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®CDx (F1CDx)
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:	P170019/S011
Date of FDA Notice of Approval:	May 6, 2020

The original PMA (P170019) for FoundationOne®CDx (F1CDx) was approved on November 30, 2017 for the detection of genetic alterations in patients who may benefit from one of fifteen FDA-approved therapies for non-small cell lung cancer (NSCLC), melanoma, breast cancer, colorectal cancer, and ovarian cancer. Subsequently, six PMA supplements were approved for expanding the indications for use of F1CDx since its original approval. PMA supplement (P170019/S005) for adding genomic loss of heterozygosity (LOH) was approved on April 10, 2019. PMA supplement (P170019/S004) for adding an indication for LYNPARZA® (olaparib) in ovarian cancer patients with BRCA1/2 alterations was approved on July 1, 2019. PMA supplement (P170019/S008) for adding an indication for TAGRISSO® (osimertinib) in NSCLC patients with EGFR exon 19 deletions and EGFR exon 21 L858R alterations was approved on July 1, 2019. PMA supplement (P170019/S006) for adding an indication for PIQRAY® (alpelisib) in breast cancer patients with PIK3CA alterations was approved on December 3, 2019. PMA supplement (P170019/S010) for adding a second site in Research Triangle Park, NC, where the F1CDx assay will be performed was approved on December 16, 2019. PMA supplement (P170019/S013) for adding an indication for PEMZYRE® (pemigatinib) in cholangiocarinoma patients with FGFR2 fusions was approved on April 17, 2020.

The current supplement was submitted to expand the intended use of F1CDx to include a companion diagnostic indication for single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping in NSCLC patients who may benefit from treatment with TABRECTA® (capmatinib).

II. INDICATIONS FOR USE

FoundationOne®CDx (F1CDx) is a next generation sequencing based *in vitro* diagnostic device for detection of substitutions, insertion and deletion alterations (indels) and copy number alterations (CNAs) in 324 genes and select gene rearrangements, as well as genomic signatures including microsatellite instability (MSI) and tumor mutational burden (TMB) using DNA isolated from formalin-fixed paraffin embedded (FFPE) tumor tissue specimens. The test is intended 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. Additionally, F1CDx is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with solid malignant neoplasms. Genomic findings other than those listed in Table 1 are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Table 1. Companion diagnostic indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions and *EGFR* exon 21 L858R alterations	GILOTRIF® (afatinib), IRESSA® (gefitinib), TAGRISSO® (osimertinib), or TARCEVA® (erlotinib)
	EGFR exon 20 T790M alterations	TAGRISSO® (osimertinib)
	ALK rearrangements	ALECENSA® (alectinib), XALKORI® (crizotinib), or ZYKADIA® (ceritinib)
	BRAF V600E	TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib)
	MET single nucleotide variants (SNVs) and indels that lead to *MET* exon 14 skipping	TABRECTA™ (capmatinib)
Melanoma	*BRAF* V600E	TAFINLAR® (dabrafenib) or ZELBORAF® (vemurafenib)
	BRAF V600E and V600K	MEKINIST® (trametinib) or COTELLIC® (cobimetinib) in combination with ZELBORAF® (vemurafenib)
Breast cancer	*ERBB2* (HER2) amplification	HERCEPTIN® (trastuzumab), KADCYLA® (ado-trastuzumab-emtansine), or PERJETA® (pertuzumab)
	PIK3CA C420R, E542K, E545A, E545D [1635G>T only], E545G, E545K, Q546E, Q546R, H1047L, H1047R, and H1047Y alterations	PIQRAY® (alpelisib)

Indication	Biomarker	Therapy
Colorectal cancer	*KRAS* wild-type (absence of mutations in codons 12 and 13)	ERBITUX® (cetuximab)
	KRAS wild-type (absence of mutations in exons 2, 3, and 4) and *NRAS* wild-type (absence of mutations in exons 2, 3, and 4)	VECTIBIX® (panitumumab)
Ovarian cancer	*BRCA1/2* alterations	LYNPARZA® (olaparib) or RUBRACA® (rucaparib)
Cholangiocarcinoma	*FGFR2* fusions and select rearrangements	Pemazyre™ (pemigatinib)

The test is also used for detection of genomic loss of heterozygosity (LOH) from formalin-fixed, paraffin-embedded (FFPE) ovarian tumor tissue. Positive homologous recombination deficiency (HRD) status (F1CDx HRD defined as tBRCA-positive and/or LOH high) in ovarian cancer patients is associated with improved progression-free survival (PFS) from RUBRACA (rucaparib) maintenance therapy in accordance with the RUBRACA product label.

The F1CDx assay is be performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC.

III. CONTRAINDICATIONS

There are no known contraindications.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the FoundationOne®CDx assay labeling.

V. DEVICE DESCRIPTION

FoundationOne®CDx (F1CDx) is performed at Foundation Medicine, Inc. sites located in Cambridge, MA and Morrisville, NC. The assay includes reagents, software, instruments and procedures for testing DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumor samples.

The assay employs a single DNA extraction method from routine FFPE biopsy or surgical resection specimens, 50-1000 ng of which undergoes whole-genome shotgun library construction and hybridization-based capture of all coding exons from 309 cancer-related genes, 1 promoter region, 1 non-coding RNA (ncRNA), and select intronic regions from 34 commonly rearranged genes, 21 of which also include the coding exons (refer to Table 2 and Table 3, below, for the complete list of genes included in F1CDx). In total, the assay therefore detects alterations in a total of 324 genes. Using the Illumina® HiSeq 4000 platform, hybrid-capture selected libraries will be sequenced to high uniform depth (targeting > 500X median coverage with > 99% of exons at coverage > 100X). Sequence data is processed using a customized analysis

pipeline designed to detect all classes of genomic alterations, including base substitutions, indels, copy number alterations (amplifications and homozygous deletions), and selected genomic rearrangements (e.g., gene fusions). Additionally, genomic signatures including microsatellite instability (MSI), tumor mutational burden (TMB), and positive homologous recombination deficiency (HRD) status (tBRCA-positive and/or LOH high) will be reported.

