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: FoundationOne® Liquid CDx (F1 Liquid CDx)

Device Procode: PQP

Applicant's Name and Address: Foundation Medicine, Inc.
                                      150 Second Street
                                      Cambridge, MA 02141

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P190032/S001

Date of FDA Notice of Approval: July 15, 2021

The FoundationOne® Liquid CDx was approved on August 26, 2020 as a companion diagnostic for *BRCA1* and *BRCA2* alterations in metastatic castration-resistant prostate cancer (mCRPC) patients who may benefit from treatment with RUBRACA® (rucaparib) and *EGFR* activating mutations (Exon 19 deletions and L858R substitution mutation) in patients with advanced and metastatic non-small cell lung cancer (NSCLC) who may benefit from treatment with IRESSA® (gefitinib), TAGRISSO® (osimertinib), and TARCEVA® (erlotinib). On October 26, 2020 the FoundationOne® Liquid CDx test was approved as a companion diagnostic for *BRCA1* and *BRCA2* alterations in epithelial ovarian cancer for patients who may benefit from treatment with RUBRACA® (rucaparib), *ALK* rearrangements in non-small cell lung cancer for patients who may benefit from treatment with ALECENSA® (alectinib), and *PIK3CA* mutations patients with breast cancer who may benefit from treatment with PIQRAY® (alpelisib). On November 6, 2020, the the FoundationOne® Liquid CDx test was approved as a companion diagnostic for *BRCA1*, *BRCA2* and *ATM* alterations in mCRPC patients who may benefit from treatment with LYNPARZA® (olaparib).

The SSEDs to support the previously approved indications are available on the CDRH website. The current supplement was submitted to expand the indication for the FoundationOne® Liquid CDx test as a companion diagnostic for the indication listed in the table below.

New Indication Being Sought in this PMA supplement submission.

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	*MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA® (capmatinib)

II.   INDICATIONS FOR USE

FoundationOne® Liquid CDx is a qualitative next generation sequencing based in vitro diagnostic test that uses targeted high throughput hybridization-based capture technology to detect and report substitutions, insertions and deletions (indels) in 311 genes, including rearrangements in four (4) genes, and copy number alterations in three (3) genes. FoundationOne® Liquid CDx utilizes circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood of cancer patients collected in FoundationOne® Liquid CDx cfDNA blood collection tubes included in the FoundationOne® Liquid CDx Blood Sample Collection Kit. The test is intended to be used as a companion diagnostic to identify patients who may benefit from treatment with the targeted therapies listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1: Companion diagnostic indications

Tumor Type	Biomarker(s) Detected	Therapy
Non-small cell lung cancer (NSCLC)	*ALK* Rearrangements	ALECENSA® (alectinib)
	EGFR Exon 19 deletions and *EGFR* Exon 21 L858R alteration	IRESSA® (gefitinib) TAGRISSO® (osimertinib) TARCEVA® (erlotinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA® (capmatinib)
Prostate cancer	*BRCA1, BRCA2, and ATM* alterations	LYNPARZA® (olaparib)
	BRCA1, BRCA2 alterations	RUBRACA® (rucaparib)
Ovarian Cancer	*BRCA1, BRCA2* alterations	RUBRACA® (rucaparib)
Breast Cancer	*PIK3CA* mutations C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	PIQRAY® (alpelisib)

Additionally, FoundationOne® Liquid CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms.

A negative result from a plasma specimen does not mean that the patient's tumor is negative for genomic findings. Patients who are negative for the mutations listed in Table 1 should be reflexed to routine biopsy and their tumor mutation status confirmed using an FDA-approved tumor tissue test, if feasible.

Genomic findings other than those listed in Table 1 of the intended use statement are not prescriptive or conclusive for labeled use of any specific therapeutic product.

FoundationOne® Liquid CDx is a single-site assay performed at Foundation Medicine, Inc. in Cambridge, MA.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

- Alterations reported may include somatic (not inherited) or germline (inherited) alterations; however, the test does not distinguish between germline and somatic alterations. If a reported alteration is suspected to be germline, confirmatory testing should be considered in the appropriate clinical context.
- The test is not intended to replace germline testing or to provide information about cancer predisposition.
- Patients for whom no companion diagnostic alterations are detected should be considered for confirmation with an FDA-approve tumor tissue test, if possible.

V. DEVICE DESCRIPTION

The FoundationOne® Liquid CDx (F1LCDx) assay is performed exclusively as a laboratory service using circulating cell-free DNA (cfDNA) isolated from plasma derived from anti-coagulated peripheral whole blood from patients with solid malignant neoplasms. The assay employs a single DNA extraction method to obtain cfDNA from plasma from whole blood. Extracted cfDNA undergoes whole-genome shotgun library construction and hybridization-based capture of 324 cancer-related genes. All coding exons of 309 genes are targeted; select intronic or non-coding regions are targeted in three genes (refer to Table 2 for the complete list of genes reported by F1LCDx).

Hybrid-capture selected libraries are sequenced with deep coverage using the NovaSeq 6000 platform. Sequence data are processed using a custom analysis pipeline designed to detect genomic alterations, including base substitutions and indels in 311 genes, copy number variants in three genes, and genomic rearrangements in four genes. A subset of targeted regions in 75 genes is baited for increased sensitivity.

Table 2: Genomic Regions in which Variants are Reported by FoundationOne® Liquid[1]

ABL1 *[Exons 4-9]*	*ACVR1B*	*AKT1* *[Exon 3]*	*AKT2*	*AKT3*	*ALK* *[Exons 20-29, Introns 18,19]*	*ALOX12B*	*AMER1 (FAM123B)*	*APC*	*AR*
ARAF *[Exons 4, 5, 7, 11, 13, 15, 16]*	*ARFRP1*	*ARID1A*	*ASXL1*	*ATM*	*ATR*	*ATRX*	*AURKA*	*AURKB*	*AXIN1*
AXL	*BAP1*	*BARD1*	*BCL2*	*BCL2L1*	*BCL2L2*	*BCL6*	*BCOR*	*BCORL1*	*BCR* [Introns 8, 13, 14]*
BRAF *[Exons 11-18, Introns 7-10]*	*BRCA1* *[Introns 2, 7, 8, 12, 16, 19, 20]*	*BRCA2* *[Intron 2]*	*BRD4*	*BRIP1*	*BTG1*	*BTG2*	*BTK* *[Exons 2, 15]*	*C11orf30 (EMSY)*	*C17orf39 (GID4)*

CALR	*CARD11*	*CASP8*	*CBFB*	*CBL*	**CCND1**	*CCND2*	*CCND3*	*CCNE1*	*CD22*
CD70	*CD74* [Introns 6-8]*	*CD79A*	*CD79B*	**CD274 (PD-L1)**	*CDC73*	**CDH1**	**CDK12**	**CDK4**	**CDK6**
CDK8	*CDKN1A*	*CDKN1B*	**CDKN2A**	*CDKN2B*	*CDKN2C*	*CEBPA*	*CHEK1*	**CHEK2**	*CIC*
CREBBP	**CRKL**	*CSF1R*	*CSF3R*	*CTCF*	*CTNNA1*	**CTNNB1 [Exon 3]**	*CUL3*	*CUL4A*	*CXCR4*
CYP17A1	*DAXX*	*DDR1*	**DDR2 [Exons 5, 17, 18]**	*DIS3*	*DNMT3A*	*DOT1L*	*EED*	**EGFR [Introns 7, 15, 24-27]**	*EP300*
EPHA3	**EPHB1**	**EPHB4**	**ERBB2**	**ERBB3 [Exons 3, 6, 7,8, 10, 12, 20, 21, 23, 24, 25]**	**ERBB4**	**ERCC4**	**ERG**	**ERRFI1**	**ESR1 [Exons 4-8]**
ETV4* [Intron 8]	**ETV5* [Introns 6, 7]**	**ETV6* [Introns 5, 6]**	**EWSR1* [Introns 7-13]**	**EZH2 [Exons 4, 16, 17, 18]**	**EZR* [Introns 9-11]**	**FAM46C**	**FANCA**	**FANCC**	**FANCG**
FANCL	**FAS**	**FBXW7**	**FGF10**	**FGF12**	**FGF14**	**FGF19**	**FGF23**	**FGF3**	**FGF4**
FGF6	**FGFR1 [Introns 1, 5, Intron 17]**	**FGFR2 [Intron 1, Intron 17]**	**FGFR3 [Exons 7, 9 (alternative designation exon 10), 14, 18, Intron 17]**	**FGFR4**	**FH**	**FLCN**	**FLT1**	**FLT3 [Exons 14, 15, 20]**	**FOXL2**
FUBP1	**GABRA6**	**GATA3**	**GATA4**	**GATA6**	**GNA11 [Exons 4, 5]**	**GNA13**	**GNAQ [Exons 4, 5]**	**GNAS [Exons 1, 8]**	**GRM3**
GSK3B	**H3F3A**	**HDAC1**	**HGF**	**HNF1A**	**HRAS [Exons 2, 3]**	**HSD3B1**	**ID3**	**IDH1 [Exon 4]**	**IDH2 [Exon 4]**
IGF1R	**IKBKE**	**IKZF1**	**INPP4B**	**IRF2**	**IRF4**	**IRS2**	**JAK1**	**JAK2 [Exon 14]**	**JAK3 [Exons 5, 11, 12, 13, 15, 16]**
JUN	**KDM5A**	**KDM5C**	**KDM6A**	**KDR**	**KEAP1**	**KEL**	**KIT [Exons 8, 9, 11, 12, 13, 17, Intron 16]**	**KLHL6**	**KMT2A (MLL) [Introns 6, 8-11, Intron 7]**
KMT2D (MLL2)	**KRAS**	**LTK**	**LYN**	**MAF**	**MAP2K1 (MEK1) [Exons 2, 3]**	**MAP2K2 (MEK2) [Exons 2-4, 6, 7]**	**MAP2K4**	**MAP3K1**	**MAP3K13**
MAPK1	**MCL1**	**MDM2**	**MDM4**	**MED12**	**MEF2B**	**MEN1**	**MERTK**	**MET**	**MITF**
MKNK1	**MLH1**	**MPL[Exon 10]**	**MRE11A**	**MSH2 [Intron 5]**	**MSH3**	**MSH6**	**MST1R**	**MTAP**	**MTOR [Exons 19, 30, 39 40, 43-45, 47, 48, 53, 56]**

MUTYH	MYB* [Intron 14]	MYC [Intron 1]	MYCL (MYCL1)	MYCN	MYD88 [Exon 4]	NBN	NF1	NF2	NFE2L2
NFKBIA	NKX2-1 (TTF-1)	NOTCH1	NOTCH2 [Intron 26]	NOTCH3	NPM1 [Exons 4-6, 8, 10]	NRAS [Exons 2, 3]	NSD3 (WHSC1L1)	NT5C2	NTRK1 [Exons 14,15, Introns 8-11]
NTRK2 [Intron 12]	NTRK3 [Exons 16, 17]	NUTM1* [Intron 1]	P2RY8	PALB2	PARK2	PARP1	PARP2	PARP3	PAX5
PBRM1	PDCD1 (PD-1)	PDCD1LG2 (PD-L2)	PDGFRA [Exons 12, 18, Introns 7, 9, 11]	PDGFRB [Exons 12-21, 23]	PDK1	PIK3C2B	PIK3C2G	PIK3CA [Exons 2, 3, 5-8, 10, 14, 19, 21 (Coding Exons 1, 2, 4-7, 9, 13, 18, 20)]	PIK3CB
PIK3R1	PIM1	PMS2	POLD1	POLE	PPARG	PPP2R1A	PPP2R2A	PRDM1	PRKAR1A
PRKCI	PTCH1	PTEN	PTPN11	PTPRO	QKI	RAC1	RAD21	RAD51	RAD51B
RAD51C	RAD51D	RAD52	RAD54L	RAF1 [Exons 3, 4, 6, 7, 10, 14, 15, 17, Introns 4-8]	RARA [Intron 2]	RB1	RBM10	REL	RET [Introns 7, 8, Exons 11, 13-16, Introns 9-11]
RICTOR	RNF43	ROS1 [Exons 31, 36-38, 40, Introns 31-35]	RPTOR	RSPO2* [Intron 1]	SDC4* [Intron 2]	SDHA	SDHB	SDHC	SDHD
SETD2	SF3B1	SGK1	SLC34A2* [Intron 4]	SMAD2	SMAD4	SMARCA4	SMARCB1	SMO	SNCAIP
SOCS1	SOX2	SOX9	SPEN	SPOP	SRC	STAG2	STAT3	STK11 (LKB1)	SUFU
SYK	TBX3	TEK	TERC* {ncRNA}	TERT* {Promoter}	TET2	TGFBR2	TIPARP	TMPRSS2* [Introns 1-3]	TNFAIP3
TNFRSF14	TP53	TSC1	TSC2	TYRO3	U2AF1	VEGFA	VHL	WHSC1	WTI
XPO1	XRCC2	ZNF217	ZNF703						

[1] As part of its FDA-approved intended use, the F1LCDx assay interrogates 324 genes, including 309 genes with complete exonic (coding) coverage and 15 genes with only select non-coding coverage (indicated with an *). Select genes and select exons (indicated in bold) are captured with increased sensitivity.

The reporting of rearrangements and copy number alterations are restricted to those genes included in Table 3, below.

