeatability of *IDH1* R132 variant detection using the ODxT Test at a single testing site were evaluated with 2 *IDH1* WT samples and 4 *IDH1* R132 variant-positive samples (2 R132C and 2 R132G). The site had 2 Ion PGM™ Dx instrument systems and 2 operators.

Each sample was tested 6 times by each operator, for a total of 12 replicates per sample. The negative call rate, positive call rate, and within-run repeatability were calculated for each *IDH1* R132 variant-positive sample at the expected *IDH1* R132 variant location. Including no calls the negative call rates for the *IDH1* WT sample were 100% at all *IDH1* R132 variant locations. Including no calls, positive call rates from the expected *IDH1* R132 positive variants was 100% for all samples, except for a single sample harboring R132C, which had a call rate of 91.6% (11/12), due to one invalid replicate.

2. External (Four Site) Panel Reproducibility

The reproducibility and repeatability of *IDH1* R132 variant detection using the ODxT Test were assessed with 1 *IDH1* WT sample and 3 *IDH1* R132 variant-positive samples at 2 allelic frequency (AF) levels, targeted at 1-1.5x and 2-3x LoD. Testing was performed at 4 testing sites, each site had 2 Ion PGM™ Dx instrument systems, 2 operators, and completed testing using 4 lots of reagents.

Table 7: Samples and analyte levels tested.

Sample ID	Variant	Observed AF	Relative LoD
D1	R132C	9.3-12.3%	2.1-2.7x
D2		4.4-6.4%	0.98-1.4x
D3	R132G	10.5-13.8%	1.9-2.5x
D4		5.0-7.2%	0.9-1.3x
D5	R132L	7.0-9.3%	1.4-1.8x
D6		3.3-4.8%	0.65-0.94x
D7	WT	N/A	N/A

Thirty-six (36) replicates per sample were tested across all sites. Overall, there were 72 sequencing events per variant and samples were run in duplicate for repeatability analysis.

The negative call rate, positive call rate, and within-run repeatability were calculated for each *IDH1* R132 variant-positive sample at the expected *IDH1* R132 variant location (Table 8). The overall positive call rate for the *IDH1* R132 variants was 92.6% (199/215) when including no calls and 97.1% (199/205) when excluding no calls. The negative call rates for the *IDH1* WT sample were 100% (36/36) at all *IDH1* R132 variant locations.

Table 8: Call Rates: Reproducibility and Repeatability.

Sample	Number of negative calls (B)	Number of positive calls (A)	# of valid calls (N)	Correct Call rate (C)	No call rate (C/N)	Positive call rate + 95% C.I.		Negative call rate + 95% C.I.		Within-run repeatability + 95% C.I.	
						Including No Calls (A/N)	Excluding No Calls (A/(A+B))	Including No Calls (B/N)	Excluding No Calls (B/(A+B))	Including No Calls	Excluding No Calls
D1	0	36	36	100%	0%	100% (90.3%, 100%)	100% (90.3%, 100%)	0% (0%, 9.7%)	0% (0%, 9.7%)	100% (76.8%, 100%)	100% (76.8%, 100%)
D2	0	35	36	97.20%	2.80%	97.2% (85.5%, 99.9%)	100% (90%, 100%)	0% (0%, 9.7%)	0% (0%, 10%)	92.9% (66.1%, 99.8%)	100% (75.3%, 100%)
D3	0	36	36	100%	0%	100% (90.3%, 100%)	100% (90.3%, 100%)	0% (0%, 9.7%)	0% (0%, 9.7%)	100% (76.8%, 100%)	100% (76.8%, 100%)
D4	0	36	36	100%	0%	100% (90.3%, 100%)	100% (90.3%, 100%)	0% (0%, 9.7%)	0% (0%, 9.7%)	100% (76.8%, 100%)	100% (76.8%, 100%)
D5	0	36	36	100%	0%	100% (90.3%, 100%)	100% (90.3%, 100%)	0% (0%, 9.7%)	0% (0%, 9.7%)	100% (76.8%, 100%)	100% (76.8%, 100%)
D6	6	20	35	74.30%	25.7%	57.1% (39.4%, 73.7%)	76.9% (56.4%, 91%)	17.1% (6.6%, 33.6%)	23.1% (9%, 43.6%)	53.8% (25.1%, 80.8%)	85.7% (42.1%, 99.6%)
D7	36	0	36	100%	0%	0% (0%, 9.7%)	0% (0%, 9.7%)	100% (90.3%, 100%)	100% (90.3%, 100%)	100% (76.8%, 100%)	100% (76.8%, 100%)