Table 2. Genes with full coding exonic regions included in F1CDx for the detection of substitutions, insertions and deletions (indels), and copy number alterations (CNAs)

ABL1	*BRAF*	*CDKN1A*	*EPHA3*	*FGFR4*	*IKZF1*	*MCL1*	*NKX2-1*	*PMS2*	*RNF43*	*TET2*
ACVR1B	*BRCA1*	*CDKN1B*	*EPHB1*	*FH*	*INPP4B*	*MDM2*	*NOTCH1*	*POLD1*	*ROS1*	*TGFBR2*
AKT1	*BRCA2*	*CDKN2A*	*EPHB4*	*FLCN*	*IRF2*	*MDM4*	*NOTCH2*	*POLE*	*RPTOR*	*TIPARP*
AKT2	*BRD4*	*CDKN2B*	*ERBB2*	*FLT1*	*IRF4*	*MED12*	*NOTCH3*	*PPARG*	*SDHA*	*TNFAIP3*
AKT3	*BRIP1*	*CDKN2C*	*ERBB3*	*FLT3*	*IRS2*	*MEF2B*	*NPM1*	*PPP2R1A*	*SDHB*	*TNFRSF14*
ALK	*BTG1*	*CEBPA*	*ERBB4*	*FOXL2*	*JAK1*	*MEN1*	*NRAS*	*PPP2R2A*	*SDHC*	*TP53*
ALOX12B	*BTG2*	*CHEK1*	*ERCC4*	*FUBP1*	*JAK2*	*MERTK*	*NT5C2*	*PRDM1*	*SDHD*	*TSC1*
AMER1	*BTK*	*CHEK2*	*ERG*	*GABRA6*	*JAK3*	*MET*	*NTRK1*	*PRKAR1A*	*SETD2*	*TSC2*
APC	*C11orf30*	*CIC*	*ERRFI1*	*GATA3*	*JUN*	*MITF*	*NTRK2*	*PRKCI*	*SF3B1*	*TYRO3*
AR	*CALR*	*CREBBP*	*ESR1*	*GATA4*	*KDM5A*	*MKNK1*	*NTRK3*	*PTCH1*	*SGK1*	*U2AF1*
ARAF	*CARD11*	*CRKL*	*EZH2*	*GATA6*	*KDM5C*	*MLH1*	*P2RY8*	*PTEN*	*SMAD2*	*VEGFA*
ARFRP1	*CASP8*	*CSF1R*	*FAM46C*	*GID4 (C17orf39)*	*KDM6A*	*MPL*	*PALB2*	*PTPN11*	*SMAD4*	*VHL*
ARID1A	*CBFB*	*CSF3R*	*FANCA*	*GNA11*	*KDR*	*MRE11A*	*PARK2*	*PTPRO*	*SMARCA4*	*WHSC1*
ASXL1	*CBL*	*CTCF*	*FANCC*	*GNA13*	*KEAP1*	*MSH2*	*PARP1*	*QKI*	*SMARCB1*	*WHSC1L1*
ATM	*CCND1*	*CTNNA1*	*FANCG*	*GNAQ*	*KEL*	*MSH3*	*PARP2*	*RAC1*	*SMO*	*WT1*
ATR	*CCND2*	*CTNNB1*	*FANCL*	*GNAS*	*KIT*	*MSH6*	*PARP3*	*RAD21*	*SNCAIP*	*XPO1*
ATRX	*CCND3*	*CUL3*	*FAS*	*GRM3*	*KLHL6*	*MST1R*	*PAX5*	*RAD51*	*SOCS1*	*XRCC2*
AURKA	*CCNE1*	*CUL4A*	*FBXW7*	*GSK3B*	*KMT2A (MLL)*	*MTAP*	*PBRM1*	*RAD51B*	*SOX2*	*ZNF217*
AURKB	*CD22*	*CXCR4*	*FGF10*	*H3F3A*	*KMT2D (MLL2)*	*MTOR*	*PDCD1*	*RAD51C*	*SOX9*	*ZNF703*
AXIN1	*CD274*	*CYP17A1*	*FGF12*	*HDAC1*	*KRAS*	*MUTYH*	*PDCD1LG2*	*RAD51D*	*SPEN*	
AXL	*CD70*	*DAXX*	*FGF14*	*HGF*	*LTK*	*MYC*	*PDGFRA*	*RAD52*	*SPOP*	
BAP1	*CD79A*	*DDR1*	*FGF19*	*HNF1A*	*LYN*	*MYCL*	*PDGFRB*	*RAD54L*	*SRC*	
BARD1	*CD79B*	*DDR2*	*FGF23*	*HRAS*	*MAF*	*MYCN*	*PDK1*	*RAF1*	*STAG2*	
BCL2	*CDC73*	*DIS3*	*FGF3*	*HSD3B1*	*MAP2K1*	*MYD88*	*PIK3C2B*	*RARA*	*STAT3*	
BCL2L1	*CDH1*	*DNMT3A*	*FGF4*	*ID3*	*MAP2K2*	*NBN*	*PIK3C2G*	*RB1*	*STK11*	
BCL2L2	*CDK12*	*DOT1L*	*FGF6*	*IDH1*	*MAP2K4*	*NF1*	*PIK3CA*	*RBM10*	*SUFU*	
BCL6	*CDK4*	*EED*	*FGFR1*	*IDH2*	*MAP3K1*	*NF2*	*PIK3CB*	*REL*	*SYK*	

BCOR	*CDK6*	*EGFR*	*FGFR2*	*IGF1R*	*MAP3K13*	*NFE2L2*	*PIK3R1*	*RET*	*TBX3*	
BCORL1	*CDK8*	*EP300*	*FGFR3*	*IKBKE*	*MAPK1*	*NFKBIA*	*PIM1*	*RICTOR*	*TEK*	

Table 3. Genes with select intronic regions for the detection of gene rearrangements, a promoter region, and an ncRNA gene

ALK introns 18, 19	*BRCA1 introns 2, 7, 8, 12, 16, 19, 20*	*ETV4 introns 5, 6*	*EZR introns 9-11*	*KIT intron 16*	*MYC intron 1*	*NUTM1 intron 1*	*RET introns 7-11*	*SLC34A2 intron 4*
BCL2 3'UTR	*BRCA2 intron 2*	*ETV5 introns 6, 7*	*FGFR1 intron 1, 5, 17*	*KMT2A (MLL) introns 6-11*	*NOTCH2 intron 26*	*PDGFRA introns 7, 9, 11*	*ROS1 introns 31-35*	*TERC ncRNA*
BCR introns 8, 13, 14	*CD74 introns 6-8*	*ETV6 introns 5, 6*	*FGFR2 intron 1, 17*	*MSH2 intron 5*	*NTRK1 introns 8-10*	*RAF1 introns 4-8*	*RSPO2 intron 1*	*TERT Promoter*
BRAF introns 7-10	*EGFR introns 7, 15, 24-27*	*EWSR1 introns 7-13*	*FGFR3 intron 17*	*MYB intron 14*	*NTRK2 Intron 12*	*RARA intron 2*	*SDC4 intron 2*	*TMPRSS2 introns 1-3*

Test Output
The output of the test includes:

Category 1: CDx Claims noted in Table 1 of the Intended Use

Category 2: Cancer Mutations with Evidence of Clinical Significance

Category 3: Cancer Mutations with Potential Clinical Significance

Genomic findings other than those listed in Table 1 of the intended use statement (i.e., Categories 2 and 3) are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Test Kit Contents
The test includes a sample shipping kit, which is sent to ordering laboratories. The shipping kit contains the following components:

- Specimen Preparation Instructions
- Shipping Instructions
- Return Shipping Label

Instruments
The F1CDx assay is intended to be performed with serial number-controlled instruments as indicated in Table 4, below. All instruments are qualified by Foundation Medicine, Inc. (FMI) under FMI's Quality System.