Table 3: Genes for which copy number alterations and rearrangements are reported for tumor profiling by F1LCDx

Alteration Type	Genes
Copy Number Alterations	*BRCA1, BRCA2, ERBB2*
Rearrangements	*ALK, BRCA1, BRCA2*

The test report includes variants reported in the following levels:

Level 1: Companion Diagnostics (CDx)
Clinical evidence should be presented from a prospectively designed clinical trial. Results can also be presented from a retrospective clinical bridging study demonstrating that the clinical endpoints are preserved using plasma samples in trials where enrollment was based on tissue test results. For follow-on markers, a clinical concordance study demonstrating non-inferioriy to the original FDA-approved cfDNA-based companion diagnostic device (refer to Li, Meijuan. Statistical Methods for Clinical Validation of Follow-On Companion Diagnostic Devices via an External Concordance Study. *Statistics in Biopharmaceutical Research.* 8: 35-363, 2016) is required. In addition to the clinical validation, analytical validation for each specific Level 1 CDx biomarker should be presented.

Level 2: cfDNA Biomarkers With Strong Evidence of Clinical Significance in cfDNA
For a Level 2 claim of cfDNA biomarkers with strong evidence of clinical significance, clinical validation needs to be from evidence presented with FDA-approved liquid biopsy companion diagnostic biomarkers for the specific tumor type at the biomarker or variant level. Such claims should also be supported by analytical performance for each biomarker from at least LoD, precision/ reproducibility, and accuracy studies.

Level 3A: Biomakers With Evidence of Clinical Significance in Tissue Supported by Strong Analytical Validation Using cfDNA and Concordance Between cfDNA and Tissue.
Clinical evidence can be provided from tissuebased companion diagnostics. This should also be supported by analytical validation (LoD, precision, analytical accuracy, and concordance study to a tissue-based test) for the specific tumor type at the biomarker or variant level, using a representative approach for SNVs and indels. Evidence evaluating concordance between cfDNA- and tissue-samples for FDA-approved tissue markers should be demonstrated using an FDA-approved tissue test or a validated tissue test.

Level 3B: Biomakers With Evidence of Clinical Significance in Tissue Supported by Analytical Validation Using cfDNA
Clinical evidence can be provided from tissue based companion diagnostics, with analytical validation supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

Level 4: Other Biomarkers With Potential Clinical Significance
Biomarkers not categorized into Levels 1, 2, or 3 can be included under Level 4 for informational purposes or to be used to direct patients toward clinical trials for which they may be eligible. Such claims can be supported by clinical rationale for inclusion in the panel. Such rationale could also include peer-reviewed publications for genes/ variants in tissue, variant information from well curated public databases, or *in vitro* pre-clinical models. Analytical validation should be supported by a representative approach for SNVs and indels from key analytical studies (such as LoD, accuracy, and precision).

FoundationOne® Liquid CDx cfDNA Blood Specimen Collection Kit Contents
The test includes a blood specimen collection kit, which is sent to ordering laboratories. The shipping kit contains the following components:
- Specimen preparation and shipping instructions
- Two FoundationOne® Liquid CDx cfDNA Blood Collection Tubes (8.5 mL nominal fill volume per tube)
- Return shipping label

Instruments
The F1LCDx assay is intended to be performed with the serial number-controlled instruments indicated in Table 5, below. All instruments are qualified by Foundation Medicine, Inc. (Foundation Medicine or FMI) under Foundation Medicine's Quality System.

Table 5: Instruments for use with the F1LCDx assay

Instrument
Illumina NovaSeq 6000
Beckman Biomek NXP Span-8 Liquid Handler
Thermo Scientific Kingfisher Flex DW 96
Bravo Benchbot
Hamilton STARlet STAR Liquid Handling Workstation

Test Process
All assay reagents including blood collection tubes included in the F1LCDx assay process are qualified by Foundation Medicine and are compliant with the medical device Quality System Regulation (QSR).

A. **Specimen Collection and Preparation**
Whole blood specimens are collected in F1LCDx cfDNA Blood Collection Tubes (BCT) provided as a component of the F1LCDx specimen collection kit. Prior to cfDNA isolation, the plasma is separated from whole blood by centrifugation, which separates the plasma from the buffy coat (white blood cells) and red blood cells. The plasma layer is removed from the buffy coat to avoid contamination of cellular DNA into the plasma sample. A residual volume of plasma remains in the tube to avoid disturbing the buffy coat. A second spin of the separated plasma at high speed further pellets cell debris and protein.

B. **DNA Extraction**

Following the separation of plasma from whole blood, cfDNA is isolated from plasma using the KingFisher™ Flex Magnetic Particle Processor, which uses an efficient and automated method to purify cfDNA. The KingFisher™ Instrument uses magnetic rods to move nucleic acid through purification phases of binding, washing, and elution to yield high purity cfDNA. After isolating cfDNA, the Agilent 4200 TapeStation is used to quantify cfDNA.

C. **Library Construction**

Library Construction (LC) begins with the normalization of cfDNA. The samples are purified, using AMPure XP Beads (Agencourt). Solid-phase reversible immobilization (SPRI) purification is used subsequent to library construction with the NEBNext kits (NEB), including mixes for end repair with blunt-end and 5'-phosphorylate the cfDNA fragments using T4 Polynucleotide Kinase and T4 DNA Polymerase. This step prepares the 3'- end for dA-addition while also preparing the 5'-end of the DNA fragment for ligation. Second, dA-addition will incorporate a single dAMP to the 3'-end of the End-Repaired material. After dA-addition, a universal Y-adaptor is ligated onto each end of the DNA fragment using a DNA ligase. These steps are performed in 96-well plates (Eppendorf) on a Bravo Benchbot (Agilent) using the "with-bead" protocol to maximize reproducibility and library yield. Indexed (Foundation Medicine customized six base pair barcodes) sequencing libraries are PCR amplified with a high-fidelity DNA polymerase (HiFi™, Kapa) for ten cycles, SPRI purified and quantified by PicoGreen fluorescence assay (Invitrogen). Process matched control (PMC) is prepared and added to the plate with other cfDNA samples at the beginning of LC.

D. **Hybrid Capture**

Hybrid Capture begins with the normalization of each library from 500 ng to 2000 ng. Solution hybridization is performed using a >50-fold molar excess of a pool of individually synthesized 5'-biotinylated DNA 120 base pair oligonucleotides (Integrated DNA Technology) for baits. The baits target regions from 324 cancer-related genes including all coding exons of 309 genes and only select introns or non-coding regions in 15 genes. Baits were designed by appointing overlapping 120 bp DNA sequence intervals covering target exons (60 bp overlap) and introns (20 bp overlap), with a minimum of three baits per target; single nucleotide polymorphism (SNP) targets were allocated one bait each. Intronic baits were filtered for repetitive elements as defined by the University of California at Santa Cruz (UCSC) Genome Repeat Masker track. Hybrid selection of targets demonstrating reproducibly low coverage was boosted by increasing the number of baits for these targets.

Upon completion of the pre-capture normalization, blocking DNA (adaptor block, Cot, Salmon Sperm DNA) is added to the sequencing library and the mixture is lyophilized in a 96-well plate. The library is then re-suspended in nuclease-free water, heat denatured at 95°C for 5 minutes, temperature ramps from 95°C to 68°C to anneal blocking DNA, and then the samples are incubated at 68°C for a minimum of 5 minutes before the addition of the bait set reagent. After a 20-24-hour

incubation, the library-bait duplexes are captured on paramagnetic MyOne™ streptavidin beads (Invitrogen) and off-target library is removed by washing one time with Saline Sodium Citrate (SSC) at 25°C and four times with SSC at 55°C. The PCR master mix is added to directly amplify the captured library from the washed beads. After amplification, the samples are SPRI purified and quantified by PicoGreen.

E. Sequencing

Sequencing on the Illumina NovaSeq 6000 platform employs on-board cluster generation (OBCG) using patterned flow cell (FC) technology to generate monoclonal clusters via ExAmp from a single DNA template. The clusters are then sequenced using sequencing by synthesis (SBS) chemistry. The NovaSeq system is capable of sequencing up to two flow cells at a time. During OBCG, a single DNA template is introduced into each of the primer substrate layered nanowells of the flow cell, where the template is immediately and rapidly amplified by ExAmp. This rapid amplification prevents other DNA templates from binding, ensuring a monoclonal cluster is formed in each nanowell. The procedure allows for fixed size and spacing of the clusters which results in improved and more accurate resolution.

A growing nucleotide chain is created on the flow cell by incorporating fluorescently labeled, 3'-blocked dNTPs. After excitation by a laser, the camera captures the emission color of the incorporated, fluorescently labeled nucleotide. The 3'-block is then removed, reverting the nucleotide to its natural form, which allows the polymerase to add another base to the growing double strand of DNA. With each successive SBS cycle, a new fluorescently labeled 3'- blocked dNTP is added. SBS allows for millions of discrete clusters of clonal copies of DNA to be sequenced in parallel.

F. Sequence Analysis

Sequence data are analyzed using mainly proprietary software developed by Foundation Medicine. External tools used include: 1) BWA (Burrows-Wheeler Aligner) v0.7.17, for aligning sequence reads to the genomic reference, 2) Samtools v1.6 for utility operations, 3) Picard tools v1.56 for metrics calculations, and 4) Biopython for the pairwise2 sequence alignment module.

Reads from each Illumina flow cell are demultiplexed (sorted into sets of reads deriving from distinct samples), and their fragment barcodes (FBCs) are extracted and encoded into the read names. For each sample, read pairs with matching, valid FBCs are aligned and processed together to: 1) identify clusters of reads originating from the same original fragment; 2) merge overlapping read pairs into single reads, where possible; and 3) generate consensus reads representing all information in the set of reads for each cluster, encoding positions with mismatches (errors) with base quality 20. The consensus reads are then aligned to the reference genome to generate the 'consensus' BAM.

For the detection of short variants (e.g., substitutions and small indels) in each target region of interest, a de novo assembly is performed. This is done using proprietary software to generate a de Bruijn graph including all k-mers in reads mapping to a particular locus. The graph is parsed to identify paths that originate and terminate in reference nodes from the locus. Increased k-mer sizes may be used to account for ambiguities, cycles, and other problematic regions within the graph. The result of the graph traversal is a set of candidate variants. For each variant, there is a set of k-mers supporting the variant and a set of k-mers that would support the reference or another variant at the location.

Each candidate variant is then scanned against reads in the locus to identify which reads support either the candidate variant or a different variant or reference at the location. The cluster membership of the supporting reads is then assessed to determine which clusters show unambiguous support for the variant and which have conflicting assignments, indicating that the variant may have arisen as an error in sequencing or library preparation. The final variant calls are made based on a model that takes into account the coverage at the location, the number of supporting read clusters and their redundancy level, and the number of error-containing clusters.

G. Report Generation

Approved results are annotated by automated software with CDx relevant information and are merged with patient demographic information and any additional information provided by Foundation Medicine as a professional service prior to approval and release by the laboratory director or designee.

H. Internal Process Controls

Positive Control

Each assay run includes a control sample run in duplicate. The control sample contains a pool of eleven HapMap cell lines and is used as a positive mutation detection control. 100 different germline SNPs present across the entire targeted region are required to be detected by the analysis pipeline.

Sensitivity Control

The HapMap control pool used as the positive control is prepared to contain variants at 0.1%, 10% mutant allele frequency (MAF) which must be detected by the analysis pipeline to ensure expected sensitivity for each run.

Negative Control

Samples are barcoded molecularly at the library construction (LC) stage. Only reads with a perfect molecular barcode sequence are incorporated into the analysis. The Analysis Pipeline includes an algorithm that analyzes the SNP profile of each specimen to identify potential contamination that may have occurred prior to molecular barcoding.

I. CDx Classification Criteria

1. *BRCA1 and BRCA2 alterations to identify patients eligible for rucaparib in prostate and ovarian cancer:*
   The CDx classification criteria and the list of *BRCA1/BRCA2* missense mutations for rucaparib, based on the trial prespecifications are described in Table 5 and Table 6; however, not all the missense mutations listed below were observed in the TRITON2, ARIEL2, and PROfound clinical studies.