At the sample level, the positive call rate was 100% across all R132 variant-positive samples when including no calls, except D2 and D6. Sample D2 carried an *IDH1* R132C mutation and had an observed AF of 4.4-6.4% (0.98-1.4x LoD). When including no calls, the positive call rate was 97.2% (35/36) and 100% (35/35) when excluding no calls. Sample D6 harbored an *IDH1* R132L mutation and had an observed AF of 3.3-4.8% (0.65-0.94x LoD). When including no calls, the positive call rate was 57.1% (20/35) and 76.9% (20/26) when excluding no calls. Similar results were observed for the within-run repeatability (Table 8).

Sample D5 is the same specimen as sample D6, except the analyte levels were higher (1.4-1.8x LoD). Sample D5 had a 100% positive call rate. Samples run at sub-LoD levels are expected to fail more often than samples run at ≥LoD levels. Failures were observed in samples with AF below 3.7% (0.73x LoD), andthe lower positive call rate for sample D6 is due to its low AF, below LoD (0.65-0.94x LoD).

v. Guard Band

A study that evaluated the tolerance levels of the ODxT Test with CC samples was conducted. The repeated study evaluated the tolerance of the proteinase K digestion and inactivation steps during FFPE sample preparation when using the ODxT Test.

The tolerance level for each test condition (volume, temperature, and time for digestion and inactivation) was evaluated by comparing DNA and RNA concentrations across 3 test levels: low, standard operating protocol (SOP)/nominal, and high. For each test condition and level, DNA and RNA were extracted from one (1) *IDH1* positive FFPE CC sample (R132C) and an FFPE BRAF V600E cell-line (in triplicate) and sequenced using the ODxT Test.

All samples tested met the prespecified acceptance criteria for all 3 test conditions.

vi. Stability Studies

CC FFPE block and slide stability using the ODxT Test was determined.

1. Block Stability

   A block stability study was conducted to determine the stability of CC FFPE tissue blocks at room temperature when tested with the ODxT Test.

   Three (3) *IDH1* positive (1 R132G and 2 R132C) clinical sample blocks were tested in duplicate at baseline, 3 months+2 weeks, 6 months+2 weeks and 12 months+2 weeks' time points.

   Linear regression analyses and stability estimates from each sample at the different timepoints demonstrated that the observed AF of CC FFPE tissue blocks do not decrease beyond a prespecified threshold and are stable for up to 12 months.

2. Slide Stability

   The slide stability study was conducted to determine the stability of paraffin dipped and un-dipped FFPE CC tissue sections mounted on slides using the ODxT Test.

   Three (3) *IDH1* positive (2 R132G and 1 R132C) clinical samples from dipped and un-dipped FFPE CC tissue sections were tested at baseline, 3 months+1 week, 6 months+1 week, 9 months+1 week and 12 months+1-week time points.

   For each sample, linear regression analyses for the *IDH1* variants demonstrated no statistically significant difference in AF for all the 5 time points tested. Furthermore, at each time point, all 3 samples were within the maximum allowable drift from baseline mean AF; demonstrating stability of both dipped and un-dipped FFPE CC tissue mounted on slides up to 12 months.

B. Animal Studies

No animal studies were performed.