Table 4. Instruments for use with the F1CDx assay

Instrument
Illumina HiSeq 4000
Illumina cBot
Beckman Biomek NXP Span-8 Liquid Handler
Thermo Scientific Kingfisher Flex DW 96
Covaris LE220

Test Process

All assay reagents included in the F1CDx assay process are qualified by FMI and are compliant with the medical device Quality System Regulation (QSR).

A. Specimen Collection and Preparation

Formalin-fixed, paraffin-embedded (FFPE) tumor specimens are collected and prepared following standard pathology practices. FFPE specimens may be received either as unstained slides or as an FFPE block.

Prior to starting the assay, a Hematoxylin and Eosin (H&E) stained slide is prepared, and then reviewed by a board-certified pathologist to confirm disease ontology and to ensure that adequate tissue (0.6 mm^3), tumor content (≥ 20% tumor) and sufficient nucleated cells are present to proceed with the assay.

B. DNA Extraction

Specimens passing pathology review are queued for DNA extraction which begins with lysis of cells from FFPE tissue by digestion with a proteinase K buffer followed by automated purification using the 96-well KingFisher™ FLEX Magnetic Particle Processor.

After completion of DNA extraction, double-stranded DNA (dsDNA) is quantified by the Quant-iT™ PicoGreen® fluorescence assay using the provided lambda DNA standards (Invitrogen) prior to Library Construction (LC). The sample must yield a minimum of 55 ng of genomic DNA to ensure sufficient DNA for quality control (QC) and to proceed with LC.

C. Library Construction

Library Construction (LC) begins with the normalization of DNA to 50-1000 ng. The normalized DNA samples are randomly sheared (fragmented) to ~200 bp by adaptive focused acoustic sonication using the Covaris LE220 before purification with a 1.8X volume of AMPure® XP Beads (Agencourt®). Solid-phase reversible immobilization (SPRI) purification and subsequent library construction with the NEBNext® reagents (custom-filled kits by NEB), including mixes for end repair, dA addition and ligation, are performed in 96-well plates (Eppendorf) on the Bravo Benchbot (Agilent) using the "with-bead" protocol[1] to maximize reproducibility and library yield. Indexed (6 bp barcodes) sequencing libraries are PCR amplified with HiFi™ (Kapa) for 10 cycles and subsequently 1.8X SPRI purified. Purification and dilution for QC are performed.

Following LC, a QC procedure is performed by quantifying single-stranded DNA (ssDNA) from purified libraries using the Quant-iT™ OliGreen® ssDNA Assay Kit (Life Technologies) read on a Molecular Devices Multimode SpectraMax M2 plate Reader. Libraries yielding insufficient sequencing library are failed.

D. Hybrid Capture

Hybrid Capture (HC) begins with normalization of each library to 500-2000 ng. Normalized samples then undergo solution hybridization which is performed using a > 50-fold molar excess of a pool of individually synthesized 5'-biotinylated DNA 120 bp oligonucleotides. The baits target ~1.8 Mb of the human genome including all coding exons of 309 cancer-related genes, introns or non-coding regions of 35 genes, plus > 3,500 single nucleotide polymorphisms (SNPs) located throughout the genome. Baits are designed by tiling 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; SNP targets are allocated one bait each. Intronic baits are filtered for repetitive elements[2] as defined by the UCSC Genome RepeatMasker track.

After hybridization, the library-bait duplexes are captured on paramagnetic MyOne™ streptavidin beads (Invitrogen), and off-target material is removed by washing one time with 1X SSC at 25°C and four times with 0.25X SSC at 55°C. The PCR master mix is added to directly amplify (12 cycles) the captured library from the washed beads.[3] After 12 cycles of amplification, the samples are 1.8X SPRI purified. Purification and dilution for QC are performed.

QC for HC is performed by measuring dsDNA yield using the Quant-iT™ PicoGreen® dsDNA Assay Kit (Life Technologies) read on a Molecular Devices Multimode SpectraMax M2 plate Reader. Captured libraries yielding less than 140 ng of sequencing library are failed.

E. Sequencing

Sequencing is performed using off-board clustering on the Illumina cBot with patterned flow cell technology to generate monoclonal clusters from a single DNA template followed by sequencing using sequencing by synthesis (SBS) chemistry on the Illumina HiSeq 4000. Fluorescently labeled 3′-blocked dNTPs along with a polymerase are incorporated through the flow cell to create a growing nucleotide chain that is excited by a laser. A camera captures the emission color of the incorporated base and then is cleaved off. The terminator is then removed to allow the nucleotide to revert to its natural form and to allow the polymerase to add another base to the growing chain. A new pool of fluorescently labeled 3′-blocked dNTPs are added with each new sequencing cycle. The color changes for each new cycle as a new base is added to the growing chain. This method allows for millions of discrete clusters of clonal copies of DNA to be sequenced in parallel.

F. Sequence Analysis

Sequence data are analyzed using proprietary software developed by FMI. Sequence data are mapped to the human genome (hg19) using Burrows-Wheeler Aligner (BWA) v0.5.9.[4] PCR duplicate read removal and sequence metric collection are performed using Picard 1.47 (http://picard.sourceforge.net) and SAMtools 0.1.12a.[5] Local alignment optimization is performed using Genome Analysis Toolkit (GATK) 1.0.4705.[6] Variant calling is performed only in genomic regions targeted by the test.

Base substitution detection is performed using a Bayesian methodology, which allows for the detection of novel somatic alterations at low mutant allele frequency (MAF) and increased sensitivity for alterations at hotspot sites through the incorporation of tissue-specific prior expectations.[7] Reads with low mapping (mapping quality < 25) or base calling quality (base calls with quality ≤ 2) are discarded. Final calls are made at MAF ≥ 5% (MAF ≥ 1% at hotspots).

To detect indels, *de novo* local assembly in each targeted exon is performed using the de-Bruijn approach.[8] Key steps are:

- Collecting all read-pairs for which at least one read maps to the target region.
- Decomposing each read into constituent k-mers and constructing an enumerable graph representation (de-Bruijn) of all candidate non-reference haplotypes present.
- Evaluating the support of each alternate haplotype with respect to the raw read data to generate mutational candidates. All reads are compared to each of the candidate haplotypes via ungapped alignment, and a read 'vote' for each read is assigned to the candidate with best match. Ties between candidates are resolved by splitting the read vote, weighted by the number of reads already supporting each haplotype. This process is iterated until a 'winning' haplotype is selected.
- Aligning candidates against the reference genome to report alteration calls.