Table 5: Classification Criteria for Deleterious Tumor *BRCA* Variants

Qualification Criteria	Sequence Classification	Methodology
A *BRCA1* or *BRCA2* alteration that includes any of the sequence classifications	Protein truncating mutations	Sequence analysis identifies premature stop codons anywhere in the gene coding region, except: 3' of and including *BRCA2* K3326*
	Splice site mutations	Sequence analysis identifies variant splice sequences at intron/exon junctions -/+ 2bp of exon starts/ends
	Homozygous deletions	Sequence analysis identifies deletions in both gene alleles of ≥1 exon in size
	Large protein truncating rearrangements	Sequence analysis identifies protein truncating rearrangements
	Deleterious missense mutations	Curated list

Table 6: Deleterious *BRCA* Missense Alterations in rucaparib

BRCA1 Alterations (Protein Change)					*BRCA2* Alterations (Protein Change)		
M1V	C44Y	R71T	R1699W	G1770V	M1V	R2336P	T2722R
M1T	C44F	R71M	R1699Q	M1775K	M1T	R2336L	D2723H
M1R	C47S	S770L	G1706R	M1775R	M1R	R2336H	D2723G
M1I	C47Y	R1495T	G1706E	C1787S	M1I	T2412I	G2724W
M18T	C47F	R1495M	A1708E	G1788V	D23N	R2602T	G2748D
L22S	C61S	R1495K	S1715R	P1812A	D23Y	W2626C	A2911E
I26N	C61G	E1559K	S1722F	A1823T	S142N	I2627F	E3002K
T37K	C61Y	E1559Q	V1736A	V1833M	S142I	R2659T	R3052W
C39R	C64R	T1685A	G1738R	W1837R	V159M	R2659K	D3095G
C39G	C64G	T1685I	G1738E	V1838E	V211I	E2663V	D3095E
C39Y	C64Y	D1692N	K1759N		V211L	S2670L	N3124I
C39W	C64W	M1689R	L1764P		Y600C	I2675V	N3187K
H41R	R71G	D1692H	I1766N		K1530N	T2722K	
C44S	R71K	D1692Y	I1766S				

2. *ATM, BRCA1 and BRCA2 alterations to identify patients eligible for olaparib in mCRPC:*

Table 7: Rules Applied to the Aforementioned Genes:

Qualification Criteria	Sequence Classification	Methodology	Comments
A gene alteration that includes any of the sequence classifications	Protein truncating mutations	Sequence analysis identifies premature stop codons anywhere in the gene coding region, except: 3' of and including *BRCA2* K3326*	Does not include VUS. Includes mutations on the canonical transcript only for genes *ATM, BRCA1,* and *BRCA2.*
	Splice site mutations	Sequence analysis identifies variant splice sequences at intron/exon junctions -/+ 2bp of exon starts/ends	Does not include VUS. Includes indels that extend through ±2bp from the intron/exon junction. Includes mutations on the canonical transcript only for genes *ATM, BRCA1,* and *BRCA2.*
	Homozygous deletions	Sequence analysis identifies deletions in both gene alleles of ≥1 exon in size	Does not include VUS Only reported for *BRCA1&2.* Not reported for *ATM.*
	Large protein truncating rearrangements	Sequence analysis identifies protein truncating rearrangements	Does not include VUS
	Deleterious missense mutations	Curated list	Protein effects from list of missense mutations on the canonical transcript only for genes *ATM, BRCA1,* and *BRCA2.*

Alterations reported are limited to those within the alteration-calling capabilities of FMI as of March 2, 2020. ATM missense mutations were identified from the ClinVar database. Should the calling capabilities expand, additional alterations that meet the above criteria may also be reported, per FDA approval

Table 8. List of Deleterious Missense Mutations by Protein Effect, Implemented on the Respective Canonical Transcript.

BRCA1		*BRCA2*		*ATM*	
Protein Effect (PE)	FMI Annotated PE	Protein Effect (PE)	FMI Annotated PE	Protein Effect (PE)	FMI Annotated PE
MIV	MIV	MIR	MIR	MIT	MIT
MlI	MlI	MlI	MlI	R2032K	R2032K
C6IG	C6IG	VI59M	VI59M	R2227C	R2227C
C64Y	C64Y	V211L	V211L	R2547 S2549del	R2547 S2549del
R7IG	R7IG	V211I	V211I	G2765S	G2765S
R7IK	R7IK	R2336P	R2336P	R2832C	R2832C
RI495M	RI495M	R2336H	R2336H	S2855 V2856delinsR1	S2855 V2856delinsRl S2855 V2856>Rl
EI559K	EI559K			R3008C	R3008C
DI692N	DI692N			R3008H	R3008H

BRCA1		BRCA2		ATM	
Protein Effect (PE)	FMI Annotated PE	Protein Effect (PE)	FMI Annotated PE	Protein Effect (PE)	FMI Annotated PE
DI692H	DI692H			[VUS from Jan 2016 HRR* List to be Excluded]	
RI699W	RI699W			V2424G	V2424G
AI708E	AI708E			[Excluded from Jan 2016 HRR List]	
G1788V	GI788V			K750K	splice site 2250G>A

HRR = Homologous Recombination Repair genes

Intronic Variants

Gene	Chr	Position	Ref	Alt	dbSNP	FMI Protein Effect
ATM	*chr11*	*108128198*	*T*	*G*	*rs730881346*	**[Variant Not Called by FMI]**
ATM	*chr11*	*108214102*	AGTGA	A	rs730881295	splice site 8418+5_8418+8delGTGA or splice site 8418+1_8418+4delGTGA

3. *CDx* classification criteria for *EGFR* alterations:
   - Base substitutions resulting in *EGFR* L858R
   - In-frame deletions occurring within *EGFR* Exon 19

4. *ALK rearrangements to identify patients eligible for treatment with ALECENSA® (alectinib):*
   CDx positivity for an *ALK* rearrangement is based on the following variant classification criteria:
   - The *ALK* rearrangement must have pathogenic driver status (FMI driver status of "known" or "likely")
   - AND the disease type must be NSCLC
   - AND one of the following two conditions must hold:
     1. The partner gene is *EML4*, or
     2. The *ALK* breakpoint occurs within *ALK* intron 19

5. *SNVs and indels that lead to MET exon 14 skipping to identify patients eligible for treatment with TABRECTA® (capmatinib).*
   A SNV or indel in *MET* shall be considered to result in skipping of exon 14 if one or more of the following criteria are met:
   1. Deletions greater than or equal to 5 bp that affect positions -3 to -30 in the intronic region immediately adjacent to the splice acceptor site at the 5′ boundary of *MET* exon 14.
   2. Indels affecting positions -1 or -2 at the splice acceptor site of the 5′ boundary of *MET* exon 14.
   3. Base substitutions and indels affecting positions 0, +1, +2, or +3 at the splice donor site of the 3′ boundary of *MET* exon 14.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are FDA-approved companion diagnostic (CDx) alternatives for the detection of genetic alterations using cfDNA isolated from plasma samples, as listed in Table 1 of the F1LCDx intended use statement. The approved CDx tests are listed in Table 9, below; for additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/media/119249/download. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

Table 9: FDA-approved companion diagnostic (CDx) alternatives

Biomarker(s) Detected	Device	Company	Technology	Therapy	Indication
EGFR Exon 19 deletions and L858R Substitution Mutation	**cobas** *EGFR* Mutation Test v2	Roche Molecular Systems, Inc.	Polymerase Chain Reaction (PCR)	TARCEVA® (erlotinib), TAGRISSO® (osimertinib), and IRESSA® (gefitinib)	NSCLC
	Guardant360 CDx	Guardant Health, Inc.	NGS		
				TAGRISSO® (osimertinib)	
PIK3CA: C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y	*therascreen PIK3CA* RGQ PCR test	QIAGEN, Inc.	PCR	PIQRAY® (alpelisib)	Breast Cancer

There are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of genomic alterations of *BRCA1, BRCA2*, and *ATM* for the identification of mCRPC patients eligible for treatment with LYNPARZA® (olaparib).

There are no FDA-approved CDx alternatives using cfDNA isolated from plasma for the detection of genomic alterations of SNVs and indels that lead to *MET* exon 14 skipping to identify patients eligible for treatment with TABRECTA® (capmatinib).

VII. MARKETING HISTORY

Foundation Medicine designed and developed F1LCDx based on previous versions of the assay, including the FoundationACT (FACT) and FoundationOne® Liquid laboratory developed test (LDT), a revised version of FACT. The first commercial sample was tested in 2016. The FACT and FoundationOne® Liquid LDT have been used to detect the presence of genomic alterations in blood and plasma specimens. Neither the FACT nor FoundationOne® Liquid LDT were FDA-cleared or -approved.

The F1LCDx assay was approved on August 26, 2020 for the detection of genomic alterations of *BRCA1* and *BRCA2* for the identification of mCRPC patients eligible for treatment with RUBRACA® (rucaparib) and the detection of *EGFR* Exon 19 deletions (Exon 19del) and L858R substitutions in plasma obtained from patients with advanced

and metastatic NSCLC for treatment with TARCEVA® (erlotinib), TAGRISSO® (osimertinib), and IRESSA® (gefitinib). The F1LCDx assay was also approved for tumor mutation profiling for substitutions and indels to be used by qualified health care professionals in accordance with professional guidelines in oncology for patients with solid malignant neoplasms. The F1LCDx assay was approved on October 26, 2020 as a companion diagnostic for *BRCA1* and *BRCA2* alterations in epithelial ovarian cancer for patients who may benefit from treatment with RUBRACA® (rucaparib), *ALK* rearrangements in NSCLC for patients who may benefit from treatment with ALECENSA® (alectinib), and *PIK3CA* mutations in patients with breast cancer who may benefit from treatment with PIQRAY® (alpelisib). The October 26, 2020 approval also included the addition of rearrangements in three (3) genes, and copy number alterations in three (3) genes for tumor profiling. F1LCDx assay was approved on November 6, 2020 as a companion diagnostic for *BRCA1, BRCA2* and *ATM* for the identification of mCRPC patients eligible for treatment with LYNPARZA® (olaparib).

The F1LCDx assay has been marketed in the United States, the European Union, and in several other foreign countries since August 2020.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect F1LCDx assay results, and subsequently, inappropriate patient management decisions. Patients with false positive CDx biomarker results may undergo treatment with one of the therapies 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 targeted therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy. For the specific adverse events related to the approved therapeutics, please see approved drug product labels.

For the specific adverse events that occurred in the clinical study, please see the FDA approved package inserts for TABRECTA® (capmatinib) which is available at Drugs@FDA.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies
The evidence in support of the analytical performance of F1LCDx in detecting SNVs and indels that lead to *MET* exon 14 skipping is presented in this section. Analytical accuracy/concordance and precision near the limit of detection (LoD) studies were conducted to support the indication for SNVs and indels that lead to *MET* exon 14 skipping using clinical samples.

For F1LCDx platform-level validation (P190032), due to the lack of sufficient volume of clinical specimens, analytical performance characteristics were established for some of the studies using contrived samples, which consisted of enzymatically sheared cell

line DNA spiked into human plasma and diluted with cfDNA isolated from healthy donor plasma. A contrived sample functional characterization (CSFC) study (Section IX.A.1) was conducted to demonstrate comparable performance of sheared cell line DNA samples as compared to cfDNA isolated from plasma specimens obtained from cancer positive patient specimens. Clinical specimens were used to assess analytical accuracy, precision and confirmation of the estimated limit of detection (LoD), and evaluate sample stability. For information regarding the platform-level validation, refer to Section IX.A. in Summary of Safety and Effectiveness Data P190032.

1. **Analytical Accuracy/Concordance**

   An analytical accuracy/concordance study was performed to demonstrate the concordance between F1LCDx and an externally validated NGS assay (evNGS) for the detection of SNVs and indels that lead to *MET* exon 14 skipping. Overall, there were 74 overlapping genes between the two assays and the evNGS bait set regions included the biomarker classification criteria for alterations that lead to *MET* exon 14 skipping. The comparison between short variants, including base substitutions and indels, detected by F1LCDx and the evNGS was evaluated for alterations leading to *MET* exon 14 skipping.

   For this study, 45 samples were selected from patients enrolled in the TABRECTA trial GEOMETRY-mono 1 study conducted to support the effectiveness of the device (refer to to Section X below). Additional 100 NSCLC samples were sourced from FMI's clinical archives, 38 samples from NSCLC patients previously evaluated in the accuracy study to support the original PMA P190032 (refer to section IX.A.2. in the SSED for the original PMA P190032), and 31 externally sourced plasma samples from NSCLC cases whose tissue specimens tested positive for *MET* exon 14 skipping alterations and were subsequently tested with F1LCDx to determine their *MET* exon 14 skipping associated alteration status prior to conducting the accuracy study statistical analysis. Samples selected from FMI's clinical archives that were positive for *MET* exon 14 skipping alterations were required to have a variant allele frequency (VAF) greater than or equal 0.40%.

   Of the 214 samples, 179 samples had DNA yield that allowed processing with F1LCDx at the specified LC DNA input of 30ng – 80ng. Thirty-five (35) samples were tested with F1LCDx at out of specification of 20ng – <30ng LC DNA input.

   Of the 179 samples that had sufficient DNA yield for testing with F1LCDx, 3 samples had a F1LCDx sequence analysis QC failure, while 4 had an evNGS QC failure.

   Analytical concordance using the evNGS assay results as the reference for the 172 samples that passed QC with both assays was determined. Forty-eight (48) of the 172 samples were identified as positive for *MET* exon 14 skipping alterations by F1LCDx. The statistical analysis using the evNGS assay results as the reference showed a positive percent agreement (PPA) of 94.87% with 95% CI (83.11%-

98.58%), a negative percent agreement (NPA) of 91.83% with 95% CI (85.80%, 95.32%), a positive predictive value (PPV) of 77.08% with 95% CI (63.46%, 86.69%) and a negative predictive value (NPV) of 98.39% with 95% CI (94.31%, 99.56%) as shown in Table 10, below. Since the samples were selected from different sources based on different assays, the unadjusted PPA/NPA and unadjusted PPV/NPV in Table 10 may be subject to potential bias.

