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 7335 Executive Way Frederick, MD 21704
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P160045/S029
Date of FDA Notice of Approval:	09/15/2021

The original PMA (P160045) Oncomine™ Dx Target (ODxT) Test was approved on June 22, 2017 for the detection of genetic alterations in patients who may benefit from one of three FDA-approved therapies for non-small cell lung cancer (NSCLC).

Subsequently, additional PMA supplements were approved for expanding the indications for use of ODxT Test for detecting RET fusions in tumors from NSCLC patients for a fourth therapeutic indication and for the identification of *IDH1* single nucleotide variants (SNVs) in cholangiocarcinoma (CC) patients since its original approval. The SSEDs to support 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 Epidermal Growth Factor Receptor (*EGFR)* exon 20 insertions in NSCLC patients who may benefit from the targeted drug therapy, EXKIVITY™ (mobocertinib).

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), insertions, and deletions in 23 genes from DNA and fusions in ROS1 and in RET from RNA isolated from formalin-fixed, paraffin-embedded (FFPE) tumor samples from patients with non-small cell lung cancer (NSCLC), and *IDH1* SNVs from FFPE

tumor tissue samples from patients with cholangiocarcinoma using the Ion PGM™ Dx System.

The test is indicated as a companion diagnostic to aid in selecting NSCLC and cholangiocarcinoma 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
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)
	EGFR	**EGFR exon 20 insertions**	**EXKIVITY™ (mobocertinib)**
Cholangiocarcinoma	*IDH1*	IDH1 R132C, R132G, R132L, R132S, and 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 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 Test 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 [isolated from NSCLC and cholangiocarcinoma formalin-fixed, paraffin-embedded (FFPE) tumor specimens] and RNA isolated from NSCLC FFPE tumor specimens.

The ODxT Test consists of the following:

Oncomine™ Dx Target Test and Controls Kit (Combo Kit):

- Oncomine™ Dx Target Test DNA and RNA Panel Kit
- Oncomine™ Dx Target DNA Control Kit
- Oncomine™ Dx Target RNA Control Kit
- 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-Well Plate 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 MgCl2.

Library Preparation workflow:
The process begins with polymerase chain reaction (PCR) and uses the Oncomine™ Dx Target 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 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), insertions, 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 FDA approved companion diagnostic (CDx) alternatives for the detection of some of the genetic alterations using FFPE tumor specimens, to those that are listed in Table 1 of the ODxT Test intended use statement. These approved alternative CDx tests

are listed in the Table 3 below. 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.

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

Gene and Variant	Therapy	Company and Device (PMA #)
BRAF V600E	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)	Foundation Medicine, Inc. – FoundationOne CDx™ (F1CDx) (P170019)
EGFR L858R and Exon 19 deletions	IRESSA® (gefitinib)	QIAGEN – *therascreen*® *EGFR* RGQ PCR Kit (P120022/S001)
		Foundation Medicine, Inc. – F1CDx (P170019)
		Roche – cobas® *EGFR* Mutation Test v2 (P120019/S019)

There is no FDA approved CDx alternative using tumor tissue specimens for the detection of *EGFR* exon 20 insertions for the identification of NSCLC patients eligible for treatment with EXKIVITY™ (mobocertinib). However, there is an FDA approved CDx alternative for the detection of *EGFR* exon 20 insertions in NSCLC patients using cfDNA isolated from plasma for treatment with RYBREVANT™ (amivantamab-vmjw) (See SSED for P200010/S001).

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 expansion to the indications for use of the Oncomine™ Dx Target Test described above in Section II is not currently approved and have not been 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.

- Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect ODxT Test results and subsequently, may lead to improper patient management decisions in NSCLC 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 clinical studies used to support this PMA 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 *EGFR* exon 20 insertions 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), limit of blank (LoB), DNA input, interference, guardbanding, and stability of assay intermediates were conducted to support the indication for *EGFR* exon 20 insertions.

1. Analytical Accuracy/Concordance

Concordance studies to support robust detection of SNVs and deletions by the ODxT Test was previously conducted using two externally validated comparator methods (See Section IX.A.1. in the Summary of Safety and Effectiveness for P160045).

An analytical accuracy study was performed to demonstrate the concordance between the ODxT Test and an externally validated next generation sequencing (NGS) assay (evNGS) for the detection of *EGFR* exon 20 insertions in NSCLC. There are 124 [114 from prior platinum treated group (PP group, efficacy population) and 10 samples from non-prior platinum treated group (Non-PP group)] *EGFR* exon 20 insertion-positive samples from the AP32788-15-101 trial. Of these, 12 samples from PP-group and 2 samples from Non-PP group were missing and were excluded from analysis, leaving 110 *EGFR* exon 20 insertion-positive samples (please see Section X.A. for study details). One hundred twenty *EGFR* exon 20 insertion mutation-negative stage-matched commercially sourced NSCLC samples were screened by enrolling local laboratory tests, PCR (cobas® *EGFR* Mutation Test v2) or and NGS-based sequencing assay (FoundationOne CDx, F1CDx). Of these, 8 samples failed the screening and were excluded from the analysis, leaving 112 *EGFR* exon 20 insertion mutation-negative commercially sourced NSCLC samples for analysis.

The concordance between ODxT Test and the ev-NGS assay was calculated (Table 4). A summary of positive percent agreement (PPA) and negative percent agreement (NPA) in reference to evNGS assay and corresponding 95% two-sided exact confidence intervals (CIs) is provided in Table 5, below. The point estimates of PPA and NPA excluding unknown [e.g. invalid or no call ODxT Test result or samples for which there was insufficient material (slides or DNA)] were all 100.0%, and when including ODxT Test Unknown results, the point estimates of PPA and NPA were 98.2% and 90.5%, respectively (Table 5). Ten samples that were negative by the Ev-NGS were called Unknowns (six invalids and 4 no calls) by the ODxT Test.