Filtering of indel candidates is carried out similarly to base substitutions, with an empirically increased allele frequency threshold at repeats and adjacent sequence quality metrics as implemented in GATK: % of neighboring bases mismatches < 25%, average neighboring base quality > 25, average number of supporting read mismatches ≤ 2. Final calls are made at MAF ≥ 5% (MAF ≥ 3% at hotspots).

Copy number alterations (CNAs) are detected using a comparative genomic hybridization (CGH)-like method. First, a log-ratio profile of the sample is acquired by normalizing the sequence coverage obtained at all exons and genome-wide SNPs (~3,500) against a process-matched normal control. This profile is segmented and interpreted using allele frequencies of sequenced SNPs to estimate tumor purity and copy number at each segment. Amplifications are called at segments with ≥ 6 copies (or ≥ 7 for triploid/≥ 8 for tetraploid tumors) and homozygous deletions at 0 copies, in samples with tumor purity ≥ 20%. Amplifications in *ERBB2* are called positive at segments with ≥ 5 copies for diploid tumors.

Genomic rearrangements are identified by analyzing chimeric read pairs. Chimeric read pairs are defined as read pairs for which reads map to separate chromosomes, or at a distance of over 10 megabase (Mb). Pairs are clustered by genomic coordinate of the pairs, and clusters containing at least five chimeric pairs (three for known fusions) are identified as rearrangement candidates. Filtering of candidates is performed by mapping quality (average read mapping quality in the cluster must be 30 or above) and distribution of alignment positions. Rearrangements are annotated for predicted function (e.g., creation of fusion gene).

To determine microsatellite instability (MSI) status, 95 intronic homopolymer repeat loci (10-20 bp long in the human reference genome) with adequate coverage on the F1CDx assay are analyzed for length variability and compiled into an overall MSI score via principal components analysis (PCA). Using the 95 loci, for each sample the repeat length is calculated in each read that spans the locus. The means and variances of repeat lengths are recorded. PCA is used to project the 190-dimension data onto a single dimension (the first principal component) that maximizes the data separation, producing an MSI score. Each sample is assigned a qualitative status of MSI-High (MSI-H) or MSI-Stable (MSS); ranges of the MSI score are assigned MSI-H or MSS by manual unsupervised clustering. Samples with low coverage (< 250X median) are assigned a status of MSI-unknown.

Tumor mutational burden (TMB) is measured by counting all synonymous and non-synonymous variants present at 5% allele frequency or greater and filtering out potential germline variants according to published databases of known germline polymorphisms including Single Nucleotide Polymorphism database (dbSNP) and Exome Aggregation Consortium (ExAC). Additional germline alterations still present after database querying are assessed for potential germline status and filtered out using a somatic-germline/zygosity (SGZ) algorithm. Furthermore, known and likely driver mutations are filtered out to exclude bias of the data set. The resulting mutation number is then divided by the coding region corresponding to the number of total variants counted, or 793 kb. The resulting number is communicated as mutations per Mb unit (mut/Mb).

After completion of the Analysis Pipeline, variant data are displayed in the FMI custom-developed CATi software applications with sequence QC metrics. As part of data analysis QC for every sample, the F1CDx assay assesses cross-contamination through the use of a SNP profile algorithm, reducing the risk of false-positive calls that could occur as a result of an unexpected contamination event. Sequence data are reviewed by trained bioinformatics personnel. Samples failing any QC metrics are automatically held and not released.

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 FMI as a professional service prior to approval and release by the laboratory director or designee.

H. Internal Process Controls Related to the System

Positive Control

Each assay run includes a control sample run in duplicate. The control sample contains a pool of ten 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. If SNPs are not detected as expected, this results in a QC failure, as it indicates a potential processing error.

Sensitivity Control

The HapMap control pool used as the positive control is prepared to contain variants at 5%-10% MAF which must be detected by the analysis pipeline to ensure the expected sensitivity for each run.

Negative Control

Samples are barcoded molecularly at the 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 and can detect contamination lower than 1%.

Biomarker Rules for SNVs and indels that lead to *MET* exon 14 skipping

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 FFPE tumor specimens, as listed in Table 1 of the F1CDx intended use statement. The approved CDx tests are listed in Table 5, below; for additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at: https://www.fda.gov/medical-devices/vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-vitro-and-imaging-tools. Each alternative has its own advantages and disadvantages. Physicians should consider the best method that suits their patients and that best meets their expectations.

Table 5. List of FDA approved CDx assays for genes targeted by F1CDx

	Device	Company	Technology	Therapy	Indication
HER2-Amplification	PathVysion HER-2 DNA Probe Kit	Abbott Molecular, Inc.	FISH	HERCEPTIN (trastuzumab)	Breast cancer
	PATHWAY Anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody	Ventana Medical Systems, Inc.	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	InSite HER-2/neu Kit	Biogenex Laboratories, Inc.	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	SPOT-Light HER2 CISH Kit	Life Technologies, Inc.	CISH	HERCEPTIN (trastuzumab)	Breast cancer
	Bond Oracle HER2 IHC System	Leica Biosystems	IHC	HERCEPTIN (trastuzumab)	Breast cancer
	HER2 CISH pharmDx Kit	Dako Denmark A/S	CISH	HERCEPTIN (trastuzumab)	Breast cancer
	INFORM HER2 Dual ISH DNA Probe Cocktail	Ventana Medical Systems, Inc.	Dual ISH	HERCEPTIN (trastuzumab)	Breast cancer
	HercepTest	Dako Denmark A/S	IHC	HERCEPTIN (trastuzumab) PERJETA (pertuzumab) KADCYLA (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
	HER2 FISH pharmDx Kit	Dako Denmark A/S	FISH	HERCEPTIN (trastuzumab) PERJETA (pertuzumab) KADCYLA (ado-trastuzumab emtansine)	Breast cancer Gastric or Gastroesophageal junction adenocarcinoma
BRAF-V600	THxID BRAF Kit	bioMerieux	PCR	MEKINIST (tramatenib)	Melanoma
	cobas 4800 BRAF V600 Mutation Test	Roche Molecular Systems, Inc.	PCR	ZELBORAF (vemurafenib)	Melanoma
BRAF-600E	THxID BRAF Kit	bioMerieux	PCR	TAFINLAR (dabrafenib)	Melanoma
	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	TAFINLAR (dabrafenib) MEKINIST (trametinib)	NSCLC
	therascreen BRAF V600E RGQ PCR Kit	QIAGEN	PCR	BRAFTOVI (encorafenib) Erbitux (cetuximab)	Colorectal cancer