Table 10. Concordance Analysis Comparing Sample-level Biomarker Detection between F1LCDx and evNGS

		evNGS			
		MET ex14 positive	*MET* ex14 negative	Total	PPV/NPV (95% CI)
F1LCDx	*MET* ex14 positive	37	11	48	PPV: 77.08% (63.46%, 86.69%)
	MET ex14 Negative	2	122	124	NPV: 98.39% (94.31%, 99.56%)
	Total	39	133	172	
	PPA/NPA (95% CI)	PPA: 94.87% (83.11%, 98.58%)	NPA: 91.83% (85.80%, 95.32%)		

Ten (10) of the eleven (11) samples that were F1LCDx-positive/evNGS-negative [F1LCDx(+)/evNGS(-)] were discordant due to differences in variant reporting by assays. Of the 11 samples, 10 samples harbored *MET* exon 14 deletions ≥6bp detectable by the evNGS variant caller, which calls variants including indels ≥6bp in *MET* exon 14 that are also included in the evNGS's loci of interest (LOI). Following variant calling, variant filtering is performed prior to reporting. The default setting of the evNGS analysis software filters out variants that are not present in the assay's LOI list and/or not annotated in public databases such as COSMIC, TCGA and dbSNP. Since *MET* ex14 indels ≥6bp are not part of the evNGS's LOI, this variant type is filtered out and not reported by the evNGS's analysis software in the default setting, and thus are considered negatives by the evNGS comparator assay. Further the remaining one (1) sample from the 11 samples that were F1LCDx (+)/evNGS(-), contained a *MET* exon 14 deletion <6bp which cannot be called with the evNGS variant caller regardless of the VAF level (i.e., this type of variant is "un-callable" not because of the sensitivity and specificity of the evNGS variant caller but because the variant caller can only output *MET* exon 14 deletions ≥6bp.

In the two (2) discordant samples that were F1LCDx negative(-)/evNGS(+), base substitutions reported by the evNGS were not detected in the variant analysis pipeline of F1LCDx. These 2 discordances seem to stem from the low frequency of the variants, 0.47% and 0.54% VAF, which are close to the LoD of F1LCDx.

Four (4) of the eleven (11) discordant samples that were F1LCDx(+)/evNGS(-) were from patients evaluated in the clinical therapeutic study for whom efficacy data was available. Of these 4 patients, 3 had partial response to TABRECTA, while one had progressive disease. Although these patients had discordant results,

these results appear to suggest that these patient with F1LCDx(+)/evNGS(-) were *MET* exon 14 deletion positive.

All of 37 samples that were F1LCDx(+)/evNGS(+) had *MET* exon 14 skipping alterations that correspond to biomarker rule category 3, i.e., these samples had base substitutions and indels affecting positions 0, +1, +2, or +3 at the splice donor site of the 3′ boundary of *MET* exon 14. Therefore, samples representative of all three biomarker classification rules were not represented in the accuracy study. Although not called by evNGS comparator as positive due to variant filtering rules, 4 of the 11 F1LCDx(+)/evNGS(-) had *MET* exon 14 skipping alterations that correspond to biomarker rule category 1, and 3 out of 11 had *MET* exon 14 skipping alterations that correspond to biomarker rule category 1 and 2. The remaining 3 out of the 11 F1LCDx(+)/evNGS(-) samples that had biomarker rule category 3 *MET* exon 14 skipping alterations These 10 samples were 100 % concordant at the variant level, i.e., these 10 samples were detected by evNGS, but were not reported due to variant filtering as described above.

As samples that were selected for evaluation from FMI's clinical archives that were positive for *MET* exon 14 skipping alterations were required to have a VAF ≥0.40%, and since the lowest VAF test result observed in the accuracy study for the F1LCDx was 0.34% VAF for base substitutions and 0.73% VAF for indels, the accuracy of F1LCDx was not demonstrated for samples with variants below these VAF levels. A limitation addressing the uncertainty of the accuracy of *MET* exon 14 skipping alteration with VAFs below those evaluated in the accuracy is included as a limitation to the device (also refer to Section XII. C. below).

2. **Analytical Sensitivity**

    a. Limit of Blank (LoB)

        See Summary of Safety and Effectiveness Data for P190032.

    b. Limit of Detection (LoD)

        The LoD of a *MET* exon 14 indel in a contrived sample was evaluated as part of the LoD study for PMA P190032 (refer to Section IX.A.3.b) in the original SSED). The *MET* indel was determined to have an estimated LoD of 0.41% VAF using the empirial hit rate approach. Although this variant (splice site 3029-1G>T) did not meet the TABRECTA CDx biomarker definition, the LoD estimated using this indel variant was used for the confirmation of LoD study (see Section IX.A.2.c., below) due to availability of *MET* exon 14 skipping alteration indel positive samples. The LoD for a *MET* exon 14 skipping base substitution alteration was extrapolated from the median LoD from all the substitutions in the narrow high region in the F1 Liquid CDx platform and thus was estimated as 0.49% VAF.

    c. LoD Confirmation

The two estimated LoD values for *MET* exon 14 skipping indels and base substitutions were used to confirm the LoD of *MET* exon 14 skipping alterations that meet the TABRECTA CDx biomarker definition. A total of three (3) clinical samples that harbored SNVs or indels that lead to *MET* exon 14 skipping were assessed in a confirmation of LoD study by F1LCDx. The SNVs evaluated correspond to the biomarker rule category 3, while the indel evaluated corresponds to the biomarker rule 1 and 2. The LoD values for *MET* exon 14 alterations were confirmed from the data generated in this study using one clinical cfDNA sample positive for a *MET* exon14 indel and two clinical cfDNA samples positive for *MET* exon14 base substitutions per *MET* exon 14 biomarker definition based on a hit rate of least 95%. In this study LoD was confirmed by testing 24 replicate measurements. The LoD for *MET* exon 14 indels is confirmed for a as the median VAF of 0.28% and the LoD for *MET* exon 14 SNVs is established as the median VAF of 0.40%, see Table 11.

Table 11: Summary of Confirmed LoD for SNVs and indels that lead to *MET* exon 14 skipping

Targeted %VAF[1,4]	Alteration Type	*MET* exon 14 Skipping Alteration	Previously Established LoD VAF [2,3,4]	Mean VAF Calculated[4]	Concordant/ Total (n/N)	Hit Rate 95%CI (%)
0.50%	Indel	*MET exon14* splice site 2888-35 2889>A	0.41%[2]	0.28%	23/24	95.8% (79.8%, 99.3%)
0.50%	SNV	*MET exon14* splice site 3028+1G>T	0.49%[3]	0.45%	23/24	95.8% (79.8%, 99.3%)
0.50%	SNV	*MET exon14* splice site 3028+2T>C	0.49%[3]	0.35%	22/23	95.7% 79.0%, 99.2%)

[1] For samples processed in this study , 0.50% VAF represents 1 - 1.5x LoD.
[2] LoD for *MET* lndels were estimated within the LoD Study in the original PMA P190032 (refer to Section IX.A.3.b)
[3] LoD established from platform subs in the narrow-high region within the LoD Study in the original PMA P190032 (refer to Section IX.A.3.b)
[4] The accuracy of %VAF has not been analytically validated

See Section IX.A.7 of Summary of Safety and Effectiveness Data for P190032 for additional analytical sensitivity data.

3. **Analytical Specificity:**
   a. Potentially Interfering Substances:
   See Summary of Safety and Effectiveness Data for P190032.

   b. Hybrid Capture Bait Specificity:
   See Summary of Safety and Effectiveness Data for P190032.

   c. Carryover/Cross-Contamination:

See Summary of Safety and Effectiveness Data for P190032.

4. Precision:

    a. <u>Repeatability and Within-laboratory Reproducibility</u>

A precision study was conducted using five NSCLC samples harboring SNVs or indels that lead to *MET* exon 14 skipping covering all categories of the *MET* exon 14 biomarker rule.

Repeatability including intra-run performance (run on the same plate under the same conditions) and reproducibility including inter-run performance (run on different plates under different conditions) were assessed and compared across three different sequencers and two different reagent lots, across multiple days of performance by multiple operators.

The results for the precision study for the NSCLC samples near LoD are summarized in Tables 12 and 13, below.

Table 12: Reproducibility results for SNVs and indels that lead to *MET* exon 14 skipping

Source Sample	Targeted VAF[1]	*MET* exon 14 Alteration	Alteration Type	Concordant/ Total (n/N)	Reproducibility 95% CI (%)[2]	Mean VAF Calculated[1]	Fold LoD
1	0.50%	*MET* exon14 splice site 2888-35_2889>A	Indel	23/24	95.8% (79.8%, 99.3%)	0.28%	1.00X
2	0.50%	*MET* exon14 splice site 3028+1G>T	SNV	23/24	95.8% (79.8%, 99.3%)	0.45%	1.13X
2	1.00%	*MET* exon14 splice site 3028+1G>T	SNV	23/23	100.% (85.7%, 100%)	0.85%	2.13X
3	0.50%	*MET* exon14 splice site 3028+2T>C	SNV	22/23	95.7% (79.0%, 99.2%)	0.35%	0.88X
3	1.00%	*MET* exon14 splice site 3028+2T>C	SNV	24/24	100% (86.2%,100%)	0.76%	1.90X
4	0.96%	*MET* exon14 splice site 2888-17_2888-3del15	Indel	24/24	100% (86.2%, 100%)	1.17%	4.18X
5	1.30%	*MET* exon 14 splice site 3005_3028+3>C	Indel	24/24	100% (86.2%, 100%)	1.67%	5.96X

[1] Quantitative reporting of %VAF/%TF has not been approved by FDA .

[2] The 95% CIs were calculated using the Wilson Method

Table 13: Repeatability results for SNVs and indels that lead to *MET* exon 14 skipping

Source Sample	Targeted VAF[1]	*MET* exon 14 Alteration	Alteration Type	Concordant / Total (n/N)	Repeatability 95% CI (%)	Mean VAF Calculated[1]	Fold LoD
1	0.50%	*MET* exon14 splice site 2888-35_2889>A	Indel	11/12	91.7% (64.6%, 98.5%)	0.28%	1.00X
2	0.50%	*MET* exon14 splice site 3028+1G>T	SNV	11/12	91.7% (64.6%, 98.5%)	0.45%	1.13X
2	1.00%	*MET* exon14 splice site 3028+1G>T	SNV	11/11	100% (74.1%, 100%)	0.85%	2.13X
3	0.50%	*MET* exon14 splice site 3028+2T>C	SNV	10/11	90.9% (62.3%, 98.4%)	0.35%	0.88X
3	1.00%	*MET* exon14 splice site 3028+2T>C	SNV	12/12	100% (75.8%, 100%)	0.76%	1.90X
4	0.96%	*MET* exon14 splice site 2888-17_2888-3del15	Indel	12/12	100% (75.8%, 100%)	1.17%	4.18X
5	1.30%	*MET* exon *14* splice site 3005_3028+3>C	Indel	12/12	100% (75.8%, 100%)	1.67%	5.96X

[1] Quantitative reporting of %VAF/%TF has not been approved by FDA.
[2] The 95% CIs were calculated using the Wilson Method

Inter-run reproducibility was evaluated across 24 replicates and intra-run repeatability was evaluated across 12 duplicates per plate. Three replicates exhibited discordances due to low coverage and low detected allele frequency, which was below pipeline reporting thresholds. Overall, the reproducibility was established as 98.2% and the repeatability was established at 96.3%. The corresponding two-sided Wilson score 95% CIs are provided for repeatability and reproducibility positive call rates.

b. Tumor Mutation Profiling Variants:
    See Summary of Safety and Effectiveness Data for P190032 and P200006 and Section XIII.

c. Reagent Lot-to-Lot Reproducibility:
    See Summary of Safety and Effectiveness Data for P190032.

d. Instrument-to-Instrument Reproducibility:
    See Summary of Safety and Effectiveness Data for P190032.

e. Reagent Lot Interchangeability:
    See Summary of Safety and Effectiveness Data for P190032.

f. Curator Precision:
    See Summary of Safety and Effectiveness Data for P190032.

5. Comparability Across Cancer Types:
   See Summary of Safety and Effectiveness Data for P190032 and P200006.

6. Stability:

    a. Reagent Stability:

The reagent stability of F1LCDx assay was assessed by analyzing data from each of eight samples in triplicate, per each of three different lots of LC, HC, and sequencing reagents. A total of nine analyses for each specimen were completed for each of six time points assessed. A total of 72 tests were assessed per time period; a total of 432 samples and six time points (one baseline timepoint and 5 subsequent experimental timepoints) were included in this study overall. Each of the three sample Master Library Pools (MPLs), representing three LC and HC reagent lots was evaluated per time point on a NovaSeq 6000 sequencer, using three different sequencing reagent lots. The analysis of baseline timepoint zero (T0) identified the baseline variant calls for each sample.

All five experimental time points have been processed and analyzed for Lot #1, Lot #2, and Lot #3. Concordance was assessed among 127,642 data points for tumor profiling variants across the five experimental timepoints. The three reagent lots achieved ≥90% concordance with the baseline variant calls for all the experimental timepoints (including the last two timepoints T4 and T5 at 12 and 13 months respectively) except for a middle timepoint T3 (9 months) which is present in Table 14. The reason for the failure of T3 (9 months) was due a technical error which resulted lower than planned DNA being transferred for LC and therefore was not a reagent failure. Reagent stability can be claimed as 12 months after the baseline testing date.