Table 4. Concordance Between ODxT Test and ev-NGS Assay for *EGFR* exon 20 insertion detection

ODxT Test	**Ev-NGS Assay**			
	Positive	**Negative**	**Unknown**	**Total**
Positive	54	0	9	63
Negative	0	95	6	101
Unknown	1	10	47	58
Total	55	105	62	222

Table 5. Positive and Negative Percent agreements between ODxT Test and ev-NGS Assay

	Without ODxT Test "Unknown"		**With ODxT Test "Unknown"**	
	Agreement % (n/N)	**95% CI (%)**	**Agreement % (n/N)**	**95% CI**
PPA	100.0% (54/54)	(93.4% - 100%)	98.2% (54/55)	(90.3% - 100%)
NPA	100.0% (95/95)	(96.2% - 100%)	90.5% (95/105)	(83.2% - 95.3%)

2. Analytical Sensitivity

a. Limit of Blank (LoB)

To assess the performance of the ODxT Test in the absence of template and to ensure that a variant-free ("blank") sample does not generate an analytical signal that might be classified as an *EGFR* exon 20 insertion, four wild-type NSCLC FFPE samples were evaluated. For each clinical sample, total of 36 library replicates were made using two lots, which is 18 library replicates per reagent lot. The study samples were divided between two operators and each operator made 72 libraries. A total of 24 runs were performed between two operators and two reagent lots. There were no positive calls at any of the variant locations analyzed by the test. The false positive rate was therefore 0%, and the limit of blank (LoB) of the test is zero. See Section IX.A.2a of

Summary of Safety and Effectiveness Data for P160045 for additional analytical sensitivity data.

b. Limit of Detection (LoD)

The LoD studies evaluated two representative insertion lengths of *EGFR* exon 20 insertion (6 bp and 9 bp) positive specimens. Six different dilution levels (AFs) per representative FFPE clinical sample were tested. Each level was tested with 10 replicates per sample for each of the two reagent lots for a total of 20 replicates per level.

The claimed LoD based on empirical hit rate approach for *EGFR* exon 20 insertions used in this study are noted in Table 6 below. The LoD results for selected *EGFR* exon 20 insertions varied from 4.8-5.2% AF. LoDs were confirmed for *EGFR* exon 20 insertions by testing NSCLC samples near the established LoD and at ~2-3x LoD in the Precision Study (See Section IX.A.4).

Table 6: Established LoDs for *EGFR* exon 20 insertions in NSCLC clinical samples

COSMIC ID	Insertion Size (bp)	Insertion type	LoD Estimates (%AF)
COSM1238028	6	His773_Val774insAH	4.8
COSM12376	9	Ala767_Val769dup	5.2

Given that not all representative *EGFR* exon 20 insertion mutations that had a high prevalence in the clinical study were evaluated in the LoD study, a post-market study is planned with additional samples harboring 3 bp and 12 bp *EGFR* exon 20 insertions (see section XIII).

See Section IX.A.2b of Summary of Safety and Effectiveness Data for P160045 for additional analytical sensitivity data.

c. DNA Input

This study was conducted to determine the the lowest amount of DNA required for the ODxT Test to detect *EGFR* exon 20 insertion variants. In this study, two FFPE clinical samples containing *EGFR* exon 20 insertion variants (6 bp and 9 bp) were blended with wildtype genomic DNA to create sample blends for each variant. Each sample blend was diluted to 5ng/µl and five DNA input levels ranging from three levels below the standard of 10 ng (5 ng, 6.5 ng, and 8.5 ng), the standard input (10 ng), and one level (15 ng) above the standard input were tested. A total of 96 DNA libraries, including the controls, were made, and a single reagent lot was used. The variants present in all FFPE DNA sample blends tested were called correctly 100% of the time across all DNA test combinations, including the 10 ng required input. The study confirmed the DNA input requirement of 10 ng as specified in the ODxT Test User Guide.

See Section IX.A.2.c. of Summary of Safety and Effectiveness Data for P160045 for additional DNA input data.

3. Analytical Specificity

Inclusivity/Cross-Reactivity

An *in silico* cross-reactivity analysis was performed to evaluate the specificity of the primers in the ODxT Test Kit panels. The primers were cheked for specificity to the human genome, human transcriptome, and representative bacterial, fungal, and viral genomes. All nucleic acid sequences in the ODxT Test, which includes those of the primers in the DNA and RNA panel, were analyzed for homology to non-target regions by comparing the nucleic acid sequence against the appropriate reference sequence using Basic Local Alignment Search Tool (BLAST) and Bowtie alignment tools. Reference sequences were obtained from the human, fungal, bacterial and viral genome or transcript databases, as applicable for DNA or RNA primers, from National Center for Biotechnology Information (NCBI). The *in silico* assessment occurred in two steps: 1) identification of secondary primer binding loci that could potentially generate a secondary amplification product and 2) evaluation of secondary amplification product for likelihood of producing false positive calls. Results from this study showed that there were primer pairs with homology to the reference sequence which produced unintended amplicons. However, the amplicons were significantly different from the intended sequence and therefore non-reportable/detectable. The study demonstrated that the primers are specific for the detection of intended targeted sequences, including *EGFR* exon 20 insertions.

4. Interference

To evaluate the potential impact of endogenous (hemoglobin and necrosis) and exogenous interferents (paraffin, xylene, ethanol, proteinase K, and wash buffer) to call *EGFR* exon 20 insertion variants, two *EGFR* exon 20 insertion positive samples 6 bp and 9 bp and one wild-type FFPE sample were tested in duplicates. The impact of potentially interfering substances on assay performance was evaluated, and the results were compared to the control (no interferents) condition. See Section IX.A.4. of Summary of Safety and Effectiveness Data for P160045 for additional interference studies.

a. Endogenous Interference

A review of clinical samples harboring variants detected by the ODxT Test, including *EGFR* exon 20 insertions in the presence of hemoglobin at 4 mg/mL did not appear to interfere with the assay. The concordance with the control condition (with no calls being excluded) across all samples, for all *EGFR* exon 20 insertions tested were calculated to be 100%. These data demonstrate that hemoglobin does not adversely impact the performance of the ODxT Test. However, the study was not performed using samples under challenging conditions (near 1-1.5x LoD), and therefore, a post-market

study is planned with NSCLC samples harboring *EGFR* exon 20 insertions near LoD (see section XIII).