C. Additional Studies

No additional studies were performed.

X. SUMMARY OF PRIMARY CLINICAL STUDY

Life Technologies conducted a clinical bridging study to establish the reasonable assurance of safety and effectiveness of the ODxT Test for detection of *IDH1* R132 SNVs in CC FFPE tumor specimens to select patients for treatment with TIBSOVO® (ivosidenib). Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The efficacy of TIBSOVO was evaluated in a randomized (2:1), multicenter, double-blind, placebo-controlled clinical trial (NDA 211192/S-8; Study AG120-C-005, ClarIDHy, NCT02989857) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an *IDH1* mutation whose disease had progressed following at least 1 but not more than 2 prior regimens, including at least one gemcitabine- or 5-FU-containing regimen. Patients were randomized to receive either TIBSOVO 500 mg orally once daily or matched placebo until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (1 or 2). Eligible patients who were randomized to placebo were allowed to cross over to receive TIBSOVO after documented radiographic disease progression. Patients with *IDH1* mutations were selected using a next generation sequencing assay performed at a central testing site. Tumor imaging assessments were performed every 6 weeks for the first 8 assessments and every 8 weeks thereafter.

To evaluate the ability of the ODxT Test to identify five *IDH1* biomarkers in FFPE cholangiocarcinoma specimens, specimens from patients that tested positive or negative by the clinical trial assay (CTA) used in the AG120-C-005 clinical trial were analyzed with the ODxT Test.

B. Accountability of PMA Cohort

In total, 383 samples were obtained for this study. Both slides cut from FFPE blocks and extracted DNA were used. Of these, 187 were identified by the enrolling CTA as *IDH1* positive, 187 were identified as *IDH1* negative, and 9 samples were invalid samples on the enrolling CTA.

The *IDH1* positive sample set was provided by the drug partner as 187 CTA identified positive subjects that were enrolled into the AG-120-C-005 clinical study; the *IDH1* negative samples were randomly selected from the CTA patient population that yielded

a valid negative result call on the CTA assay; and the *IDH1* invalid samples were randomly selected from the CTA patient population that yielded invalid results.

Of the 187 *IDH1* positive samples tested, 6 were not tested by the ODxT Test due to low or insufficient sample availability, results from 6 were invalid, 1 was *IDH1* negative, and the remaining 174 were *IDH1* positive by the ODxT Test. Two *IDH1* positive patients were enrolled after the primary end point data cutoff and therefore excluded, leaving 172 *IDH1* positive patients.

Of the 187 samples provided by the pharmaceutical partner, which were *IDH1* CTA negative, 0 were identified as *IDH1* positive by the ODxT Test, and 14 were invalid, 5 yielded no calls, 2 were not tested due to low or insufficient sample availability, leaving 166 confirmed *IDH1* negative samples by the ODxT Test.

Of the 9 CTA invalid samples tested, 3 yielded ODxT Test positive results, 3 yielded negative results, 2 were confirmed invalid and 1 was not tested due to insufficient sample availability.

In summary, 9 samples were not tested, 22 had invalid ODxT Test results, 5 samples were no calls, 177 were *IDH1* positive, and 170 were *IDH1* negative by the ODxT Test and were included in the analyses.

C. Study Population Demographics and Baseline Parameters

The median patient age was the same (62 years old) in the evaluable (N=172) and unevaluable (N=13) groups. Other characteristics of race, ethnicity, BMI etc. appeared comparable in the evaluable and unevaluable groups. There are slightly more male patients in the evaluable population comparing with the unevaluable groups (38% vs. 23% male) respectively; and these comparisons should be interpreted with caution as the "unevaluable" group has a small sample size.

Table 9: Patient demographics and disease characteristics between CDx evaluable and unevaluable set for CTA+ patients in AG120-C-005; Efficacy Population.