Table 14. Concordance for Tumor Profiling Variants at Replicate Level by Reagent Lot and by Timepoint

Reagent Lot	Timepoint	# Concordant	# Total	Concordance (%)	95% CI (%)
LOT#1	3 months	1921	1966	97.71%	(96.95%, 98.28%)
	6 months	2082	2151	96.79%	(95.96%, 97.46%)
	9 months	1916	2151	89.07%	(87.69%, 90.32%)
	12 months	1609	1656	97.16%	(96.25%, 97.86%)
	13 months	1918	1973	97.21%	(96.39%, 97.85%)
LOT#2	3 months	2083	2148	96.97%	(96.16%, 97.62%)
	6 months	2091	2160	96.81%	(95.98%, 97.47%)
	9 months	1851	2160	85.69%	(84.15%, 87.11%)
	12 months	2087	2160	96.62%	(95.77%, 97.3%)
	13 months	2089	2160	96.71%	(95.87%, 97.39%)
LOT#3	3 months	2086	2139	97.52%	(96.77%, 98.10%)
	6 months	2098	2154	97.4%	(96.64%, 97.99%)
	9 months	1855	2154	86.12%	(84.59%, 87.51%)
	12 months	2097	2154	97.35%	(96.59%, 97.95%)

Reagent Lot	Timepoint	# Concordant	# Total	Concordance (%)	95% CI (%)
	13 months	1924	1977	97.32%	(96.51%, 97.94%)

    b.   <u>Stability of cfDNA and Plasma Samples:</u>
See Summary of Safety and Effectiveness Data for P190032.

    c.   <u>Whole Blood Specimen Stability and Inverted Tube Stability:</u>
See Summary of Safety and Effectiveness Data for P190032 and Section XIII.

7. <u>Guard-banding and Robustness:</u>
    a.   <u>DNA Extraction:</u>
See Summary of Safety and Effectiveness Data for P190032.

    b.   <u>cfDNA Input:</u>
See Summary of Safety and Effectiveness Data for P190032 and P200006 and Section XIII.

    c.   <u>Molecular Index Barcode Performance:</u>
See Summary of Safety and Effectiveness Data for P190032.

    d.   <u>Automation Line Equivalence:</u>
See Summary of Safety and Effectiveness Data for P190032.

B. <u>Animal Studies</u>

Not Applicable

C. <u>Additional Studies</u>
    1.<u>Blood Collection Tube Equivalence:</u>
See Summary of Safety and Effectiveness Data for P190032.

X.   SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical bridging study to establish a reasonable assurance of safety and effectiveness of F1LCDx for the detection of SNVs and indels that lead to *MET* exon 14 skipping in the plasma of patients with NSCLC who may benefit from TABRECTA (capmatinib). Pre-treatment plasma samples and clinical outcome data from patients with NSCLC enrolled in the clinical study GEOMETRY mono-1 were used to establish a reasonable assurance of safety and effectiveness of F1LCDx for the indication for use of this PMA supplement. A summary of the clinical study is presented below.

A. <u>F1LCDx Clinical Bridging Study for SNVs and indels that lead to *MET* exon 14 skipping</u>

GEOMETRY mono-1 Study Design

The GEOMETRY mono-1 study is a prospectively designed, multicenter, open- label, single arm Phase II study to evaluate the safety and efficacy of the MET inhibitor TABRECTA (capmatinib) in adult patients with *EGFR* wild-type (wt) and *AL*K-rearrangement negative, locally advanced or metastatic NSCLC harboring *MET* exon 14 skipping alterations. The primary objective was to assess overall response rate (ORR) by a Blinded Independent Review Committee (BIRC) assessment per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria by cohort to determine whether treatment with TABRECTA is effective. Duration of response (DOR) as assessed by BIRC is the key secondary endpoint. GEOMETRY mono-1 is an ongoing study that was initiated on June 11, 2015 with first patient first visit.

- Cohort 4 only enrolled pretreated (second and third line) patients with *MET* exon 14 deletions, and
- Cohort 5b only enrolled treatment-naïve patients with *MET* exon 14 deletions.

Patients were screened for enrollment into Cohorts 4 and 5b for *MET* exon 14 deletion status using tissue based *MET* exon 14 deletion reverse-transcriptase PCR (RT-PCR) clinical trial assay (CTA). Plasma samples were collected and stored prior to study treatment for retrospective testing. Patients enrolled in Cohorts 4 and 5b received 400mg of TABRECTA orally twice daily in tablet form. Efficacy was evaluated every six weeks from the first day of treatment until RECIST 1.1 disease progression.

Plasma samples from other cohorts from GEOMETRY mono-1, cohorts 1b, 2 and 3 (*MET* exon 14 deletion negative) were included in the bridging study to supplement the analysis to calculate NPA for the sensitivity analysis.

Clinical Bridging Study

A clinical bridging study was conducted to evaluate: 1) the concordance between *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping status by the CTA and F1LCDx, and 2) the clinical validity of F1LCDx in identifying NSCLC patients with *MET* exon 14 skipping mutations who may be eligible for treatment with TABRECTA.

Plasma samples from GEOMETRY mono-1 patients were collected by the therapeutic investigational sites per the study protocol and study documents and shipped to the central testing laboratories. Blood samples were collected on Cycle 1 Day 1 prior to treatment with the study drug for patients enrolled into the GEOMETRY mono-1 study, including *MET* exon 14 deletion positive patients in cohorts 4 and 5b, and *MET* exon 14 deletions negative patients in cohorts 1b, 2, and 3. In addition to *MET* mutation negative plasma samples were also collected from the GEOMETRY mono- 1 trial, additional tissue-matched NSCLC samples from commercial sources were used to supplement this population. Plasma samples were shipped to Foundation Medicine for retrospective testing with F1LCDx assay.

1. Clinical Inclusion and Exclusion Criteria
   The sample inclusion and exclusion criteria for the the retrospective testing of the clinical bridging study were:

   Sample inclusion criteria:
   - Samples from enrolled patients from Cohorts 1b, 2, 3, 4, and 5b with informed consent provided in the GEOMETRY mono-1 trial
   - Samples from commercial sources with informed consent confirmed under purchase contract
   - Samples from Cohorts 1b, 2, and 3 must have a valid CTA negative result from tissue
   - Frozen plasma specimens with a minimum plasma volume of 2.5mL
   - Samples were required to meet minimum criteria for F1LCDx assay operational testing requirements

   Sample exclusion criteria:
   - Lack of clear subject identification or label on stored patient sample
   - Obvious physical damage of stored patient sample
   - Tissue and other liquid samples
   - Samples with plasma volume <2.5mL

   Specimens included in the clinical bridging study were tested according to the standard testing protocol for the F1LCDx assay test with a minimum recommended cfDNA input of ≥ 30 ng for the library construction step. A subset of patient specimens were also tested at lower cfDNA inputs of ≥ 20 ng and <30 ng cfDNA input based on pre-specified assay procedures and processed only if the samples passed pre-specified in-process quality criteria. : In the instances where a sample had ≥20 and <30ng following DNA extraction, the sample was tested. This reflects FMI's current practice of processing samples with <30 ng cfDNA for input into the assay in cases where the clinician is contacted and there is not sufficient sample to be re-run.

2. Follow up Schedule
   The F1LCDx clinical bridging study involved retrospective testing of plasma samples; as such, no additional patient follow-up was conducted.

3. Clinical Endpoints
   The primary endpoint of GEOMETRY mono-1 is the overall response rate (ORR) by Blinded Independent Review Committee (BIRC) assessment by cohort to determine whether treatment with capmatinib is effective. Duration of response (DOR) as assessed by BIRC is the key secondary endpoint.

B. **Accountability of PMA Cohort**
   As of clinical study data cut-off of April 15, 2019, 223 patients were enrolled into Cohorts 1b, 2, 3, 4, and 5b of GEOMETRY mono-1 and included for the device clinical bridging study. Of these 223 patients, 97 were enrolled into Cohorts 4 and 5b based on

MET exon 14 skipping status determined using FFPE tissue by the CTA. Of the 97 CTA-enrolled patients, 69 were enrolled in Cohort 4 (2nd and 3rd line, pre-treated) and 28 were enrolled in Cohort 5b (1st line, treatment-naïve). Ninety-three (93) of the 97 CTA enrolled patients had available plasma and were included for the retrospective F1LCDx testing. Among them, 81 samples met the F1LCDx recommended sample input of cfDNA ≥ 30 ng, while 7 additional samples met the minimum F1LCDx sample input criteria of cfDNA ≥ 20 ng.
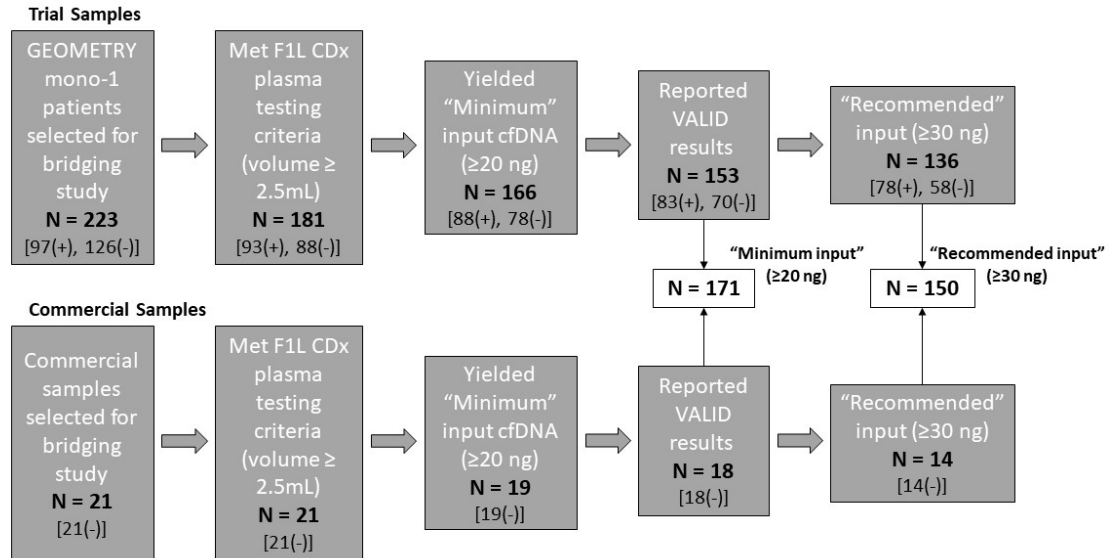
Five (5) patient samples did not yield sufficient cfDNA of ≥ 20 ng and were not tested by F1LCDx.

The remaining 126 out of 223 patients have also been tested for *MET* exon 14 skipping status by the CTA, either prospectively or retrospectively. These are NSCLC patients with various levels of *MET* amplification enrolled into Cohorts 1b, 2, or 3 of GEOMETRY mono-1 study. Of the 126 patients, 88 were CTA(-) for *MET* exon 14 skipping and had plasma samples available to be included in retrospective F1LCDx testing. Twenty-one (21) CTA(-) samples from NSCLC patients from commercial source with plasma volume ≥ 2.5 mL were also included for F1LCDx testing.

As described above, a total of 202 samples, including 93 from Cohorts 4 and 5b, 88 from Cohorts 1b, 2, and 3, and 21 from commercial sources were sent to FMI for processing. Once accessioned by FMI, cfDNA was subsequently extracted and samples were tested only when cfDNA available for test input was ≥ 20 ng. A total of 185 of the 202 samples mentioned above have met these criteria after extraction at FMI. One hundred sixty-six (166) samples from GEOMETRY mono-1 and 19 commercial samples were confirmed to have pooled plasma volumes ≥ 2.5 mL and yielded the minimum F1LCDx input required of cfDNA (≥20 ng).

Samples tested with ≥ 30 ng and ≥ 20 ng cfDNA input were included in both the primary concordance analyses and the primary clinical efficacy analyses. Of the 185 samples tested by F1LCDx, 150 were tested with ≥ 30 ng of cfDNA and reported valid results. An additional 21 samples were tested with ≥ 20 ng and < 30 ng cfDNA with valid results. This makes up a total of 171 samples with valid F1LCDx results for statistical analysis. Among the 202 samples sent to FMI, 31 were excluded from the statistical analysis due to not being evaluated or producing invalid results. Within them, 17 had cfDNA yields below the 20 ng minimum required test input and were therefore not tested by F1LCDx. The other 14 were excluded due to failed quality metrics during F1LCDx testing and reported as invalid. The detailed sample accountability is available in Figure 1.

Figure 1: GEOMETRY mono-1 sample accountability in combined cohorts

Trial Samples

GEOMETRY mono-1 patients selected for bridging study
N = 223
[97(+), 126(-)]

→

Met F1L CDx plasma testing criteria (volume ≥ 2.5mL)
N = 181
[93(+), 88(-)]

→

Yielded "Minimum" input cfDNA (≥20 ng)
N = 166
[88(+), 78(-)]

→

Reported VALID results
N = 153
[83(+), 70(-)]

→

"Recommended" input (≥30 ng)
N = 136
[78(+), 58(-)]

"Minimum input" (≥20 ng) **N = 171**

"Recommended input" (≥30 ng) **N = 150**

Commercial Samples

Commercial samples selected for bridging study
N = 21
[21(-)]

→

Met F1L CDx plasma testing criteria (volume ≥ 2.5mL)
N = 21
[21(-)]

→

Yielded "Minimum" input cfDNA (≥20 ng)
N = 19
[19(-)]

→

Reported VALID results
N = 18
[18(-)]

→

"Recommended" input (≥30 ng)
N = 14
[14(-)]

The statistical analysis was performed on all CTA(+) subjects from Cohort 4 and 5b, CTA(-) subjects from Cohort 1b, Cohort 2 and Cohort 3 of GEOMETRY mono-1, as well as all available plasma samples from commercial sources meeting minimum requirements of 2.5mL plasma and CTA(-) tissue-matched NSCLC.