To evaluate the potential impact of tumor necrosis on *EGFR* exon 20 insertion mutation variant calling, analysis based on tumor content (0-30%, 30-40%, 40-60%, and 60-100%) was performed. Since the 95% confidence intervals of the PPA and NPA overlapped between the tumor content levels, the performance of the ODxT Test was considered to be similar across tumor content levels. However, since *EGFR* exon 20 insertion positive variants without necrosis were not compared to NSCLC samples with necrosis, a post-market study is planned with NSCLC samples near LoD, harboring *EGFR* exon 20 insertions (see section XIII).

b. Exogenous Interference

In the study with exogenous interferents (paraffin, xylene, ethanol, proteinase K, and wash buffer), the concordance with the control condition across all samples and interferents for all *EGFR* exon 20 insertions tested were calculated to be 100%. These data demonstrate that the interfering substances do not impact the performance of the ODxT Test at the interferent levels tested.

5. Precision and Reproducibility

a. External Panel Reproducibility Study (Assay Reproducibility)

An external reproducibility and repeatability study was conducted across 3 sites with 2 operators per site, 3 lots of the ODxT Test controls, no template control Kits, IVD Ion PGM Dx Library Kits, OneTouch Dx Template Kits, Ion PGM Dx Sequencing Kits and Dx Chip Kits used at each site using two wild-type and two *EGFR* exon 20 insertion positive NSCLC FFPE clinical samples . The two *EGFR* variant positive samples were blended with wild-type sample DNA to target near LoD AFs (0.9x-1.3x and 1.5x-3x). However, the observed LoDs were 1.1x-2.4x and 2.09-2.2x. The positive call rates, negative call rates and within-run repeatability, both including and excluding no calls, at two *EGFR* exon 20 variant locations for all samples are outlined in Table 7. The positive and negative call rates for the expected variant excluding no calls was 100% and 0%; while the positive call rates for the expected variant including no calls was 98.6% (with a 95% confidence interval of 92.5-100%) for sample blend 1 (COSM1238028) and 100% (with a 95% confidence interval of 95-100%) for sample blend 2 (COSM12376), the negative call rates for the expected variant including no calls was 0% for both the sample blends . For the no call made in COSM1238028, the observed AF (0.033) was below the LoD.

Table 7: Call Rates: Reproducibility and Repeatability

Sample	Variant	Insertion size	# of negative calls (B)	# of positive calls (A)	# of No calls (C)	# of valid calls (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 (A/N)	Excluding No Calls [A/(A+B)]	Including No Calls (A/N)	Excluding No Calls [A/(A+B)]
D1	COSM1238028	6 bp	0	71	1	72	98.6% (92.5%, 100%)	100% (94.9%, 100%)	0% (0%, 5%)	0% (0%, 5.1%)	100% (73.5%, 100%)	100% (73.5%, 100%)
D2	COSM12376	9 bp	0	72	0	72	100% (95.0%, 100%)	100% (95.0%, 100%)	0% (0%, 5%)	0% (0%, 5%)	100% (73.5%, 100%)	100% (73.5%, 100%)
D4	COSM1238028	6 bp	0	72	0	72	100% (95.0%, 100%)	100% (95.0%, 100%)	0% (0%, 5%)	0% (0%, 5%)	100% (73.5%, 100%)	100% (73.5%, 100%)
D5	COSM12376	9 bp	0	72	0	72	100% (95.0%, 100%)	100% (95.0%, 100%)	0% (0%, 5%)	0% (0%, 5.1%)	100% (73.5%, 100%)	100% (73.5%, 100%)

Repeatability for the detection of *EGFR* exon 20 insertion variants was estimated with respect to positive variant locations for within-run, between-system, between-operator, between-site, between-lot and total variability. When including or excluding No Calls from the assay reproducibility study data, the within-run repeatability was 100%.

When the variance components were assessed, the within-run component had the greatest contribution to the total variability, up to 15.3% coefficient of variation (CV, Table 8).

Table 8: Variance Component Analysis

Sample	Variant	Insertion size	Mean AF range	N	Within-run		Between-system		Between-operator		Between-site		Between-lot		Total	
					SD	CV	SD	CV	SD	CV	SD	CV	SD	CV	SD	CV
D1	COSM1238028	6 bp	0.0535	72	0.00821	15.3%	0.00159	3%	0.00278	5.2%	0.0013	2.4%	0.00	0%	0.0891	16.7%
D2	COSM12376	9 bp	0.1274	72	0.01568	12.3%	0.000	0%	0.00	0%	0.00	0%	0.0012	0.9%	0.01572	12.3%
D4	COSM1238028	6 bp	0.1062	72	0.00980	9.2%	0.00434	4.1%	0.00318	3.0%	0.00	0%	0.00439	4.1%	0.01201	11.3%
D5	COSM12376	9 bp	0.1091	72	0.01555	14.3%	0.000	0%	0.00	0%	0.00	0%	0.00327	3.0%	0.01589	14.6%

The external sample reproducibility and within-run repeatability studies for COSM12376 (D2) was not performed under challenging conditions [the mean AF range was 12.74% (2.45 x LoD)]. Therefore, a post-market study is planned with additional samples near LoD (see section XIII).

b. External Sample Processing Reproducibility

Two (2) wild-type samples and two *EGFR* exon 20 insertion positive samples 6 bp and 9bp were evaluated at three US testing sites, each with two Ion PGM™ Dx Systems and one operator, to determine the reproducibility

and repeatability of sample processing. Each sample was tested 6 times at each site, for a total of 18 replicates per sample, 36 data points across two *EGFR* exon 20 insertion positive samples, and 36 data points across two wild-type (WT) samples at each site.. The call rate, no call rate, positive call rate, negative call rate, and within-run repeatability were computed at each variant location of interest. The positive call rate for the *EGFR* exon 20 insertion positive samples is 100%, and for the *EGFR* exon 20 insertion-negative variants is 0%. The within run repeatability was 100% for all samples at all *EGFR* insertion variant loci. Since the external sample reproducibility and within-run repeatability studies did not include sufficient replicates and was not performed under challenging conditions (near 1-1.5x LoD), a post-market study is planned with additional replicates/sample near LoD (see section XIII).