Demographic and Disease Characteristics						
Demographic and Disease Characteristics	**TIBSOVO (500 mg daily)**			**Placebo**		
	CDx Evaluable (n=116)	**CDx Uneval. (n=8)**	**CTA+ (n=124)**	**CDx Evaluable (n=57)**	**CDx Uneval. (n=4)**	**CTA+ (n=61)**
Demographics						
Age (Years) Median (Min, Max)	61 [33, 80]	60 [46, 72]	61 [33, 80]	63 [40, 83]	61 [55, 69]	63 [40, 83]
Age Categories, n/N (%)						
<65 years	62.9% (73/116)	62.5% (5/8)	62.9% (78/124)	59.6% (34/57)	50.0% (2/4)	59.0% (36/61)
≥65 years	37.1% (43/116)	37.5% (3/8)	37.1% (46/124)	40.4% (23/57)	50.0% (2/4)	41.0% (25/61)
Sex, n/N (%)						
Male	35.3% (41/116)	37.5% (3/8)	35.5% (44/124)	42.1% (24/57)	0% (0/4)	39.3% (24/61)
Female	64.7% (75/116)	62.5% (5/8)	64.5% (80/124)	57.9% (33/57)	100.0% (4/4)	60.7% (37/61)
Race, n/N (%)						

Demographic and Disease Characteristics						
Demographic and Disease Characteristics	**TIBSOVO (500 mg daily)**			**Placebo**		
	CDx Evaluable (n=116)	**CDx Uneval. (n=8)**	**CTA+ (n=124)**	**CDx Evaluable (n=57)**	**CDx Uneval. (n=4)**	**CTA+ (n=61)**
White	57.8% (67/116)	37.5% (3/8)	56.5% (70/124)	61.4% (35/57)	0% (0/4)	57.4% (35/61)
Black or African American	0.9% (1/116)	0% (0/8)	0.8% (1/124)	1.8% (1/57)	0% (0/4)	1.6% (1/61)
Asian	12.1% (14/116)	12.5% (1/8)	12.1% (15/124)	10.5% (6/57)	50.0% (2/4)	13.1% (8/61)
Native Hawaiian or Pacific Islander	0.9% (1/116)	0% (0/8)	0.8% (1/124)	0% (0/57)	0% (0/4)	0% (0/61)
American Indian or Alaskan Native	0.9% (1/116)	0% (0/8)	0.8% (1/124)	0% (0/57)	0% (0/4)	0% (0/61)
Other/Not Provided	27.6% (32/116)	50.0% (4/8)	29.0% (36/124)	26.3% (15/57)	50.0% (2/4)	27.9% (17/61)
Disease Characteristics						
Prior Line of Therapy, n/N (%)						
1 Prior Line of Therapy	51.7% (60/116)	75.0% (6/8)	53.2% (66/124)	52.6% (30/57)	75.0% (3/4)	54.1% (33/61)
2 Prior Lines of Therapy	48.3% (56/116)	25.0% (2/8)	46.8% (58/124)	47.4% (27/57)	25.0% (1/4)	45.9% (28/61)
ECOG PS, n/N (%)						
0	42.2% (49/116)	0% (0/8)	39.5% (49/124)	26.3% (15/57)	100.0% (4/4)	31.1% (19/61)
1	57.8% (67/116)	87.5% (7/8)	59.7% (74/124)	71.9% (41/57)	0% (0/4)	67.2% (41/61)
2	0% (0/116)	0% (0/8)	0% (0/124)	1.8% (1/57)	0% (0/4)	1.6% (1/61)
3	0% (0/116)	12.5% (1/8)	0.8% (1/124)	0% (0/57)	0% (0/4)	0% (0/61)
***IDH1* Mutation, n/N (%)**						
R132C	69.8% (81/116)	37.5% (3/8)	67.7% (84/124)	73.7% (42/57)	75.0% (3/4)	73.8% (45/61)
R132G	12.9% (15/116)	25.0% (2/8)	13.7% (17/124)	8.8% (5/57)	25.0% (1/4)	9.8% (6/61)
R132H	0% (0/116)	0% (0/8)	0% (0/124)	3.5% (2/57)	0% (0/4)	3.3% (2/61)
R132L	15.5% (18/116)	37.5% (3/8)	16.9% (21/124)	12.3% (7/57)	0% (0/4)	11.5% (7/61)
R132S	1.7% (2/116)	0% (0/8)	1.6% (2/124)	1.8% (1/57)	0% (0/4)	1.6% (1/61)
Cholangiocarcinoma Type at Initial Diagnosis, n/N (%)						
Intrahepatic	89.7% (104/116)	87.5% (7/8)	89.5% (111/124)	94.7% (54/57)	100.0% (4/4)	95.1% (58/61)
Extrahepatic	0.9% (1/116)	0% (0/8)	0.8% (1/124)	1.8% (1/57)	0% (0/4)	1.6% (1/61)
Perihilar	3.4% (4/116)	0% (0/8)	3.2% (4/124)	0% (0/57)	0% (0/4)	0% (0/61)
Unknown	6.0% (7/116)	12.5% (1/8)	6.5% (8/124)	3.5% (2/57)	0% (0/4)	3.3% (2/61)
Extent of Disease at Baseline, n/N (%)						
Local/regional	6.9% (8/116)	12.5% (1/8)	7.3% (9/124)	8.8% (5/57)	0% (0/4)	8.2% (5/61)
Metastatic	93.1% (108/116)	87.5% (7/8)	92.7% (115/124)	91.2% (52/57)	100.0% (4/4)	91.8% (56/61)
Underlying Liver Cirrhosis at Screening, n/N (%)						
Yes	5.2% (6/116)	0% (0/8)	4.8% (6/124)	5.3% (3/57)	0% (0/4)	4.9% (3/61)
No	94.8% (110/116)	100.0% (8/8)	95.2% (118/124)	94.7% (54/57)	100.0% (4/4)	95.1% (58/61)