All the CTA(-) enrolled subjects were randomly assigned to Cohort 4 and Cohort 5b with the probabilities proportional to the samples size of each cohort in order to conduct cohort-based statistical analyses. The CTA(-) tissue-matched commercial samples were assigned to Cohort 4 and Cohort 5b based on pre-treatment status. Any samples with unknown pre-treatment status were randomly assigned to Cohort 4 and Cohort 5b with the probabilities proportional to the sample size of each cohort.

The primary analysis set for Cohort 4 (PAS-A) in the bridging study included all these CTA(+) subjects from the Cohort 4 of original GEOMETRY mono-1 trial who have one or two prior lines of systemic therapy. It also included the CTA(-) subjects assigned to this population as described above. The PAS-A was evaluated for the concordance analysis and the efficacy analysis.

The primary analysis set for Cohort 5b (PAS-B) in the bridging study included all these CTA(+) subjects from the Cohort 5b of original GEOMETRY mono-1 trial who must be treatment naive for advanced disease. It also included the CTA- negative subjects assigned to this population as described above. The PAS-B was evaluated for the concordance analysis and the efficacy analysis.

Overall, the primary concordance analysis of F1LCDx with the CTA was performed using the combined sample numbers from PAS-A and PAS-B from the GEOMETRY mono-1 trial and commercial sources. A total of 150 patients (136 from GEOMETRY mono-1 and 14 from commercial source) with valid CTA results were tested with F1LCDx at ≥ 30 ng cfDNA input and yielded valid F1LCDx results. The concordance

analysis was also performed on the 171 patients (153 from GEOMETRY mono-1 and 18 from commercial source) with valid CTA results that were tested with F1LCDx at ≥ 20 ng cfDNA input and yielded valid F1LCDx results. Full disposition of the patient samples from GEOMETRY mono-1 and those used for the F1LCDx bridging study is shown in Tables 15 and 16.

Table 15: Disposition of all GEOMETRY mono-1 bridging subjects

	Total patients	Samples sent to FMI for CDx[1]	Actual Tested by CDx[2]
Total enrolled in Cohort 1b, 2, 3, 4 and 5b (as of 04/15/19 data cut-off)	223	181	166
Tested as CTA-positive (enrolled only in C4 and C5b)	97	93	88
Enrolled in Cohort 4	69	66	61
Enrolled in Cohort 5b	28	27	27
Tested as CTA-negative (enrolled only in C1b, C2 and C3)	126	88	78
Randomized to cohort 4 for bridging analysis	63	63	57
Randomized to cohort 5b for bridging analysis	25	25	21
Total commercial CTA-negative	21	21	19
Assigned to cohort 4 for bridging analysis	2	2	2
Assigned to cohort 5b for bridging analysis	19	19	17
Total samples included	244	202	185
Samples not sent to FMI	42	0	0
Samples sent to FMI for CDx testing but not tested by CDx	17	17	0
Samples tested as invalid by CDx	14	14	14

[1]Samples with estimated volume ≥ 2.5 mL
[2]Samples with cfDNA input level ≥ 20 ng

Table 16: Disposition of GEOMETRY mono-1 bridging subjects for CDx and CTA (PAS-A/PAS-B)

	CTA	
CDx	**Positive N=97 (%)**	**Negative N=109 (%)**
Tested with cfDNA input ≥30 ng		
Positive	55 (56.7)	0
Negative	23 (23.7)	72 (66.1)
Invalid	3 (3.1)	6 (5.5)
Tested with cfDNA input ≥20 ng		
Positive	**57** (58.8)	0
Negative	**26** (26.8)	**88** (80.7)
Invalid	5 (5.2)	9 (8.3)
Not tested	9 (9.3)	12 (11.0)

The analysis of clinical utility based on ORR was performed in only GEOMETRY mono-1 patients who have been assigned into Cohorts 4 and 5b, respectively, according to the statistical analysis plan. The clinical utility results presented here include only the F1LCDx *MET* exon 14 skipping mutation positive population of 39 patients from Cohort 4 and 16 patients from Cohort 5b with valid F1LCDx results, tested with cfDNA ≥ 30 ng. Efficacy analysis on ORR was also performed for the F1LCDx *MET* exon 14 skipping mutation positive population of 41 patients from Cohort 4 and 16 patients from Cohort 5b with valid F1LCDx results, tested with cfDNA ≥ 20 ng.

Sensitivity analyses were conducted on the concordance and efficacy results to determine the impact of missing F1LCDx results patients. It included those not tested, invalid result under the ≥30 ng and ≥20 ng cfDNA input, and those tested with cfDNA ≥ 20 ng and < 30 ng under the recommended input. The sensitivity analysis demonstrated that the clinical efficacy analyses are robust to missing F1LCDx results.

C. **Study Population Demographics and Baseline Parameters**

The demographics, disease characteristics and specimen characteristics for the F1LCDx evaluable and F1LCDx-unevaluable patients were similar for all of the CTA- enrolled patients in both the GEOMETRY mono-1 *MET* exon 14 skipping positive Cohorts 4 and 5b (Tables 17 and 18).

Table 17: Comparison of demographic and disease characteristics between F1LCDx-evaluable and F1LCDx-unevaluable set for CTA(+) patients in Cohort 4 by F1LCDx sample requirements (PAS-A)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

Baseline characteristics	CDx evaluable N=53	CDx unevaluable N=16	All N=69
Age (years)			
n	53	16	69
Mean	70.7	71.9	71.0
SD	7.93	9.74	8.32
Median	71.0	70.0	71.0
Minimum	54.0	49.0	49.0
Maximum	88.0	90.0	90.0
Sex-n (%)			
Female	32 (60.4)	8 (50.0)	40 (58.0)
Male	21 (39.6)	8 (50.0)	29 (42.0)
Race-n (%)			
Caucasian	38 (71.7)	11 (68.8)	49 (71.0)
Asian	14 (26.4)	5 (31.3)	19 (27.5)
Native American	1 (1.9)	0	1 (1.4)
ECOG at baseline-n (%)			
0	13 (24.5)	3 (18.8)	16 (23.2)
1	39 (73.6)	13 (81.3)	52 (75.4)
2	1 (1.9)	0	1 (1.4)
Histological grade-n (%)			
Well Differentiated	3 (5.7)	2 (12.5)	5 (7.2)
Moderately Differentiated	6 (11.3)	3 (18.8)	9 (13.0)

Baseline characteristics	CDx evaluable N=53	CDx unevaluable N=16	All N=69
Poorly Differentiated	15 (28.3)	4 (25.0)	19 (27.5)
Undifferentiated	4 (7.5)	1 (6.3)	5 (7.2)
Unknown	25 (47.2)	6 (37.5)	31 (44.9)
Stage at study entry-n (%)			
Stage IIIB	1 (1.9)	1 (6.3)	2 (2.9)
Stage IV	52 (98.1)	15 (93.8)	67 (97.1)

- All % calculated using N as denominator
- SD = Standard Deviation

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

Baseline characteristics	CDx evaluable N=57	CDx unevaluable N=12	All N=69
Age (years)			
n	57	12	69
Mean	70.9	71.5	71.0
SD	7.73	11.14	8.32
Median	71.0	68.0	71.0
Minimum	54.0	49.0	49.0
Maximum	88.0	90.0	90.0
Sex-n (%)			
Female	33 (57.9)	7 (58.3)	40 (58.0)
Male	24 (42.1)	5 (41.7)	29 (42.0)
Race-n (%)			
Caucasian	39 (68.4)	10 (83.3)	49 (71.0)
Asian	17 (29.8)	2 (16.7)	19 (27.5)
Native American	1 (1.8)	0	1 (1.4)
ECOG at baseline-n (%)			
0	14 (24.6)	2 (16.7)	16 (23.2)
1	42 (73.7)	10 (83.3)	52 (75.4)
2	1 (1.8)	0	1 (1.4)
Histological grade-n (%)			
Well Differentiated	3 (5.3)	2 (16.7)	5 (7.2)
Moderately Differentiated	7 (12.3)	2 (16.7)	9 (13.0)
Poorly Differentiated	17 (29.8)	2 (16.7)	19 (27.5)
Undifferentiated	4 (7.0)	1 (8.3)	5 (7.2)
Unknown	26 (45.6)	5 (41.7)	31 (44.9)
Stage at study entry-n (%)			
Stage IIIB	1 (1.8)	1 (8.3)	2 (2.9)
Stage IV	56 (98.2)	11 (91.7)	67 (97.1)

- All % calculated using N as denominator
- SD = Standard Deviation

Table 18: Comparison of demographic and disease characteristics between CDx-evaluable and CDx-unevaluable set for CTA-positive patients in Cohort 5b by CDx sample requirements (PAS-B)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

Baseline characteristics	CDx evaluable N=25	CDx unevaluable N=3	All N=28

Age (years)			
n	25	3	28
Mean	72.5	71.7	72.4
SD	6.58	12.01	7.02
Median	71.0	71.0	71.0
Minimum	57.0	60.0	57.0
Maximum	86.0	84.0	86.0
Sex-n (%)			
Female	15 (60.0)	3 (100)	18 (64.3)
Male	10 (40.0)	0	10 (35.7)
Race-n (%)			
Caucasian	21 (84.0)	3 (100)	24 (85.7)
Asian	4 (16.0)	0	4 (14.3)
ECOG at baseline-n (%)			
0	7 (28.0)	0	7 (25.0)
1	18 (72.0)	3 (100)	21 (75.0)
Histological grade-n (%)			
Well Differentiated	4 (16.0)	0	4 (14.3)
Moderately Differentiated	0	2 (66.7)	2 (7.1)
Poorly Differentiated	6 (24.0)	0	6 (21.4)
Undifferentiated	2 (8.0)	0	2 (7.1)
Unknown	13 (52.0)	1 (33.3)	14 (50.0)
Stage at study entry-n (%)			
Stage IV	25 (100)	3 (100)	28 (100)

- All % calculated using N as denominator
- SD = Standard Deviation

F1LCDx sample requirement: Minimum (cfDNA input $\geq$ 20 ng)

Baseline characteristics	CDx evaluable N=26	CDx unevaluable N=2	All N=28
Age (years)			
n	26	2	28
Mean	72.5	72.0	72.4
SD	6.45	16.97	7.02
Median	71.0	72.0	71.0
Minimum	57.0	60.0	57.0
Maximum	86.0	84.0	86.0
Sex-n (%)			
Female	16 (61.5)	2 (100)	18 (64.3)
Male	10 (38.5)	0	10 (35.7)
Race-n (%)			
Caucasian	22 (84.6)	2 (100)	24 (85.7)
Asian	4 (15.4)	0	4 (14.3)
ECOG at baseline-n (%)			
0	7 (26.9)	0	7 (25.0)
1	19 (73.1)	2 (100)	21 (75.0)
Histological grade-n (%)			
Well Differentiated	4 (15.4)	0	4 (14.3)
Moderately Differentiated	1 (3.8)	1 (50.0)	2 (7.1)
Poorly Differentiated	6 (23.1)	0	6 (21.4)

Baseline characteristics	CDx evaluable N=26	CDx unevaluable N=2	All N=28
Undifferentiated	2 (7.7)	0	2 (7.1)
Unknown	13 (50.0)	1 (50.0)	14 (50.0)
Stage at study entry-n (%)			
Stage IV	26 (100)	2 (100)	28 (100)

- All % calculated using N as denominator
- SD = Standard Deviation

D. Safety and Effectiveness Results

1. Safety Results

The safety with respect to treatment with TABRECTA 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 TABRECTA® (capmatinib).

2. Effectiveness Results

Concordance Results
Concordance of the F1LCDx assay with the enrolling *MET* exon 14 skipping CTA was demonstrated with the CDx-evaluable population (PAS-A and PAS-B combined). The primary concordance analysis of the status of *MET* SNVs and indels that lead to *MET* exon 14 skipping between F1LCDx and the tissue CTA test results were evaluated in both analysis sets that met ≥30 ng cfDNA input and ≥20 ng cfDNA input. The analysis on the ≥30 ng cfDNA input population evaluated 150 patients (78 *MET* exon 14 skipping positive patients, and 72 *MET* exon 14 skipping negative patients), without invalid CDx results. The analysis on the ≥20 ng cfDNA input population evaluated 171 patients (83 *MET* exon 14 skipping positive patients, and 88 *MET* exon 14 skipping negative patients), without invalid CDx results.

Agreement (PPA, NPA and OPA) for combined Cohort 4 and 5b by ≥30 ng cfDNA input and ≥20 ng cfDNA input CDx are shown in Table 19. For the 150 patients meeting the ≥30 ng cfDNA input, the PPA, NPA and OPA and respective confidence intervals were determined to be 70.5% (59.1, 80.3), 100% (95.0, 100) and 84.7% (77.9, 90.0). For the 171 patients meeting the the ≥20 ng cfDNA input, the PPA, NPA and OPA and respective confidence intervals were determined to be 68.7% (57.6, 78.4), 100% (95.0, 100) and 84.8% (78.5, 89.8).