	Device	Company	Technology	Therapy	Indication
NRAS	Praxis Extended RAS Panel	Illumina, Inc.	NGS	VECTIBIX (panitumumab)	Colorectal cancer
KRAS	**cobas** KRAS Mutation Test	Roche Molecular Systems, Inc.	PCR	ERBITUX (cetuximab) VECTIBIX (panitumumab)	Colorectal cancer
	therascreen KRAS RGQ PCR Kit	QIAGEN	PCR	ERBITUX (cetuximab) VECTIBIX (panitumumab)	Colorectal cancer
	Praxis Extended RAS Panel	Illumina, Inc.	NGS	VECTIBIX (panitumumab)	Colorectal cancer
***ALK* - fusion**	Vysis ALK Break Apart FISH Probe Kit	Abbott Molecular, Inc.	FISH	XALKORI (crizotinib)	NSCLC
	ALK (D5F3) CDx Assay	Ventana Medical Systems, Inc.	IHC	XALKORI (crizotinib)	NSCLC
***EGFR* – Exon 19 deletions & L858R**	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	TARCEVA (erlotinib) TAGRISSO (osimertinib) IRESSA (gefitinib)	NSCLC
	therascreen EGFR RGQ PCR Kit	QIAGEN	PCR	GILOTRIF (afatinib) IRESSA (gefitinib)	NSCLC
	Oncomine Dx Target Test	Life Technologies, Inc.	NGS	IRESSA (gefitinib)	NSCLC
***EGFR* T790M**	**cobas** EGFR Mutation Test v2	Roche Molecular Systems, Inc.	PCR	TAGRISSO (osimertinib)	NSCLC
BRCA1/2	FoundationFocus CDx$_{BRCA}$	Foundation Medicine, Inc.	NGS	RUBRACA (rucaparib)	Advanced ovarian cancer
PIK3CA	*therascreen* PIK3CA RGQ PCR Kit	QIAGEN	PCR	PIQRAY (alpelisib)	Breast cancer

Abbreviations: FISH – fluorescence *in situ* hybridization; IHC – immunohistochemistry; CISH – chromogenic *in situ* hybridization; ISH – in situ hybridization; PCR – polymerase chain reaction; NGS – next generation sequencing.

VII. MARKETING HISTORY

Foundation Medicine, Inc. initially designed and developed the FoundationOne® laboratory developed test (F1 LDT), and the first commercial sample was tested in 2012. The F1 LDT has been used to detect the presence of genomic alterations in FFPE tumor tissue specimens. The F1 LDT is not FDA-cleared or -approved.

The F1CDx Premarket Approval (PMA) was originally approved on November 30, 2017 by FDA (P170019) and is commercially available in the U.S. since March 30, 2018.

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 test results, and subsequently, inappropriate patient management decisions. Patients with false positive results may undergo treatment with one of the therapies listed in the above intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy. For the specific adverse events related to the approved therapeutics, please see the approved drug product labels.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

The evidence in support of the performance of F1CDx in detecting SNVs and indels that lead to *MET* exon 14 skipping was from the data presented using intended use specimens across all validation studies. Analytical accuracy/concordance study and precision studies at the limit of detection (LoD) were conducted to support the indication for SNVs and indels that lead to *MET* exon 14 skipping.

For F1CDx platform-level validation (P170019), performance characteristics were established using DNA derived from a wide range of FFPE tissue types; tissue types associated with CDx indications were included in each study. For information regarding the platform-level validation, please see Section IX.A.10, Table 24 in Summary of Safety and Effectiveness Data P170019).

1. Analytical Accuracy/Concordance

a. Comparison to an Orthogonal Method for Detecting SNVs and Indels that lead to *MET* exon 14 Skipping

An analytical accuracy study was performed to demonstrate the concordance between F1CDx and an externally validated NGS assay (evNGS) for the detection of SNVs and indels that lead to *MET* exon 14 skipping. This study evaluated a set of 168 NSCLC FFPE specimens, (50 patients positive for SNVs and indels that lead to *MET* exon 14 skipping and 118 patients negative

for SNVs and indels that lead to *MET* exon 14 skipping) from NSCLC patients from archival specimens and from the GEOMETRY-mono 1 clinical trial (please see Section X.A for study details). Positive samples included 19 patients positive for SNVs and indels that lead to *MET* exon 14 skipping with sufficient remaining DNA from the GEOMETRY-mono 1 clinical trial. Due to the low prevalence of some SNVs and indels that lead to *MET* exon 14 skipping, samples from Foundation Medicine's clinical archive (31 samples positive for SNVs and indels that lead to *MET* exon 14 skipping) were included to cover rare SNVs and indels that lead to *MET* exon 14 skipping. 118 NSCLC samples without SNVs and indels that lead to *MET* exon 14 skipping were leveraged from prior studies (please refer to Section IX.A.1.a of Summary of Safety and Effectiveness Data P170019) and supplemented with archival specimens with remaining DNA of sufficient quantity and quality in this study. Samples were selected by F1CDx and then tested by evNGS. A summary of positive percent agreement (PPA) and negative percent agreement (NPA) in reference to an externally validated NGS assay and corresponding 95% two-sided exact confidence intervals (CIs) is provided in Table 6, below.

Table 6. Concordance summary for samples with SNVs and indels that lead to *MET* exon 14 skipping.

Variant	F1CDx+/ evNGS+	F1CDx- /evNGS+	F1CDx+ /evNGS-	F1CDx- /evNGS-	Unadjusted PPA (95%CI)	Unadjusted NPA (95%CI)	Adjusted PPA (95%CI)*	Adjusted NPA (95%CI)*
SNVs and indels that lead to *MET* exon 14 skipping	49	0	1	118	100.00% (92.8%, 100.0%)	99.2% (95.4%, 100.0%)	100% (47.31%, 100%)	99.94% (99.66%, 100%)

* Samples were selected by F1CDx, so a prevalence of 3% for MET exon 14 alterations in the NSCLC population was used to calcualte the adjusted PPA/NPA in reference to the evNGS.

2. Analytical Sensitivity

a. **Limit of Detection (LoD)**

The LoD of SNVs and indels that lead to *MET* exon 14 skipping was assessed by F1CDx. A total of 4 NSCLC specimens positive for SNVs or indels that lead to MET exon 14 skipping (all biomarker rules were covered by the 4 samples) were tested to assess the mutant allele frequency (MAF) necessary for accurate detection and sensitivity of SNVs and indels that lead to MET exon 14 skipping. LoD was estimated using 5 levels of MAF ranging from 2.5% to 20% (2.5%, 5%, 10%, 15% and 20%) with 10 replicates per level. The LoDs of SNVs and indels that lead to *MET* exon 14 skipping were determined empiraclly and are summarized in Table 7, below.