6. Guard Band Studies

The repeated studies consisted of 11 critical assay steps of the workflow from target amplification to library elution using samples to impact assay performance, which included variations in DNA control volume, DNA panel volume, HiFi mix volume, FuPa reagent volume, switch solution volume, barcode adapter volume, incubation time, bubble formation after adding AMPure, residual ethanol, thermal cycling temperature offset, and ES final volume titration. The study was conducted as previously described in Section IX. A.9.a. of the P160045 SSED. To evaluate the workflow tolerances, a DNA blend containing *EGFR* exon 20 insertion variant (9 bp) was used as the input material. Additional test conditions were added to narrow the acceptable tolerance range based on results. The ODxT Test did not tolerate a 2.5 µL residual ethanol volume, therefore, a narrower residual ethanol volume of 1.75 µL was tested for acceptability.

No significant differences between the high and low conditions, relative to the standard operating procedure (SOP), were observed. The AF was not significantly different from the AF observed when testing using the SOP condition, and no statistically significant difference in percent AF was observed in any resulting *EGFR* exon 20 insertion data.

7. Stability of Assay Intermediates Studies

The workflow for the ODxT Test incorporates several optional stopping points to hold partially completed reactions (or assay intermediates). The stability of the intermediate products was evaluated by incorporating all of the pre-defined hold times specified in the User Guide. Two unique *EGFR* exon 20 insertion variants (3bp and 12bp) were included in this study. Each sample was tested under three different test conditions (Table 9 below).

Table 9. Designated hold time test conditions

Condtion	Eluted Library Hold Time
A) Nomial Hold[1]	No hold
B) Library Hold	30 day hold 3 month hold
C) Combo Hold[2]	No hold
[1] Libraries prepared for condition A were used to test condition B [2] Includes steps 1-2, and steps 4-9 (refer to the ODxT Test user guide)	

For each hold condition investigated in this study, the relative percentage change in mean DNA variant AF from the corresponding mean AF at the nominal condition were used as metrics to evaluate stability. The study results support the conclusion that the 30-day library hold and combo hold conditions did not result in a decrease in ODxT Test performance relative to the nominal test condition.

8. Cross-Contamination

Please refer to the Summary of Safety and Effectiveness Data of P160045 (Section IX.C) for platform-level carryover/cross-contamination data for ODxT Test.

9. Reagent Lot Interchangeability

Please refer to the Summary of Safety and Effectiveness Data of P160045 (Section X.D) for platform-level reagent lot interchangeability data for ODxT Test.

10. Stability

Please refer to the Summary of Safety and Effectiveness Data of P160045 (Section X) for platform-level stability data including reagent shelf-life stability, in-use stability, stored slide stability, store block stability, and transport stability data for ODxT Test. An expansion of shelf-life claim of the ODxT Test from 9 to 23 months was approved (P160045/S021). However, the studies for expansion of shelf-life claim tested only SNVs and deletions. Therefore, additional shelf-life stability studies using *EGFR* exon 20 insertions or similar insertions will be completed as conditions of approval (see section XIII).

B. Animal Studies

Not Applicable

C. Additional Studies

Not Applicable

X. SUMMARY OF PRIMARY CLINICAL STUDIES

Life Technologies conducted a clinical bridging study to establish the reasonable assurance of safety and effectiveness of the ODxT Test for detection of *EGFR* exon 20 insertions in NSCLC FFPE tumor specimens to select patients for treatment with EXKIVITY™ (mobocertinib) in the US. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. ODxT Test Clinical Bridging Study for *EGFR* exon 20 insertions

The safety and effectiveness of the ODxT Test for detecting *EGFR* exon 20 insertions in NSCLC patients who may benefit from treatment with mobocertinib was demonstrated in a retrospective analysis of samples from patients enrolled in Takeda AP32788-15-101 trial (NCT02716116). A bridging study was conducted to evaluate the concordance between *EGFR* exon 20 insertions tested with the local laboratory tests (LLTs) and the ODxT Test in the intent-to-test population and to assess the clinical efficacy of the ODxT Test in identifying patients positive for *EGFR* exon 20 insertions for treatment with mobocertinib. Retrospective testing with the ODxT Test was done for *EGFR* exon 20 insertion positive samples from patients enrolled in Takeda AP32788-15-101 trial and with stage-matched commercially sourced *EGFR* exon 20 insertion negative NSCLC samples, that were screened with representative LLTs.

For the bridging study analysis, the retrospective testing population consisted of 222 samples [110 samples positive for *EGFR* exon 20 insertions (102 samples from prior platinum treated group and 8 samples from non-prior platinum treated group as shown in Figure 1), and 112 commercially sourced *EGFR* exon 20 insertion-negative samples (120 LLT negatives out of which eight were LLT screen fail samples; Figure 1)].

1. Therapeutic Study Design

Takeda AP32788-15-101 (NCT02716116) trial is a prospectively designed, international, open-label, multicohort clinical trial in adult patients with *EGFR* exon 20 insertion mutation-positive locally advanced or metastatic NSCLC whose disease had progressed on or after platinum-based chemotherapy. The major efficacy outcome measure was overall response rate (ORR) as assessed by a blinded independent central review (BICR) assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine the effectiveness of mobocertinib in NSCLC patients. Additional efficacy outcome measures included duration of response (DOR) by BICR. Patients were enrolled into multiple parts of the study, out of which the bridging study was focused on the *EGFR* exon 20 insertion mutation-positive patients who were previously treated with platinum-based chemotherapy (Parts 1-3, primary efficacy population). Patients were screened for *EGFR* exon 20 insertion mutation-positive status using LLTs for enrollment. The left-over tissue after the initial screening, was stored for retrospective testing. This clinical study was used to support the approval of EXKIVITY™ (mobocertinib) under NDA 215310.