D. Safety and Effectiveness Results

i. Safety Results

The safety with respect to treatment with ivosidenib was addressed during the review of the NDA and is not addressed in detail in this Summary of Safety and Effectiveness Data. The evaluation of safety was based on the analysis of adverse events (AEs), clinical laboratory evaluations, physical examinations,

and vital signs. Please refer to Drugs@FDA for complete safety information on TIBSOVO® (ivosidenib).

The most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash. The most common laboratory abnormalities (≥10%) in patients with cholangiocarcinoma were hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased.

In addition, the safety findings in this study are consistent with the known safety profile of ivosidenib and no new or unexpected safety signals were identified. No adverse events were reported in connection with the bridging study used to support this PMA supplement, as the study was performed retrospectively using banked samples.

ii. Effectiveness Results

1. Concordance Results

The primary concordance analysis was conducted on 383 (187 *IDH1* mutant positive, 187 *IDH1* mutant negative, and 9 *IDH1* mutant invalid) CC samples tested by CTAs.

The point estimate of PPA and NPA between the ODxT Test and the CTAs were calculated using the CTA results as a reference for the CTA-enrolled patients (Table 10). PPA and NPA with and without invalid CDx results, were 96.1% (92.2%, 98.4%), 89.7% (84.4%, 93.7%) and 99.4% (96.9%, 100.0%), 100.0% (97.8%, 100.0%), respectively.

Table 10. Positive and Negative Percent agreements between ODxT and CTA in reference to CTA results in all patients.