Table 7. Summary of LoD for SNVs and indels that lead to *MET* exon 14 skipping

Alteration	LoD* Allele Fraction (%)
MET Exon 14 substitutions	2.93%
MET Exon 14 insertion and deletion	5.73%

*LoD calculations for the CDx variants were based on the hit rate approach, as there were less than three levels with hit rate between 10% and 90% for all CDx variants. LoD from the hit rate approach is defined as the lowest level with 100% hit rate (worst scenario).

LoDs were confirmed by testing NSCLC samples near the established LoD in the Precision Study (See Section IX.A.8). See Section IX.A.2 of Summary of Safety and Effectiveness Data for P170019 for additional analytical sensitivity data.

3. Analytical Specificity

See Section IX.A.3 of Summary of Safety and Effectiveness Data for P710019

4. Carryover/Cross-Contamination

See Section IX.A.4 of Summary of Safety and Effectiveness Data for P170019

5. Precision and Reproducibility

a. Intermediate Precision for SNVs and indels that lead to *MET* exon 14 skipping

A precision study was conducted using eight NSCLC samples harboring SNVs or indels that lead to *MET* exon 14 skipping (four samples near LoD and four samples at 2-3x LoD) covering all of the biomarker rules. 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 (typical assay workflow spans 10 days) of performance by multiple operators. A full factorial design for this study was carried out with four replicates per reagent lot/sequencer combination for samples with 24 replicates. The previous precision studies for F1CDx (P170019) and FoundationFocus CDx$_{BRCA}$ (P160018) were conducted with 36 replicates using a full factorial study design and yielded high agreement rates; thus, 24 replicates per sample to demonstrate F1CDx precision for SNVs and indels that lead to *MET* exon 14 skipping were deemed acceptable to support this PMA supplement.

The results for the precision study for the NSCLC samples near LoD and at 2-3x LoD are summarized in Table 8, below. There were two replicates from two different samples that failed post-sequencing QC metrics due to low sequencing coverage. These replicates were excluded from the analysis. Among the remaining replicates, two replicates from two samples were discordant. Intra-run repeatability was evaluated across 12 duplicates per plate as percent agreement and two replicates exhibited discordances due to low

allele frequency, which was below pipeline reporting thresholds. Inter-run reproducibility was evaluated across 24 replicates as percent agreement, which is the fraction of calls consistent with the majority call. Reproducibility and repeatability were 100% across six out of eight replicates. The corresponding two-sided exact 95% CIs are provided for repeatability and reproducibility positive call rates.

Table 8. Precision results for SNVs and indels that lead to *MET* exon 14 skipping

Sample	Target Alteration	Mutant Allele Fraction (MAF) (%)	# Valid Results	Reproducibility Positive Call Rate (95% exact CI)	Repeatability Positive Call Rate (95% exact CI)
1	splice site 2888-10_2911del34	7.0	24	100.0% (85.8, 100.00)	100.0% (73.5, 100.0)
2	splice site 2888-37_2888-30delCGTCTTTA	4.1	23	95.8% (78.9, 99.9)	91.7% (61.5, 99.8)
3	splice site 2888-18_2888-5del14	11.0	23	100.0% (85.2, 100.0)	100.0% (71.5, 100.0)
4	D1010N	3.0	23	95.8% (78.9, 99.9)	91.7% (61.5, 99.8)
5	splice site 3028+2T>C	3.3	24	100.0% (85.8, 100.0)	100.0% (73.5, 100.0)
6	splice site 2999_3028+4del34	4.2	24	100.0% (85.8, 100.0)	100.0% (73.5, 100.0)
7	splice site 3028+1G>A	6.0	24	100.0% (85.8, 100.0)	100.0% (73.5, 100.0)
8	splice site 3028_3028+2delGGT	10.5	23	100.0% (85.8, 100.0)	100.0% (71.5, 100.0)

b. Site-to-site reproducibility (SNVs and indels that lead to *MET* exon 14 skipping)

A reproducibility study to include the new second site in Morrisville, North Carolina was not conducted. Site-to-site reproducibility is being provided as a post-market study.

6. Reagent Lot Interchangeability

There were no changes to the reagents and specifications between FoundationFocus™ CDx*BRCA* assay and F1CDx. Therefore, for reagent lot interchangeability results, see Section IX.A.g of Summary of Safety and Effectiveness Data for P160018.

B. Animal Studies

No animal studies were conducted using the F1CDx assay.

C. Additional Studies

No additional studies were conducted using the F1CDx assay.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The clinical performance of FoundationOne®CDx (F1CDx) for detecting SNVs and indels that lead to *MET* exon 14 skipping in NSCLC patients who may benefit from treatment with capmatinib (Table 1), was established with clinical data generated from the GEOMETRY-mono 1 study, and a clinical bridging study to demonstrate concordance between the enrollment assay and the F1CDx assay to establish the clinical efficacy of the F1CDx assay.

A. FoundationOne®CDx Clinical Bridging Study for SNVs and indels that lead to *MET* exon 14 skipping

The safety and effectiveness of F1CDx for detecting SNVs and indels that lead to *MET* exon 14 skipping in NSCLC patients who may benefit from treatment with capmatinib was demonstrated in a retrospective analysis of samples from patients enrolled in the GEOMETRY-mono 1 trial (CINC280A2201). A bridging study was conducted to assess the clinical efficacy of F1CDx in identifying patients positive for SNVs and indels that lead to *MET* exon 14 skipping for treatment with capmatinib and the concordance between SNVs and indels that lead to *MET* exon 14 skipping tested with the clinical trial assay (CTA) and F1CDx in the intent-to-test population. Retrospective testing with F1CDx was done for patients from the drug efficacy population Cohorts 4 and 5b, and a random selection of *MET* exon 14 skipping negative patients. The retrospective testing population consisted of 204 patients (78 patients positive for *MET* exon 14 skipping, and 126 patient samples negative for MET exon 14 skipping), originally tested by the MET exon 14 skipping CTA for patient selection.

1. Study Design

GEOMETRY-mono 1 is a prospectively designed, multi-cohort, multicenter, non-randomized, open-label, Phase II trial of oral cMET inhibitor (capmatinib) in adult patients with *EGFR* wild-type (wt) metastatic NSCLC. The primary endpoint was to assess overall response rate (ORR) and the key secondary endpoint was duration of response (DOR) by a blinded independent review committee (BIRC) assessment according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to determine the effectiveness of capmatinib in NSCLC patients. Patients were enrolled into multiple cohorts of the study, out of which the bridging study was focused on the fully-enrolled *MET* exon 14 skipping positive Cohorts 4 and 5b (efficacy population). Cohort 4 only enrolled pretreated (second and third line) *MET* exon 14 skipping patients and Cohort 5b only enrolled treatment-naïve *MET* exon 14 skipping patients. Patients were screened for enrollment in Cohorts 4 and 5b for *MET* exon 14 skipping status as detected using a *MET* exon 14 deletion reverse-transcriptase PCR (RT-PCR) CTA. After the initial patient screening, clinical samples were stored for retrospective testing. GEOMETRY-mono 1 is an ongoing trial that was initiated on June 11, 2015 with

first patient first visit (FPFV). Patients receive 400 mg of capmatinib orally twice daily in tablet form. Dose adjustments for capmatinib are permitted for safety concerns. Efficacy is evaluated every six weeks from the first day of treatment until RECIST 1.1 disease progression. Safety and tolerability is evaluated in all subjects who received at least one dose of capmatinib by assessment of incidence of adverse events (AEs) and serious adverse events (SAEs), change in vital signs, laboratory results, and electrocardiogram (ECG).