2. ODxT Test Clinical Bridging Study

The aim of the bridging study was to determine the concordance between *EGFR* exon 20 insertion results from the enrolling LLTs generated at the time of patient

screening for AP32788-15-101 study and the results of *EGFR* exon 20 insertions using the ODxT Test. The study was also conducted to establish the clinical validity of the ODxT Test in identifying patients positive for *EGFR* exon 20 insertions for treatment with mobocertinib. Retrospective testing with the ODxT Test was performed for 110 *EGFR* exon 20 insertion mutation-positive patients from Parts 1-3 of AP32788-15-101 study (102 samples from prior platinum treated group and 8 samples from non-prior platinum treated group) and commercially procured *EGFR* exon 20 insertion mutation-negative NSCLC samples (n = 112, 120 LLT negatives, out of which eight were LLT screen fail samples) that were screened by representative LLTs used for patient selection. Concordance between the ODxT Test and the LLTs was demonstrated with the companion diagnostic (CDx)-evaluable patient population from the AP32788-15-101 trial that produced valid ODxT Test results. Clinical validity of the ODxT Test was evaluated by estimation of clinical efficacy in the LLT-enrolled *EGFR* exon 20 insertion mutation-positive patient population as assessed by the primary objective of ORR by BICR. Baseline demographic and disease characteristics were compared between the CDx-evaluable and CDx-unevaluable populations within all enrolled LLT-positive patients. All the covariates were well balanced between the two groups of patients (See Section X.B below).

3. <u>Acountability of PMA Cohort</u>

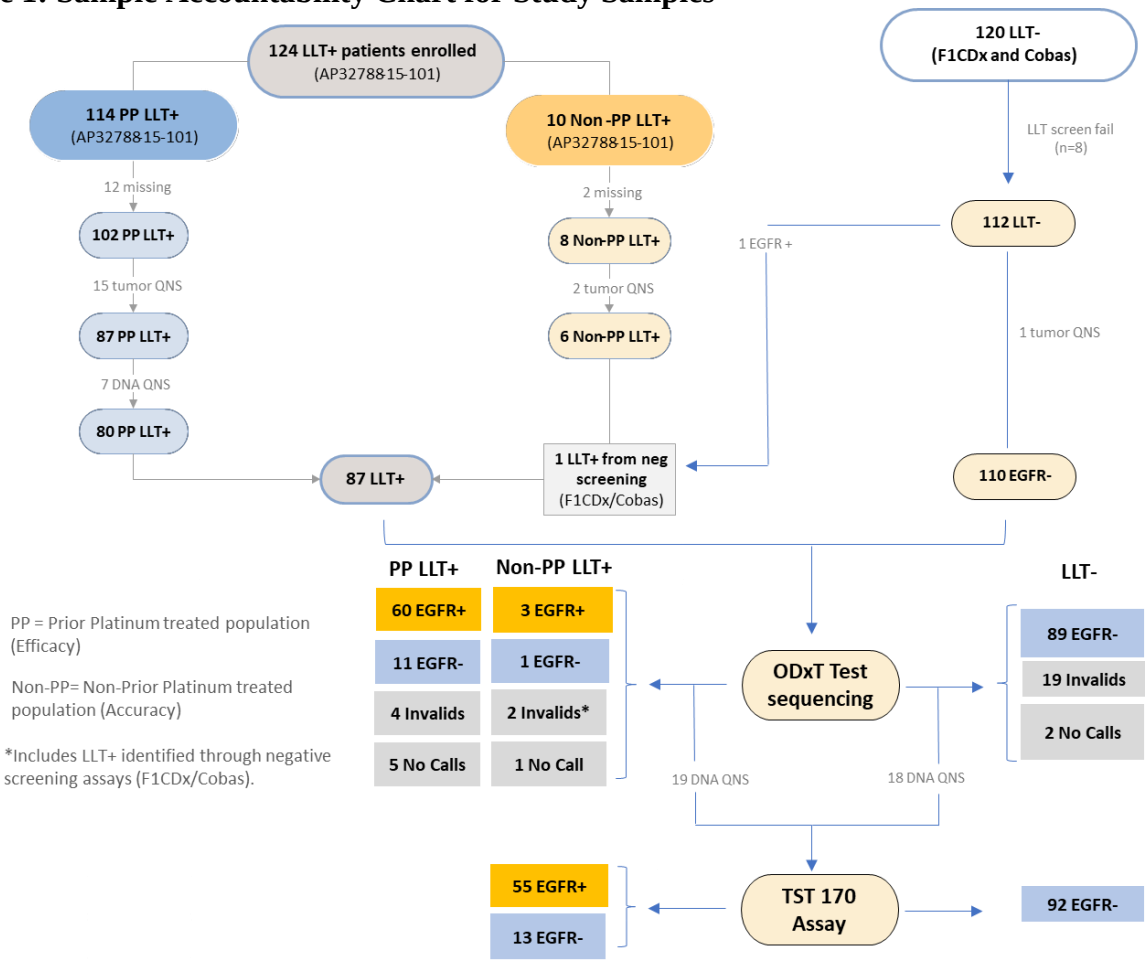
As shown in Figure 1, below, a total of, 244 samples were evaluated in the study; 124 *EGFR* exon 20 insertion-positive samples and 120 EGFR exon20 insertion-mutation-negative samples.