	Without ODxT Test "Invalid"		**With ODxT Test "Invalid"**	
	Agreement % (n/N)	**95% CI (%)**	**Agreement % (n/N)**	**95% CI (%)**
PPA	99.4% (174/175)	96.9%, 100.0%	96.1% (174/181)	92.2%, 98.4%
NPA	100.0% (166/166)	97.8%, 100.0%	89.7% (166/185)	84.4%, 93.7%

Clinical Efficacy

The clinical effectiveness of the ODxT Test was evaluated by measuring progression-free survival (PFS) for patients with CC who tested positive for *IDH1* R132 variants by both the Clinical Trial Assay (CTA) and the

ODxT Test. Progression-free survival and hazard ratio were calculated for patients who were selected for treatment with ivosidenib.

The primary efficacy outcome measurements between treatment and control arms (including PFS, hazard ratio, and overall survival) were examined in the AG120-C-005 study, based on the evaluable ODxT Test results (confirmed positive by the ODxT Test; 172 total patients) and the study population (185 total patients) that included samples not confirmed with the ODxT Test.

The clinical efficacy (represented by PFS) determined in the CTA+/ODxT+ population (N=115 treatment vs. 57 placebo) showed a HR=0.37 with 95% CI of (0.25, 0.55), and is similar to the ODxT Test positive plus unevaluable population (N=123 treatment vs. 61 placebo; HR=0.38; 95% CI: 0.26, 0.55) and the overall CTA+ population (primary endpoint of the AG120-C-005 study) (N=124 treatment vs. 61 placebo; HR = 0.37; 95% CI: 0.25, 0.54). The NPA (Pr(ODxT-|CTA-)) is 100% when excluding ODxT Test "Invalid" results and it indicates that there are no subjects that are CTA- and ODxT+. Therefore, the drug efficacy for the ODxT+ intended use population can be estimated from the drug efficacy for CTA+/ODxT+ patients in the trial with a HR of 0.37 with a 95% CI of (0.25, 0.55).

A sensitivity analysis was performed to evaluate the impact of missing ODxT Test results on the efficacy of the drug in the ODxT intended use population.

Progression-free survival (PFS) in CTA+/ODxT+ subjects was estimated using the Kaplan-Meier method (Figure 1). PFS was significantly longer for patients treated with TIBSOVO ($p<0.0001$, log-rank test). Median survival time was 2.69 months (95% CI: 1.54, 4.24) in patients randomized to treatment with TIBSOVO vs 1.45 months (95% CI: 1.38, 1.58) for patients randomized to treatment with a placebo.