Table 19: Agreement between CDx and CTA based on CTA results in combined cohorts by CDx sample requirements (PAS-A/PAS-B)
F1LCDx sample requirement Recommended (cfDNA input ≥ 30 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 4 and Cohort 5b	PPA	70.5 (55/ 78)	(59.1, 80.3)

	NPA	100 (72/ 72)	(95.0, 100)
	OPA	84.7 (127/150)	(77.9, 90.0)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 4 and Cohort 5b	PPA	68.7 (57/ 83)	(57.6, 78.4)
	NPA	100 (88/ 88)	(95.9, 100)
	OPA	84.8 (145/171)	(78.5, 89.8)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

The point estimates (95% CI) of PPA, NPA and OPA in Cohort 4 for samples meeting "Recommended" CDx sample requirements were 73.6% (59.7%, 84.7%), 100% (91.8%, 100%) and 85.4% (76.7%, 91.8%) respectively, when excluding CDx invalid results (Table 20).

The point estimates (95% CI) of PPA, NPA and OPA in Cohort 4 for samples meeting "Minimum" CDx sample requirements were 71.9% (58.5%, 83.0%), 100% (93.4%, 100%) and 85.6% (77.6%, 91.5%) respectively, when excluding CDx invalid results (Table 20).

Table 20: Agreement between CDx and CTA based on CTA results in Cohort 4 by CDx sample requirements (PAS-A)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 4	PPA	73.6 (39/ 53)	(59.7, 84.7)
	NPA	100 (43/ 43)	(91.8, 100)
	OPA	85.4 (82/ 96)	(76.7, 91.8)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 4	PPA	71.9 (41/ 57)	(58.5, 83.0)
	NPA	100 (54/ 54)	(93.4, 100)
	OPA	85.6 (95/111)	(77.6, 91.5)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

The point estimates (95% CI) of PPA, NPA and OPA in Cohort 5b for samples meeting "Recommended" CDx sample requirements were 64.0% (42.5%, 82.0%), 100% (88.1%, 100%) and 83.3% (70.7%, 92.1%) respectively, when excluding CDx invalid results (Table 20).

The point estimates (95% CI) of PPA, NPA and OPA in Cohort 5b for samples meeting "Minimum" CDx sample requirements were 61.5% (40.6%, 79.8%), 100% (89.7%, 100%) and 83.3% (71.5%, 91.7%) respectively, when excluding CDx invalid results (Table 21).

Table 21: Agreement between CDx and CTA based on CTA results in Cohort 5b by CDx sample requirements (PAS-B)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 5b	PPA	64.0 (16/ 25)	(42.5, 82.0)
	NPA	100 (29/ 29)	(88.1, 100)
	OPA	83.3 (45/ 54)	(70.7, 92.1)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

	Measure of agreement	Percent agreement % (n/N)	95% CI[1]
Cohort 5b	PPA	61.5 (16/ 26)	(40.6, 79.8)
	NPA	100 (34/ 34)	(89.7, 100)
	OPA	83.3 (50/ 60)	(71.5, 91.7)

N: The total number of patients. It is the denominator for percentage (%) calculation n: Number of patients with agreement between CTA and CDx
[1] The 95% CI calculated using Clopper-Pearson method

The point estimate for NPA is 100% in combined cohorts or individually for Cohort 4 and Cohort 5b, for either "Recommended" or "Minimum" sample requirements. The point estimate for PPA varies between 61.5% (Table 20, using "Minimum" sample requirements in Cohort 5b) and 73.6% (Table 19, using "Recommended" samples requirements in Cohort 4)".

A total of 26 of the 185 samples (CTA positive and negative) tested by CDx showed discordant *MET* exon 14 skipping mutation status compared to the CTA. All 26 samples are CTA(+), and there are no discordant cases for CTA-. Of the 26 CTA(+)/CDx- samples,

- 2 samples were detected by F1LCDx as a rearrangement but reported as negative as a result of the F1LCDx biomarker definition not including rearrangement alterations;
- 1 sample was detected by F1LCDx as having an indel with both breakpoints within *MET* exon 14 but reported as a negative result. An indel with both breakpoints was not included in the biomarker definition therefore the cause of discordance was related to biomarker definition for the F1LCDx study;
- In the 6 samples with F1LCDx negative results, MET x14 biomarker alterations were detected by F1LCDx below assay reporting thresholds and filtered out from the final analysis results. Alteration calling by the F1LCDx variant analysis pipeline is based on multiple characteristics supporting the variant. The final variant calls are made based on a model that takes into account the coverage at the location, the number of supporting read clusters and their redundancy level, and the number of error-containing clusters (refer to Woodhouse R, et al. (2020) Clinical and Analytical Validation of FoundationOne Liquid CDx, a Novel 324-Gene cfDNA-based Comprehensive Genomic Profiling Assay for Cancers of Solid Tumor Origin. PLoS ONE 15(9): e0237802.

Based on the low PPA between F1LCDx and the tissue CTA as shown in Tables 19-21, since the F1LCDx failed to detect a significant proportion of the patients, a reflex testing using tissue specimens to an FDA approved tissue test will be required, if feasible, if the plasma test is negative.

Efficacy Results

The GEOMETRY mono-1 clinical trial met its primary objective demonstrating a statistically significant improvement in ORR by BIRC assessments in patients with *MET* exon 14 skipping positive tumors by cohort.

TABRECTA demonstrated an estimated 40.6% ORR by CTA in the *MET* exon 14 skipping positive Cohort 4 at 95% CI with upper and lower limits of between 28.9 - 53.1% and an estimated 67.9% ORR in the *MET* exon 14 skipping mutation positive cohort 5b at 95% CI with upper and lower limits of between 47.6 - 84.1%.

Tables 22 and 23 present the clinical efficacy of TABRECTA analyzed in CTA(+) patients who were tested as CDx(+) ("double positive" patients) in each cohort that met the ≥30 ng cfDNA input and ≥20 ng cfDNA input CDx sample requirements, respectively. In Cohort 4 there were 39 patients with ≥30 ng cfDNA

input and 41 with ≥20 ng cfDNA input with valid results for analysis of ORR. In Cohort 5b there were 16 patients, all of whom met the ≥30 ng cfDNA input.

Patients in Cohort 4 that met the ≥30 ng cfDNA input experienced an ORR of 51.3% and a 95% CI with upper and lower limits of between 34.8% – 67.6%. Patients from Cohort 4 that met the ≥20 ng cfDNA input requirements experienced an ORR of 48.8% and a 95% CI with upper and lower limits of between 32.9 – 64.9%. For patients in Cohort 5b, all patients met the ≥30 ng cfDNA input and experienced an ORR of 81.3% and a 95% CI with upper and lower limits of between 54.4% – 96.0%

Table 22: Best overall response per BIRC assessment in CTA(+)/CDx(+), CTA(-)/CDx(+), CTA(+), and CDx(+) patients in Cohort 4 by CDx sample requirements (PAS-A)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

	CTA(+)/CDx(+) N=39		CTA(+) N=69	
	n (%)	95% CI[1]	n (%)	95% CI[1]
Overall Response Rate (ORR: CR + PR)	20 (51.3)	(34.8, 67.6)	28 (40.6)	(28.9, 53.1)

[1] The 95% CI calculated using Clopper-Pearson method

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

	CTA(+)/CDx(+) N=41		CTA(+) N=69	
	n (%)	95% CI[1]	n (%)	95% CI[1]
Overall Response Rate (ORR: CR + PR)	20 (48.8)	(32.9, 64.9)	28 (40.6)	(28.9, 53.1)

[1] The 95% CI calculated using Clopper-Pearson method

Table 23: Best overall response per BIRC assessment in CTA(+)/CDx(+), CTA(-)/CDx(+), CTA(+), and CDx(+) patients in Cohort 5b by CDx sample requirements (PAS-B)

F1LCDx sample requirement: Recommended (cfDNA input ≥ 30 ng)

	CTA(+)/CDx(+) N=16		CTA(+) N=28	
	n (%)	95% CI[1]	n (%)	95% CI[1]
Overall Response Rate (ORR: CR + PR)	13 (81.3)	(54.4, 96.0)	19 (67.9)	(47.6, 84.1)

[1] The 95% CI calculated using Clopper-Pearson method

F1LCDx sample requirement: Minimum (cfDNA input ≥ 20 ng)

	CTA(+)/CDx(+) N=16		CTA(+) N=28	
	n (%)	95% CI[1]	n (%)	95% CI[1]
Overall Response Rate (ORR: CR + PR)	13 (81.3)	(54.4, 96.0)	19 (67.9)	(47.6, 84.1)

[1] The 95% CI calculated using Clopper-Pearson method

Samples with VAF as low as 0.16% for indels and 0.21% for SNVs were considered positive by F1LCDx in the clinical bridging study. Since F1LCDx does not have a strict VAF cut-off for positivity, it is possible that patients with VAF below 0.16% for indels and 0.21% for SNVs that lead to MET 14 skipping can be reported as positive. The clinical effectiveness of F1LCDx has not been demonstrated for patients with NSCLC that have SNVs and indels that lead to MET exon 14 skipping with variant allele frequencies (VAF) below 0.21% for SNVs and 0.16% VAF for indels. A limitation addressing the uncertainty of the clinical effectiveness of the device for MET exon 14 skipping alteration with VAFs below those evaluated in the clinical study is included as a limitation to the device (also refer to Section XII. C. below).

Estimated drug efficacy in F1LCDx(+) patients
The ORR by BIRC assessment in F1LCDx(+) patients was calculated for Cohort 4 and Cohort 5b, separately. Because all CTA(-) patients are tested as negative by CDx (i.e. NPA=100%) and thus PPV is estimated as 100%, the results do not vary with Pr(CTA+) values and the ORR in F1LCDx(+) population is estimated as the same as the ORR in F1LCDx [CTA(+)/CDx(+)] population. For F1LCDx(+) patients meeting "Recommended" CDx sample requirement (cfDNA input ≥ 30 ng), the ORR (95% CI) is 51.3% (34.8%, 67.6%) in Cohort 4 and 81.3% (54.4%, 96.0%) in Cohort 5b, respectively. For CDx(+) patients meeting "Minimum" CDx sample requirement (cfDNA input ≥ 20 ng), the ORR (95% CI) is 48.8% (32.9%, 64.9%) in Cohort 4 and 81.3% (54.4%, 96.0%) in Cohort 5b, respectively.

Sensitivity analysis on missing F1LCDx results
The impact of missing F1LCDx results on the concordance between CTA and F1LCDx and final drug efficacy in F1LCDx(+) patients was evaluated by imputing the missing F1LCDx results using multiple imputation method. Samples were considered missing if the samples were not tested, if they were tested but returned an invalid result or if they did not satisfy cfDNA input level. Multivariate logistic regression analyses were performed to identify the clinically relevant covariates that were associated with the F1LCDx device output and clinical outcome, respectively. The sensitivity analysis using the multiple imputation method for ORR by BIRC for CDx(+) patients in Cohort 4 was performed for the different sample input requirements. As the NPA was assumed as 100%, the ORR in CDx(+) population was estimated only based on ORR in the CTA(+)/CDx(+) population and did not vary with Pr(CTA+). For Cohort 4, the imputed ORR (95% CI) by BIRC were estimated to be 46.5% (32.6%, 60.9%) given "Recommended" sample requirement and 47.2% (33.3%, 61.5%) given "Minimum" sample requirement, similar to the estimated ORRs in F1LCDx(+) patients based on observed data and similar to estimated ORRs in CTA(+) patients obtained in the GEOMETRY mono-1 trial Cohort 4 [40.6% (28.9%, 84.1%)]. For Cohort 5b, the imputed ORRs and two-sided 95% CIs by BIRC were estimated to be 75.3% (53.3%, 94.4%) given "Recommended" sample requirement and 78.1% (55.6%, 95.5%) given "Minimum" sample requirement, similar to the estimated ORRs in

F1LCDx(+) patients based on observed data and similar to estimated ORRs in CTA+ patients obtained in the GEOMETRY mono-1 trial Cohort 5b [67.9% (47.6%, 84.1%)]. The sensitivity analysis results demonstrated that the concordance between CTA and F1LCDx and final drug efficacy in F1LCDx(+) population are robust to missing F1LCDx results.

Duration of Response

The Duration of Response (DOR) data from patients enrolled in GEOMETRY mono-1 utilized in the bridging study were derived from the October 28, 2019 study data cut-off. DOR analysis was performed on all available patient samples for DOR analysis met "Recommended" and "Minimum" criteria by F1LCDx, which is 20 patients for both sample requirements in Cohort 4 and 13 patients for both sample requirements in Cohort 5b.

Table 24 shows summary of DOR by BIRC for CTA(+)/CDx(+) patients in Cohort 4 given different sample requirements. The median time (95% CI) in month was estimated to be 9.84 (4.17, 14.06) given both "Recommended" and "Minimum" sample requirements, similar to the estimates obtained in the GEOMETRY mono-1 trial Cohort 4 [9.7 (5.5, 13.0)] (refer to TABRECTA label and Table 25). Table 25 shows summary of DOR by BIRC for CTA(+)/CDx(+) patients in Cohort 5b given different sample requirements. The median time (95% CI) in month was estimated to be 25.33 (4.24, 25.33) given both "Recommended" and "Minimum" sample requirements, longer than the estimates obtained in the GEOMETRY mono-1 trial Cohort 5b [12.6 (5.5, 25.3)] (refer to TABRECTA label and Table 25). This was probably caused by the small number of events in CTA(+)/CDx(+) patients (n: number of events = 7, Table 25).