The 124 EGFR exon 20 insertion-positive samples were acquired from local laboratory test (LLT)-positive patients enrolled in the the AP32788-15-101 trial (Parts 1-3): 114 from the prior platinum (PP) treated group (efficacy population) and 10 samples from the non-prior platinum (Non-PP) treated group. Of these, 12 samples from the PP treated group and 2 samples from non-PP treated group were missing and excluded from the study, leaving 110 *EGFR* exon 20 insertion-positive samples (102 from the PP group and 8 from the Non-PP group) available for testing by the ODxT Test. Prior to sequencing, 17 samples (15 from the PP group and 2 from the Non-PP group) were cancelled due to failure to meet the tumor content cutoff, and 7 samples from the PP group failed the DNA concentration cutoff, leaving 86 LLT positive patient samples (80 from the PP efficacy group and 6 from the Non-PP group). Of the 87 *EGFR* exon 20 insertion-positive samples (86 LLT-positive and 1 from the LLT- screened *EGFR* exon 20 insertion mutation-negative sample set, described below), 63 samples (60 from PP efficacy group, two from Non-PP group, and one from LLT- group) were called positive by the ODxT Test, 12 samples (11 from PP efficacy group and 1 from Non-PP group) were called negative, 6 samples (four from PP efficacy group and two from Non-PP group) yielded an invalid result, and 6 samples (five from PP efficacy group and one from Non-PP group) generated “No Calls.”

One hundred and twenty *EGFR* exon 20 insertion-negative stage-matched commercially sourced NSCLC samples were screened by an enrolling PCR LLT

(cobas® EGFR Mutation Test v2) or an NGS-based sequencing LLT (FoundationOne CDx, F1CDx). Of these, 8 samples failed screening and were excluded from the analysis, 1 was *EGFR* exon 20 insertion-positive, and 1 was canceled due to insufficient tumor content, leaving 110 *EGFR* exon 20 insertion-negative commercially sourced NSCLC samples available for testing by the ODxT Test. Of the 110 *EGFR* mutation-negative samples, 89 samples were called negative by the ODxT Test, 19 samples yielded an invalid result, and 2 samples generated "No Calls."

Figure 1: Sample Accountability Chart for Study Samples



4. Study Population Demographics and Baseline Parameters

The demographics, disease characteristics, and specimen characteristics for the CDx evaluable and CDx unevaluable patients were assessed and these characteristics were not statistically significant between the CDx evaluable and unevaluable subgroups (Table 10).

Table 10: Patient demographics, Disease and Sample Characteristics for LLT Positive Prior Platinum Subjects: CDx Evaluable vs CDx Unevaluable

Characteristics		CDx Evaluable	CDx Unevaluable	*p*-value	LLT+
Subject	**(N)**	71	31		102
Age	**Years**	60 ± 12 61* [27, 80]	59 ± 10 59* [34, 76]	0.762	59 ± 12 60* [27, 80]
Gender	**Female**	43 (60.6%)	22 (71.0%)	0.3148	65 (63.7%)
	Male	28 (39.4%)	9 (29.0%)		37 (36.3%)
Race	**Asian**	44 (62%)	20 (64.5%)	0.4106	64 (62.7%)
	Black	3 (4.2%)	0 (0%)		3 (2.9%)
	White	24 (33.8%)	10 (32.3%)		34 (33.3%)
	Unknown	0 (0%)	1 (3.2%)		1 (10%)
Ethnicity	**Hispanic/ Latino**	1 (1.4%)	0 (0%)	1.0000	1 (1.0%)
	Not Hispanic/ Latino	70 (98.6%)	31 (100.0%)		101 (99.0%)
Stage at Study Entry	**IIIB**	1 (1.4%)	0 (0%)	1.0000	1 (1%)
	IV	70 (98.6%)	31 (100%)		101 (99%)
LLT Sample	**Plasma**	4 (5.6%)	3 (9.7%)	0.5301	7 (6.9%)
	Tissue	64 (90.1%)	28 (90.3%)		92 (90.2%)
	Unknown	3 (4.2%)	0 (0%)		3 (4.2%)
LLT Assay Type	**Sequencing**	35 (49.3%	12 (38.7%)	0.5740	47 (46.1%)
	PCR	16 (22.5%)	8 (25.8%)		24 (23.5%)
	Other	18 (25.4%)	11 (35.5%)		29 (28.4%)
		* Mean ± SD (N), Median [Min, Max]			

Sample characteristics for the commercially sourced NSCLC samples were not statistically significant between the CDx evaluable and CDx unevaluable with the exception of race (Table 11).

Table 11: Patient demographics, Disease and Sample Characteristics for LLT Negative Subjects: CDx Evaluable vs CDx Unevaluable

Characteristics		CDx Evaluable	CDx Unevaluable	*p*-value	LLT-
Subje	**(N)**	89	23		112
Age	**Years**	64 ± 10 (87) 64 [40, 85]	63 ± 12 (23) 64 [33, 84]	**0.4589**	64 ± 10 (110) 64 [33, 85]
Sex	**Female**	35 (39.3%)	10 (43.5%)	**0.8832**	65 (58.0%)
	Male	52 (58.4%)	13 (56.5%)		65 (58.0%)
	Unknown	2 (2.2%)	0 (0%)		2 (1.8%)
Race	**Asian**	30 (33.7%)	7 (30.4%)	**0.0002**	37 (33.0%)
	Black	6 (6.7%)	1 (4.3%)		7 (6.3%)
	White	40 (44.9%)	8 (34.8%)		48 (42.9%)
	Hispanic/Latino	1 (1.1%)	7 (30.4%)		8 (7.1%)
	Unknown	12 (13.5%)	0 (0%)		12 (10.7%)
Stage	**IA**	14 (15.7%)	3 (13.0%)	**0.7903**	17 (15.2%)
	IB	13 (14.6%)	5 (21.7%)		18 (16.1%)
	IIA	9 (10.1%)	2 (8.7%)		11 (9.6%)
	IIB	8 (9.0%)	3 (13.0%)		11 (9.6%)
	IIIA	32 (36.0%)	6 (26.1%)		38 (33.9%)
	IIIB	5 (5.6%)	3 (13.0%)		8 (7.1%)
	IV	3 (3.4%)	0 (0%)		3 (2.7%)
	IVA	3 (3.4%)	0 (0%)		3 (2.7%)
	Unknown	2 (2.2%)	1 (4.3%)		3 (2.7%)
LLT Assay Type	**PCR**	32 (36.0%)	9 (39.1%)	**0.7781**	41 (36.6%)
	Sequencing	57 (64.0%)	14 (60.9%)		71 (63.4%)

Continuous variables summarized: Mean +/- SD (N), Median [Min, Max]. p-value for continuous variables from t-test or Wilcoxon Rank Sum Test, as appropriate.
Categorical variables summarized: Proportion (n/N). p-value for categorical variables from Chisquare or Fisher's exact test, as appropriate.