2. Bridging Study

The aim of the bridging study was to determine the concordance between *MET* exon 14 skipping results from the enrolling CTA generated at the time of patient screening for GEOMETRY-mono 1 and the results of SNVs and indels that lead to *MET* exon 14 skipping using F1CDx. The study was also conducted to establish the clinical utility of F1CDx in identifying patients positive for SNVs and indels that lead to *MET* exon 14 skipping for treatment with capmatinib.

Retrospective testing with F1CDx was done for patients from Cohort 4 (previously treated) and Cohort 5b (treatment naïve) and a random selection of *MET* exon 14 skipping negative samples. The bridging study population consisted of 204 patients (78 *MET* exon 14 skipping positive patients, and 126 *MET* exon 14 skipping negative patient samples), originally tested by the *MET* exon 14 CTA for patient selection.

Concordance between F1CDx and the CTA was demonstrated with the companion diagnostic (CDx)-evaluable patient population from GEOMETRY-mono 1 trial that produced valid F1CDx results. Clinical utility of F1CDx was evaluated by estimation of clinical efficacy in the CTA-enrolled *MET* exon 14 skipping positive patient population as assessed by the primary objective of ORR by BIRC. Baseline demographic and disease characteristics were compared between the CDx-evaluable and CDx-unevaluable populations within all enrolled CTA-positive patients in Cohort 4 and Cohort 5b. All the covariates were well balanced between the two groups of patients (See Section X.B below).

B. Study Population Demographics and Baseline Parameters

The demographics, disease characteristics and specimen characteristics for the CDx-evaluable and CDx-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 (Table 9).

Table 9. Comparison of demographic and disease characteristics between CDx-evaluable and CDx-unevaluable set for CTA-positive patients by cohort and CDx sample requirements for CDx samples that met the minimum sample requirements.

	Cohort 4			Cohort 5b		
Baseline characteristics	**CDx evaluable N=53**	**CDx unevaluable N=16**	**All N=69**	**CDx evaluable N=20**	**CDx unevaluable N=8**	**All N=28**
Age (Years)						
N	53	16	69	20	8	28
Mean	71.8	68.2	71.0	71.4	75.1	72.4
SD	8.97	4.90	8.32	6.40	8.18	7.02
Median	73.0	68.5	71.0	70.5	75.5	71.0
Min	49	59	49	57	60	57
Max	90	78	90	83	86	86
Sex - n (%)						
Female	29 (54.7)	11 (68.8)	40 (58.0)	11 (55.0)	7 (87.5)	18 (64.3)
Male	24 (45.3)	5 (31.3)	29 (42.0)	9 (45.0)	1 (12.5)	10 (35.7)
Race - n (%)						
Caucasian	36 (67.9)	13 (81.3)	49 (71.0)	16 (80.0)	8 (100)	24 (85.7)
Black	0	0	0	0	0	0
Asian	16 (30.2)	3 (18.8)	19 (27.5)	4 (20.0)	0	4 (14.3)
Native American	1 (1.9)	0	1 (1.4)	0	0	0
Other	0	0	0	0	0	0
Unknown	0	0	0	0	0	0
ECOG at baseline - n (%)						
0	13 (24.5)	3 (18.8)	16 (23.2)	6 (30.0)	1 (12.5)	7 (25.0)
1	39 (73.6)	13 (81.3)	52 (75.4)	14 (70.0)	7 (87.5)	21 (75.0)
2	1 (1.9)	0	1 (1.4)	0	0	0
Histological grade - n (%)						
Well differentiated	5 (9.4)	0	5 (7.2)	2 (10.0)	2 (25.0)	4 (14.3)
Moderately differentiated	8 (15.1)	1 (6.3)	9 (13.0)	1 (5.0)	1 (12.5)	2 (7.1)
Poorly differentiated	12 (22.6)	7 (43.8)	19 (27.5)	5 (25.0)	1 (12.5)	6 (21.4)
Undifferentiated	3 (5.7)	2 (12.5)	5 (7.2)	2 (10.0)	0	2 (7.1)
Unknown	25 (47.2)	6 (37.5)	31 (44.9)	10 (50.0)	4 (50.0)	14 (50.0)
Stage at study entry - n (%)						
IIIB	1 (1.9)	1 (6.3)	2 (2.9)	0	0	0
IV	52 (98.1)	15 (93.8)	67 (97.1)	20 (100)	8 (100)	28 (100)

- All percentages calculated using N as denominator.
- ECOG=Eastern Cooperative Oncology Group; SD=standard deviation.

C. Accountability of sPMA Cohort

A total of 3,036 patients were screened for trial eligibility from 152 investigational sites across 25 countries. 2551 patients within the original 3,036 were screened for *MET* exon 14 skipping by RT-PCR CTA. Within that screened population, 2295 patients produced valid CTA results (positive and negative) by which the patient could be deemed eligible or ineligible for the trial. As of April 15, 2019, a total of 334 patients were enrolled into all available cohorts. Of the patients whose samples produced valid CTA results, 97 were enrolled in Cohorts 4 and 5b of the GEOMETRY-mono 1 trial, with 69 and 28 patients respectively. *MET* exon 14 skipping negative patients were not enrolled in the GEOMETRY- mono 1 trial. Available *MET* exon 14 skipping negative patients identified through screening for the GEOMETRY-mono 1 trial were evaluated for the clinical bridging study from which 130 CTA-negative patients were randomly selected. Out of the 130 CTA-negative samples, 93 were randomly assigned to Cohort 4 and 37 to Cohort 5b. Of the 227 positive and negative samples (97 positive and 130 negative), retrospective retesting with F1CDx was performed for 204 CTA tested patient samples that met F1CDx minimum sample testing criteria (78 of the *MET* exon 14 skipping positive enrolled patients and 126 *MET* exon 14 skipping negative not-enrolled patients). F1CDx testing yielded 198 CDx-evaluable results and six (6) invalid results which were used for the CDx and CTA concordance analysis.