Table 24: Summary of duration of response (CR+PR) per BIRC assessment for CTA(+)/CDx(+) patients in Cohort 4 by F1LCDx sample requirement (PAS-A)

	CTA(+)/CDx(+) F1LCDx sample requirements		
	Recommended (cfDNA input ≥ 30 ng)	Minimum (cfDNA input ≥ 20 ng)	CTA(+)
Duration of Response (DOR)			
Total number of patients with confirmed PR or CR	N=20	N=20	N= 28
Median (months) (95% CI)	9.84 (4.17, 14.06)	9.84 (4.17, 14.06)	9.7 (5.5, 13.0)
Patients with DOR > 12 months – (%)	40%	40%	32%

N: The total number of patients with confirmed CR or PR in (CTA+, CDx+). It is the denominator for percentage (%) calculation

Table 25: Summary of duration of response (CR+PR) per BIRC assessment for CTA(+)/CDx(+) patients in Cohort 5b by F1LCDx sample requirement (PAS-B)

| | CTA(+)/CDx(+) F1LCDx sample requirements | | CTA(+) |
	Recommended (cfDNA input ≥ 30 ng)	Minimum (cfDNA input ≥ 20 ng)	
Duration of Response (DOR)			
Total number of patients with confirmed PR or CR	N=13	N=13	N= 19
Median (months) (95% CI)	25.33 (4.24, 25.33)	25.33 (4.24, 25.33)	(12.6 (5.5, 25.3)
Patients with DOR > 12 months – (%)	46%	46%	47%

N: The total number of patients with confirmed CR or PR in (CTA+, CDx+). It is the denominator for percentage (%) calculation

3. 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 was a full-time employee of the sponsor and 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: 1
- 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 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 SNVs and indels that lead to *MET* exon 14 skipping in NSCLC patients to be treated with capmatinib, the effectiveness of the F1LCDx assay was demonstrated through a clinical bridging study using specimens from patients screened for enrollment into the GEOMETRY mono-1 study. The data from the analytical validation and clinical bridging studies support the reasonable assurance of safety and effectiveness of the F1LCDx assay when used in accordance with the indications for use. Data from the GEOMETRY mono-1 study show that patients who had qualifying SNVs and indels that lead to *MET* exon 14 skipping received benefit from treatment with capmatinib and support the addition of the CDx indication to F1LCDx.

B. Safety Conclusions

The risks of the device are based on data collected in the validation studies conducted to support sPMA approval, as described above. The F1LCDx assay assay is an in vitro diagnostic test, which involves testing of cfDNA extracted from blood or plasma.

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 indicated therapy.

C. Benefit-Risk Determination

The GEOMETRY mono-1 study is a prospectively designed, multicenter, open- label, single arm Phase II study to evaluate the safety and efficacy of the MET inhibitor TABRECTA (capmatinib) in adult patients with EGFR wild-type (wt) and ALK-rearrangement negative, locally advanced or metastatic NSCLC harboring MET exon 14 skipping alterations. The primary objective was to assess overall response rate (ORR) by a Blinded Independent Review Committee (BIRC) assessment per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria by cohort to determine whether treatment with TABRECTA (capmatinib) is effective. Duration of response (DOR) as assessed by BIRC is the key secondary endpoint. GEOMETRY mono-1 is an ongoing study that was initiated on June 11, 2015 with first patient first visit. Cohort 4 only enrolled pretreated (second and third line) patients with MET exon 14 deletions, and Cohort 5b only enrolled treatment-naïve patients with MET

exon 14 deletions. Patients were screened for enrollment into Cohorts 4 and 5b for MET exon 14 deletion status using tissue based MET exon 14 deletion reverse-transcriptase PCR (RT-PCR) clinical trial assay (CTA). Plasma samples were collected and stored prior to study treatment for retrospective testing. Patients enrolled in Cohorts 4 and 5b received 400mg of TABRECTA (capmatinib) orally twice daily in tablet form. Efficacy was evaluated every six weeks from the first day of treatment until RECIST 1.1 disease progression.

The GEOMETRY-mono 1 clinical trial met its primary objective demonstrating a statistically significant improvement in ORR by a blinded independent review committee (BIRC) in patients with MET exon 14 skipping positive tumors. TABRECTA (capmatinib demonstrated an estimated 40.6% (95% CI 28.9 - 53.1%) best overall response rate (ORR) by CTA in the MET exon 14 skipping positive patients from Cohort 4. An estimated 67.9% (95% CI 47.6 - 84.1%) best overall response rate was calculated in the MET exon 14 skipping positive patients from Cohort 5b. This trial demonstrated meaningful clinical benefit of TABRECTA (capmatanib) treatment in NSCLC patients with MET exon 14 skipping.

A clinical bridging study was conducted to evaluate: 1) the concordance between *MET* single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping status by the CTA and FoundationOne Liquid CDx and 2) the clinical validity of FoundationOne Liquid CDx in identifying NSCLC patients with MET exon 14 skipping mutations who may be eligible for treatment with TABRECTA (capmatanib). The point estimates (95% CI) of PPA, NPA and OPA in Cohort 4 for samples meeting "Minimum" CDx sample requirements were 71.9% (58.5%, 83.0%), 100% (93.4%, 100%) and 85.6% (77.6%, 91.5%) respectively, when excluding CDx invalid results. The point estimates (95% CI) of PPA, NPA and OPA in Cohort 5b for samples meeting "Minimum" CDx sample requirements were 61.5% (40.6%, 79.8%), 100% (89.7%, 100%) and 83.3% (71.5%, 91.7%) respectively, when excluding CDx invalid results. Of note, the point estimate for NPA is 100% in combined cohorts or individually for Cohort 4 and Cohort 5b, for either "Recommended" or "Minimum" sample requirements, thus the bridged efficacy is equivalent to the efficacy of the CTA+/F1L+ population. For the double positive samples (CTA+, F1L+), that met the "Minimum" sample requirement, ORR was determined to be 48.8% (32.9%, 64.9%) in Cohort 4 and 81.3% (54.4%, 96.0%) in Cohort 5b, respectively. Sensitivity analysis maintained the efficacy at 47.2% (33.3%, 61.5%) in Cohort 4 and 78.1% (55.6%, 95.5%) in Cohort 5, given "Minimum" sample requirement. This data demonstrates the meaningful clinical benefit of FoundationOne Liquid CDx in selecting NSCLC patients with alterations that lead to MET exon 14 skipping, for treatment with TABRECTA (capmatinib). There is potential risk associated with the use of this device, mainly due to 1) false positive, false negatives, or failure to provide a result and 2) incorrect interpretation of test results by the user.

The risks of the FoundationOne Liquid CDx for the selection of NSCLC patients with alterations leading to *MET* Exon 14 skipping, 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 combination 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 false results are partially mitigated by the validation results summarized above.

In addition, the significant risks of false negative results are partially mitigated by a recommendation that those patients whose plasma generate a negative result for those included in Table 1 should have their tumor mutation status verified by using a FDA approved tumor test. Additional factors to be considered in determining probable risks and benefits for FoundationOne Liquid CDx included: analytical performance of the device, representation of variants in the major effectiveness studies, and the availability of alternative tests. The FoundationOne Liquid CDx assay has been analytically validated as summarized above; however, multiple post-market studies are also planned to confirm the data provided for. To supplement the premarket data, some post-market studies are planned as summarized in Section XIII, below. Further given the uncertainties that remain based on the analytical and clinical validation data, the following limitations are included in the device labeling:

- The analytical accuracy for the FoundationOne Liquid CDx assay for the detection of SNVs and indels that lead to MET exon 14 skipping has not been demonstrated for samples with variant allele frequencies (VAF) below 0.34% for base substitutions and 0.73% VAF for small insertions and small deletions.
- TABRECTA® efficacy has not been established in patients with MET single nucleotide variants (SNVs) <0.21% VAF and in patients with MET indels <0.16% VAF tested with FoundationOne Liquid CDx
- Representation of SNV and indels that lead to MET exon 14 skipping that represent biomarker rule category 1 and 2 (refer to Section V.I.5. for CDx biomarker definition), were limited in the analytical validation studies.

The data support that for the FoundationOne Liquid CDx assay, and the indications noted in the intended use statement, the probable benefits outweigh the probable risks.
To supplement the premarket data, some post-market studies are planned as summarized in Section XIII, below.

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 selection of NSCLC patients with *MET* single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping alterations, for treatment with TABRECTA

(capmatinib), the probable benefits of FoundationOne Liquid CDx 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 studies support the clinical utility of the F1LCDx assay assay as an aid for the identification of cancer patients for whom the therapies listed in Table 1 of the Intended Use/Indications for Use statement may be indicated.

Data from the clinical bridging study supports the utility of F1LCDx assay as an aid in selecting NSCLC patients with relevant SNVs and indels leading to *MET* exon 14 skippin who may be eligible for treatment with capmatinib.

XIII. CDRH DECISION

CDRH issued an approval order on July 15, 2021. The final clinical conditions of approval cited in the approval order are described below.

1. Blood Collection Tubes
    a. FMI must demonstrate clinically insignificant variability when different lots of the FoundationOne® Liquid CDx Blood Collection tube are used with the FoundationOne® Liquid CDx assay. FMI must provide data from a robust and high confidence precision study. This study must confirm the FoundationOne® Liquid CDx assay's precision when the FoundationOne® Liquid CDx cfDNA Blood Collection tubes are used and must use replicate samples from each of multiple different patients. Each patient who donates specimens for this study must have plasma collected in a total of four tubes, each from two tube lots; three lots are required to be represented in the study. This is important to assess variability between tube lots and across patient specimens. Each replicate must be run at or near the minimum standardized cfDNA input (i.e., at a target concentration of 30 ng). The samples must be collected from patients with at least 10 different tumor types and the study must include at least 10 pathogenic substitutions and 10 pathogenic indels that are identified by the FoundationOne® Liquid CDx assay. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens collected in the FoundationOne® Liquid cfDNA Blood Collection tubes in the intended use population.

    b. FMI must provide robust and high confidence data from a well-designed and well-controlled study which is intended to confirm the shelf-life claims for the FoundationOne® Liquid cfDNA Blood

Collection tubes when used in conjunction with the FoundationOne® Liquid CDx assay. FMI must provide evidence that when samples from the same patient collected in newly manufactured tubes, as well as in tubes that are at the end of their shelf life, are used in the FoundationOne® Liquid CDx assay, the FoundationOne® Liquid CDx assay performance meets the clinical and analytical performance claim in the FoundationOne® Liquid CDx assay authorized labeling.

c. FMI must provide robust and high confidence data that the impact of preanalytical variables associated with the use of the FoundationOne® Liquid CDx cfDNA Blood Collection tubes, such as hemolysis, has been validated for the FoundationOne® Liquid CDx test system and that any impact of these factors on the FoundationOne® Liquid CDx assay has been appropriately mitigated. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens collected in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes in the intended use population.

d. To support use of results submitted in FMI's clinical study generated from samples collected within 24 hours from cancer patients, FMI must provide robust and high confidence data from an appropriately designed study to confirm the claimed stability of cfDNA in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes. This study must compare FoundationOne® Liquid CDx results generated from freshly drawn blood specimens to FoundationOne® Liquid CDx assay results generated from matched specimens (i.e., collected at the same time from the same patient) stored in the FoundationOne® Liquid CDx cfDNA Blood Collection tube for a minimum of 24 hours. This study must be performed with replicate samples, when feasible, at each time point, and the samples tested must adequately represent all variant types across several tumor types at each tested time point. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens the intended use population.

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e. FMI must provide robust and high confidence data from a stability study which demonstrates acceptable stability of whole blood collected from the CDx intended use patients and stored in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes. The study must confirm the claimed cfDNA storage stability and must confirm the suppression of white blood cells lysis across multiple lots. This study must also use the amount of cfDNA isolated and electropherogram data as a comparator method, in addition to sequencing results and quality metrics. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when used on specimens

collected in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes in the intended use population.

    f. FMI must demonstrate clinically insignificant variability on the performance of the FoundationOne® Liquid CDx assay when specimens collected in FoundationOne® Liquid CDx cfDNA Blood Collection tubes are handled at different centrifugation conditions. The study must assess conditions that are below and above recommended relative centrifugal force and centrifugation time to account for potential performance issues that could occur due to centrifuge malfunction or operator errors. The data from this study must be adequate to demonstrate that clinically significant inaccurate results are minimized when expected handling conditions are used on specimens collected in the FoundationOne® Liquid CDx cfDNA Blood Collection tubes in the intended use population.

2. Software:
    a. FMI must appropriately validate modifications to the curating and reporting of variant results, including reporting levels for mutation profiling, and modifications to the report formatting that were made to the software following review. FMI must provide software validation documentation adequate to demonstrate that these modifications do not adversely affect the safety and effectiveness of the device.

    b. FMI must appropriately validate software infrastructure changes and migration to of the analysis pipeline and associated software to cloud services, including any impact of these software modifications on the cybersecurity of FoundationOne® Liquid CDx assay test system. FMI must provide software validation documentation adequate to demonstrate that these modifications do not adversely affect he safety and effectiveness of the device.

In addition to the conditions of approval above, FMI agreed to implement alternative controls to address violations of the current good manufacturing practice requirements of the Quality System regulations found at Title 21, Code of Federal Regulations, Part 820 identified at the manufacturing facility of the cfDNA blood collection tubes used with the FoundationOne® Liquid CDx assay. FDA subsequently approved a variance plan on August 26, 2020 that met the requirements set forth in 21 C.F.R. 820.1(e)(2).

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.

XV. <u>**REFERENCES**</u>

None.