B. Safety and Effectiveness Results

1. Safety Results

The safety with respect to treatment with mobocertinib 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 EXKIVITY™ (mobocertinib).

The most common adverse reactions were QTc Prolongation and Torsades de Pointes, Interstitial Lung Disease/Pneumonitis, Cardiac Failure, and Diarrhea. In addition, the safety findings in this study are consistent with the known safety profile of mobocertinib 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.

2. Effectiveness Results

a. Concordance Results

The primary concordance analysis was conducted on 222 [110 *EGFR* exon 20 insertion mutation-positive patients (102 samples from PP efficacy group and eight samples from Non-PP group), and 112 *EGFR* exon 20 insertion mutation-negative stage-matched commercially sourced NSCLC samples (120 samples of which eight were LLT screen fail samples)] that had both LLT and ODxT Test results. Agreement between the ODxT Test and the LLTs was calculated (Table 12). The point estimates of PPA between the ODxT Test (CDx) and the LLTs with and without invalid CDx results, using the LLT results as a reference for the LLT-enrolled patients (Table 13), were 84.0% (73.7% - 91.4%) and 57.3% (47.5% - 66.7%), respectively. The CDx unknown in the following tables includes: invalid CDx results, No calls, and no CDx results due to insufficient material available to run using the CDx.

Table 12. Concordance Between ODxT Test and LLT Results

	LLT		
ODxT Test	**Positive**	**Negative**	**Total**
CDx+	63[a]	0	63
CDx-	12[b]	89	101
CDx Unknown	35[c]	23[d]	58
Total	110	112	222

a: 60 from PP group, 2 from Non-PP group, and 1 from LLT- group (see Fig. 1)
b: 11 from PP group, 1 from Non-PP group (see Fig. 1)
c: 15 tumor QNS (PP) + 2 tumor QNS (Non-PP) + 7 DNA QNS (PP) + 5 Invalids (1 Invalid comes from the LLT- screen) + 6 No Calls [31 from PP-group, 4 from Non-PP group (see Fig. 1)]
d: 1 LLT- excluded/UNK due to positive screening result + 1 LLT tumor QNS + 19 Invalids + 2 No Calls (see Fig. 1)

Table 13. Positive and Negative Percent Agreements Between CDx and LLT

	Without CDx "Unknown"		With CDx "Unknown"	
	Agreement % (n/N)	**95% CI (%)**	**Agreement % (n/N)**	**95% CI**
PPA	84.0% (63/75)	(73.7% - 91.4%)	57.3% (63/110)	(47.5% - 66.7%)
NPA	100% (89/89)	(95.9% - 100%)	79.5% (89/112)	(70.8% - 86.5%)

b. Clinical Efficacy Results In The AP32788-15-101 *EGFR* Exon 20 Insertion Mutation-Positive Patients Who Were Previously Treated With Platinum-Based Chemotherapy

In the AP32788-15-101 trial, the confirmed overall response rates (ORR) per BICR in the full NSCLC patients previously treated with platinum-based chemotherapy (N=114) was 28.1% (20.1% - 37.3%) with 32 patients having achieved best confirmed response (partial response). In the primary efficacy population, the BICR-assessed median DOR was 17.5 months (95% CI: 7.4, 20.3). The efficacy results of EXKIVITY™ (mobocertinib) are summarized in Table 14.

Table 14. Efficacy Results of AP32788-15-101 Clinical Study

	Prior-Platinum-Based Chemotherapy Treated (N=114)
Overall Response Rate (95% CI)	28% (20% - 37%)
Complete Response	0 (0%)
Partial Response	28% (N=32)
Duration of Response (DOR) Median months (95% CI)*	17.5 (7.4, 20.3)
Patients with DOR ≥6 months	59%
* Based on Kaplan-Meier estimates, CI= confidence interval	

See EXKIVITY™ drug label for details.

c. Clinical Efficacy Results In Patients Positive by ODxT Test for *EGFR* Exon 20 Insertions

In the ODxT evaluable patient population (102/114, see Fig. 1), the ORR was 26.5% (18.2%- 36.1%) with 27 patients having achieved best confirmed response (partial response). ORRs stratified by ODxT Test results in the primary efficacy analysis population were shown in Table 15. The observed results are judged to be clinically meaningful when considering the intended patient population, patients with metastatic *EGFR* exon 20 insertion mutation-positive NSCLC, and available therapy. AP32788-15-101 efficacy was also assessed by DOR by BICR for the ODxT Test and full efficacy (Table 16).

Table 15: Overall Response Rate For Prior Platinum Treatment Subjects: ODxT Test Positive, Negative, and Unevaluable

	LLT+/CDx+		LLT+/CDx-		LLT+/CDx Unknown		LLT+	
	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs	ORR% (n/N)	95% CIs
ORR (Partial Response)	26.7% (16/60)	(16.1%, 39.7%)	18.2% (2/11)	(2.3%, 51.8%)	29.0% (9/31[a])	(14.2%, 48.0%)	26.5% (27/102[b])	(18.2%, 36.1%)
a: 15 tumor QNS + 7 DNA QNS + 4 invalids + 5 No calls (see Fig. 1) b: 114 PP LLT positive – 12 missing (see Fig. 1)								

Table 16: Duraton of Response For Prior Platinum Treatment Subjects: ODxT Test Positive, Negative, and Unevaluable

	LLT+/CDx+		LLT+/CDx-		LLT+/CDx Not Evaluable		LLT+	
	DOR (N)	95% CIs	DOR (N)	95% CIs	DOR (n/N)	95% CIs	DOR (n/N)	95% CIs
DOR-Median months	11.07 (16)	(5.49, 23.03)	13.83 (2)	(11.07, 16.59)	9.23 (9)	(1.84, N/A)	11.07 (27)	(9.13, 16.59)
Estimates from Kaplan-Meier analysis. N/A indicate that the statistic was inestimable.								

d. Sensitivity Analysis

The primary objective analysis described above demonstrated mobocertinib efficacy in the ODxTT CDx-positive, and LLT-positive subset of the ODxTT intended use population. However, there are missing data from samples that were unevaluable by ODxT Test due to invalid results, insufficient slides, unacceptable tumor content, or insufficient DNA concentration. As missing data can potentially impact concordance estimates and drug efficacy, several sensitivity analyses were performed using variables which may have an impact on ODxT Test results, concordance, and clinical outcome.