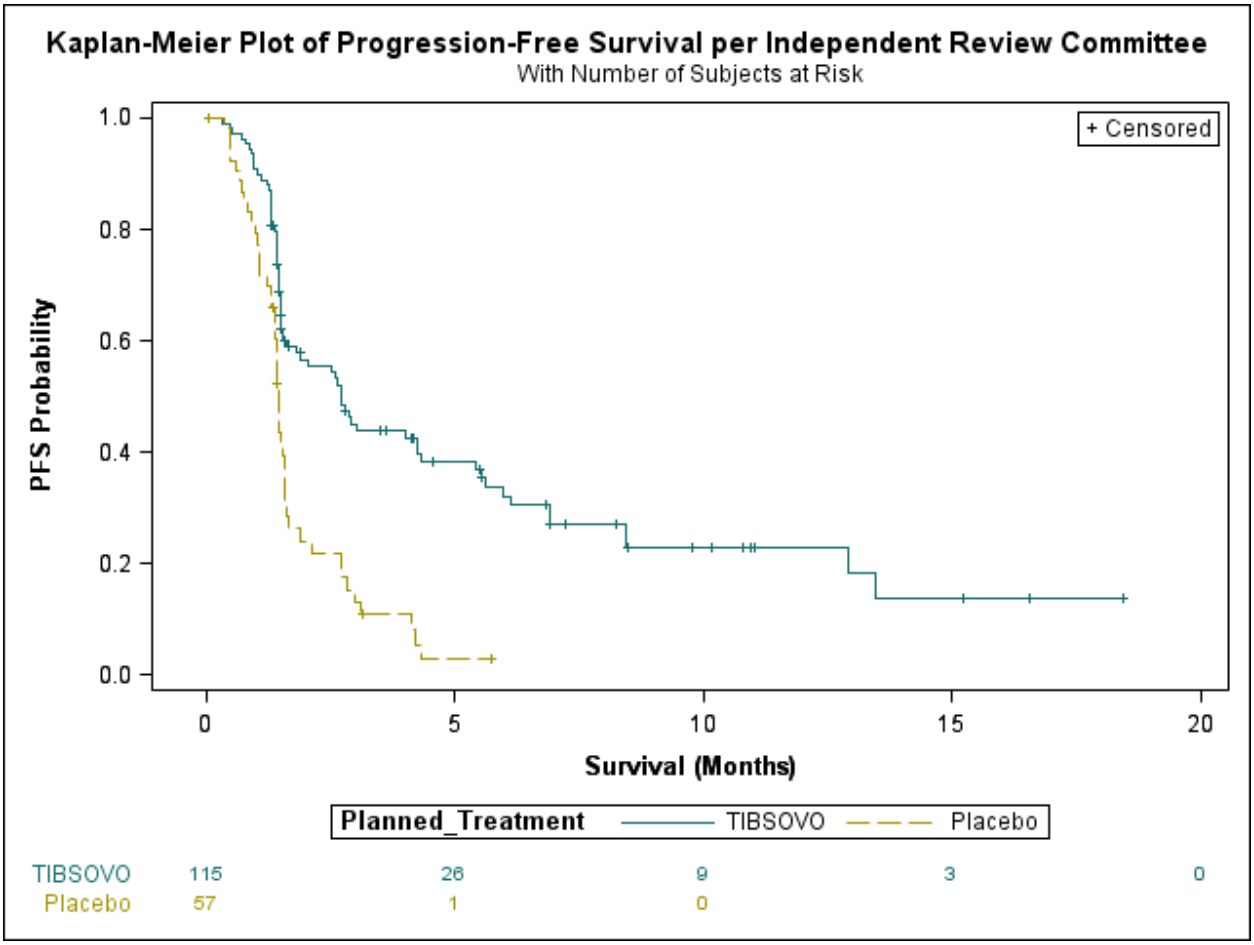

Figure 1: Kaplan-Meier Plot of PFS in CC patients treated with TIBSOVO (solid curve) vs. placebo (dashed curve).

2. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included one investigator of which one was a full-time or part-time employees of the sponsor and one investigator had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 0
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Molecular and Clinical Genetics Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For the intended use to identify *IDH1* mutations in cholangiocarcinoma patients to be treated with ivosidenib, the effectiveness of the ODxT Test was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the AG120-C-005 study. The data from the analytical validation and clinical bridging studies support the reasonable assurance of safety and effectiveness of the ODxT Test when used in accordance with the indications for use. Data from the AG120-C-005 study show that patients who had qualifying *IDH1* mutations received benefit from treatment with ivosidenib and support the addition of the CDx indication to the ODxT Test.

B. Safety Conclusions

The risks of the device are based on data collected in the analytical studies conducted to support PMA approval as described above. The ODxT Test is an in vitro diagnostic test, which involves testing of DNA and RNA extracted from FFPE tumor tissue. The analytical performance of the ODxT was demonstrated to have acceptable performance reproducibility and analytical sensitivity (limit of detection), as well as other analytical performance as discussed above in Section IX.

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in cancer treatment. Patients with false positive results may undergo treatment

with one of the therapies listed in Table 1 of the intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy.

C. Benefit-Risk Determination

Treatment of cholangiocarcinoma patients with TIBSOVO® (ivosidenib) provides a meaningful clinical benefit in patients harboring *IDH1* mutations as demonstrated in Study AG120-C-005, which was a randomized (2:1), multicenter, double-blind, placebo-controlled clinical trial of 185 adult patients with locally advanced or metastatic CC with an *IDH1* mutation. The probable benefit of the ODxT Test in identifying *IDH1* mutant cholangiocarcinoma patients for treatment with TIBSOVO® (ivosidenib) was demonstrated through a clinical bridging study, which showed a high degree of concordance between the ODxT Test and the enrolling clinical trial assays and also showed a clinically meaningful effectiveness with a hazard ratio of 0.37 (95% CI: 0.25, 0.55), compared to placebo treated controls, in patients whose disease had progressed following at least one (1) but not more than two (2) prior regimens. Given the data from the clinical bridging study and the analytical data provided in the submission, the data support the conclusion that the ODxT Test has probable benefit in selecting CC patients with *IDH1* mutations for treatment with TIBSOVO® (ivosidenib).

There is potential risk associated with the use of this device, mainly due to 1) false positives, false negatives, and failure to provide a result and 2) incorrect interpretation of test results by the user.

The risks of the ODxT Test for selection of CC patients with *IDH1* mutations are associated with the potential mismanagement of patient's treatment resulting from false results of the test. Patients who are determined to be false positive by the test may be exposed to a drug that is not beneficial and may lead to adverse events or may have delayed access to other treatments that could be more beneficial. A false negative result may prevent a patient from accessing a potentially beneficial therapeutic regimen. The risks of erroneous results are partially mitigated by the analytical performance of the device.

The likelihood of false results was assessed by analytical and clinical validation studies, which partially mitigate the probable risk of the ODxT Test device. Additional factors, including the clinical and analytical performance of the device included in this submission, have been taken into account and demonstrate that the assay is expected to have acceptable performance. However, conditions of approval are planned to address additional issues.

1. Patient Perspective

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the ODxT device, the probable benefits of the ODxT in selecting *IDH1* mutations in patients with cholangiocarcinoma for treatment with TIBSOVO® (ivosidenib), outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the clinical bridging study support the performance of the ODxT Test as an aid for the identification of *IDH1* R132C, *IDH1* R132G, *IDH1* R132L, *IDH1* R132S, and *IDH1* R132H mutations in CC patients for whom TIBSOVO® (ivosidenib) may be indicated.

XIII. CDRH DECISION

CDRH issued an approval order on August 25, 2021. The final clinical conditions of approval cited in the approval order are described below.

1. Thermo Fisher Scientific/Life Technologies Corp. must provide data from a well-designed and well-controlled interference study, whereby the effects of conjugated bile salts are tested on the assay workflow of the ODxT Test using intended use specimens carrying IDH1 mutations detected by the assay at analyte levels near LoD. The data from this study must be adequate to support that conjugated bile salts do not affect the performance of the assay.

2. Thermo Fisher Scientific/Life Technologies Corp. (TFS) must provide data to support that implementation of a new user training program (started June 2018) does not result in unacceptably high assay failures. TFS will also provide an analysis comparing the failure rate prior to and after the implementation of the new user training program by comparing:
    - the assay failure rate and quality metrics of every run performed by TFS from the date of implementation of the new training program to 9 months after the PMA approval date to
    - the assay failure rate and quality metrics prior to the implementation of the new user training program using a similar time range and a similar number of runs performed

    This analysis should show that the new user training program has reduced the number of assay failures to an acceptable value.

3. Thermo Fisher Scientific/Life Technologies Corp. will provide a final approved aggregation validation protocol for the merging of multiple assay definition files (ADF) associated with approved companion diagnostic indications and associated updates to the Torrent Suite Dx software for a final ADF and Torrent Suite Dx versions to be commercialized to support new approved indications within 60 days of approval of this PMA supplement.

4. Thermo Fisher Scientific/Life Technologies Corp. will provide results and software validation documentation from regression testing on the commercial release configuration to confirm there are no defects for the merged assay definition files based on the approved aggregation validation protocol and no new defects other than those listed in the approved Torrent Suite Dx versions within 6 months of approval of this PMA supplement.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.