Differences between ODxT Test evaluable and unevaluable groups were compared for the following variables: age, sex, ethnicity, race, tumor stage at study entry, and LLT assay type. With the exception of race comparison, the calculated p-values (using t-test or Wilcoxon rank sum test for continuous variables and chi-square or Fisher's exact test for categorical variables) demonstrated that there were no statistically significant differences ($p>0.05$) observed between these 2 groups, suggesting that the ODxT Test evaluable samples are representative of the primary efficacy population.

Multivariate logistic regression analyses were also performed to identify the clinically relevant covariates that were associated with the CDx test device output and clinical outcome, respectively. Given that the results are clinically

meaningful based on ORR and DOR for the AP32788-15-101 trial, when compared to available therapies, and there were no significant differences observed between the ODxT Test evaluable and unevaluable groups for any of the demographic and clinical covariates, it can be concluded that the missing results do not impact the estimates of both concordances and drug efficacy.

The efficacy ORR in the ODxT Test+|LLT- patients (i.e. δ2) was assumed to be c times that observed in the ODxT Test+|LLT+ (i.e. δ1) with a factor c ranging from 0 (no δ2 efficacy) to 1.0 (δ2 efficacy being the same as δ1). The simulated ORR (i.e. δCDx+), its variance and the corresponding 95% confidence intervals are shown in Table 17 and show robustness of ORR (point estimate) and its variance (var) for different assumed values of c.

Table 17: Simulated ORR Adjusted for ODxT Test Results

Where c	Point Estimate of Adjusted ORR	Variance	95% Lower	95% Upper
1	0.283505	0.002132	0.193005	0.374005
0.8	0.281875	0.002133	0.191347	0.372404
0.6	0.280246	0.002137	0.189632	0.37086
0.4	0.278617	0.002144	0.187861	0.369372
0.2	0.276987	0.002153	0.186033	0.367942
0.0	0.275358	0.002166	0.184149	0.366567

This analysis demonstrated that the estimated final drug efficacy in ODxT Test CDx *EGFR* exon 20 insertion positive patients remains robust with the missing CDx results.

3. Pediatric Extrapolation

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

C. 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 [2] investigators of which [none] were full-time or part-time employee of the sponsor and [none] 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 *EGFR* exon 20 insertions in patients with metastatic NSCLC to be treated with mobocertinib, the effectiveness of the ODxT Test was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the AP32788-15-101 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 AP32788-15-101 study show that patients who had qualifying *EGFR* exon 20 insertions received benefit from treatment with mobocertinib 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.

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 with mobocertinib provides a meaningful clinical benefit to NSCLC patients with *EGFR* exon 20 insertions, as demonstrated in the AP32788-15-101 trial. The probable benefit of the ODxT Test was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the AP32788-15-101 study, showing clinically meaningful ORR and median DOR response in patients with prior platinum treatment with metastatic *EGFR* exon 20 insertion-positive NSCLC detected by the ODxT Test. Given the available information and the analytical data provided in the submission, the data supports the conclusion that the ODxT Test has probable benefit in selecting patients with *EGFR* exon 20 insertions, for treatment with mobocertinib in patients with NSCLC.

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 for selection of NSCLC patients with *EGFR* exon 20 insertions 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 an analytical and clinical validation studies, which partially mitigate the probable risk of the ODxT 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.

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 *EGFR* exon 20 insertions in NSCLC patients for whom EXKIVITY™ (mobocertinib) may be indicated.

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for the indications of the ODxT device the probable benefits outweigh the probable risks.

XIII. CDRH DECISION

CDRH issued an approval order on 09/15/2021. The final non-clinical conditions of approval cited in the approval order are described below.

1. Thermo Fisher Scientific/Life Technologies Corp. must provide an additional LoD study using intended use clinical samples. The data from this study must be adequate to demonstrate an appropriate LoD for 3bp, 9bp, and 12bp *EGFR* exon 20 insertion variants.

2. Thermo Fisher Scientific/Life Technologies Corp. must provide data from well-designed and well-controlled precision studies:

    i. Provide data from an external panel reproducibility and within-run repeatability study using intended use specimens carrying *EGFR* exon 20 insertions at or near the LoD levels (~1-1.5x LoD). The data from this study must be adequate to support precision near the LoD for *EGFR* exon 20 insertions in the intended use population.

    ii. Provide data from an external sample processing reproducibility and within-run repeatability with an adequate number of replicates using intended use specimens carrying *EGFR* exon 20 insertions at or near the LoD levels (~1-1.5x LoD). The data from this study must be adequate to support precision (starting from sample processing) near the LoD for *EGFR* exon 20 insertions in the intended use population.

3. Thermo Fisher Scientific/Life Technologies Corp. must provide data from a well-designed and well-controlled endogenous interference substances study evaluating the effects of hemoglobin and tumor necrosis on the *EGFR* exon 20 insertion variant calling using intended use specimens near 1-1.5x LoD. The data from this study must be adequate to support the finding that the potential endogenous interfering substances in NSCLC do not adversely impact *EGFR* exon 20 insertion mutations calling.

4. Thermo Fisher Scientific/Life Technologies Corp. must provide additional data from a well-designed and well-controlled shelf-life stability study using *EGFR* exon 20 insertion or similar insertion intended use specimens. The data from this study must be adequate to support stability claims for insertions in the intended use population.

5. 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.

6. 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.