Sensitivity analyses were conducted with all 227 samples from PAS-A (Primary Analysis Set-A: Cohort 4 69 positive samples and its randomly assigned 93 CTA-negative samples) and PAS-B (Primary Analysis Set-B: Cohort 5b 28 positive and its randomly assigned 37 CTA-negative samples) to determine the impact of missing F1CDx results on concordance and efficacy results. Standard F1CDx processing metrics require samples to have tissue volume ≥ 0.6 mm^3, tumor content $\geq 20\%$ and DNA yield ≥ 55 ng. To increase retention of clinical trial samples in the clinical bridging study, samples were also processed down to the minimum sample inputs (Tested with deviation). Samples meeting minimum sample inputs fell below the standard F1CDx requirements listed above, but no lower than tissue volume 0.1 mm^3, tumor content $\geq 10\%$ and DNA yield ≥ 22 ng. Nineteen (19) CTA-positive patient samples were not tested due to failing to meet the F1CDx minimum tissue input requirements (13 and 6 from Cohorts 4 and 5b, respectively). Full disposition of the patient samples from GEOMETRY-mono 1 and those used for the F1CDx bridging study is shown in Tables 10 and 11.

Table 10. Disposition of all screened subjects in the GEOMETRY mono-1 trial

	Total patients	Actual Tested by CDx
All screened (positive and negatives)	3036	227
Screened by CTA	2551	204
Prescreen failures (not enrolled)	2605	125
Patients with valid CTA results (positives and negatives)	2295	204
Total enrolled in GEOMETRY mono-1 (as at 04/15/19 DBL)	334	78
Tested as CTA-positive (enrolled only in C4 and C5b)	97	78

	Total patients	Actual Tested by CDx
Enrolled in Cohort 4	69	56
Enrolled in Cohort 5b	28	22
Tested as CTA-negative (pre-screen failure; not enrolled)	1882	126
Randomized to Cohort 4 for bridging analysis	93	89
Randomized to Cohort 5b for bridging analysis	37	37
Tested as invalid per CDx	6	6
Not tested by CDx for positive and negative by CTA	23	0

Table 11. Disposition of bridging subjects for CDx and CTA (Primary analysis set, CTA-enrolled)

	CTA	
CDx	**Positive N=97 (%)**	**Negative N=130 (%)**
Tested without deviation		
Positive	44 (45.4)	0 (0)
Negative	1 (1.0)	121 (93.1)
Invalid	0 (0.0)	0 (0.0)
Tested with deviation		
Positive	28 (28.9)	0 (0.00)
Negative	0 (0.0)	4 (3.1)
Invalid	5 (5.2)	1 (0.8)
Not tested	19 (19.6)	4 (3.1)

For concordance between F1CDx and CTA, the point estimates of PPA, NPA, and OPA are detailed in Tables 12 and 13 below.

D. Safety and Effectiveness

1. Safety Results

The safety with respect to treatment with capmatinib 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).

The majority of adverse events (AEs) reported were grade 1 or 2. In addition, the safety findings in this study are consistent with the known safety profile of capmatinib and no new or unexpected safety signals were identified.

Most of the on-treatment deaths occurred in the context of disease progression. Serious AEs were reported in 169 subjects (50.6%), however, the incidence of specific individual serious adverse events (SAEs) was low (<5%; except for dyspnea occurring in 6.9% subjects). ILD/pneumonitis grouped AEs were

infrequent (4.5% of subjects) and mostly of low severity. Hepatotoxicity grouped AEs were reported in 28.1% of subjects during treatment with capmatinib, and mainly consist of asymptomatic AST/ALT elevations which were reversible with dose adjustment or interruption. The AEs are manageable with medical therapies and/or dose modifications. Overall, the safety in Cohorts 4 and 5b which have longer exposure to study drug is similar to safety in other cohorts in which subjects have shorter exposure.

No adverse events were reported in connection with the bridging study used to support this PMA supplement, as the study was performed retrospectively using banked samples.

2. Effectiveness Results

a. Concordance Results

The primary concordance analysis was conducted on 204 (78 *MET* exon 14 skipping positive patients, and 126 *MET* exon 14 skipping negative patient samples) CDx-evaluable CTA-positive and CTA-negative population which included the patients that met the F1CDx standard and minimum testing criteria and yielded valid CDx results.

Agreement between F1CDx and the CTA was demonstrated. The point estimates of PPA, NPA, and OPA between F1CDx and the CTA for CDx samples that met that standard DNA input requirement (Table 12) and those using the minimum DNA input requirement (Table 13) were calculated with and without invalid CDx results, using the CTA results as reference for the CTA-enrolled patients. The concordance analysis was performed with and without treating samples that met minimum sample requirements as ascertained for CDx.

Table 12. Agreement between CDx and CTA based on CTA results in Cohorts 4 and 5b for samples that met the F1CDx standard sample requirements.

		Without CDx "Invalid"		With CDx "Invalid"	
	Measure of agreement	**Percent agreement % (n/N)**	**95% CI (1)**	**Percent agreement % (n/N)**	**95% CI (1)**
Cohort 4	PPA	96.8 (30/ 31)	(83.3, 99.9)	96.8 (30/ 31)	(83.3, 99.9)
	NPA	100 (84/ 84)	(95.7, 100)	100 (84/ 84)	(95.7, 100)
	OPA	99.1 (114/115)	(95.3, 100)	99.1 (114/115)	(95.3, 100)
Cohort 5b	PPA	100 (14/ 14)	(76.8, 100)	100 (14/ 14)	(76.8, 100)
	NPA	100 (37/ 37)	(90.5, 100)	100 (37/ 37)	(90.5, 100)
	OPA	100 (51/ 51)	(93.0, 100)	100 (51/ 51)	(93.0, 100)

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

Table 13. Agreement between CDx and CTA based on CTA results in Cohorts 4 and 5b for samples that met the minimum F1CDx sample requirements.

		Without CDx "Invalid"		With CDx "Invalid"	
	Measure of agreement	**Percent agreement % (n/N)**	**95% CI (1)**	**Percent agreement % (n/N)**	**95% CI (1)**
Cohort 4	PPA	98.1 (52/ 53)	(89.9, 100)	92.9 (52/ 56)	(82.7, 98.0)
	NPA	100 (88/ 88)	(95.9, 100)	98.9 (88/ 89)	(93.9, 100)
	OPA	99.3 (140/141)	(96.1, 100)	96.6 (140/145)	(92.1, 98.9)
Cohort 5b	PPA	100 (20/ 20)	(83.2, 100)	90.9 (20/ 22)	(70.8, 98.9)
	NPA	100 (37/ 37)	(90.5, 100)	100 (37/ 37)	(90.5, 100)
	OPA	100 (57/ 57)	(93.7, 100)	96.6 (57/ 59)	(88.3, 99.6)

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

b. Clinical Efficacy Results in the GEOMETRY-mono 1 *MET* Exon 14 Skipping Cohort

The GEOMETRY-mono 1 clinical trial met its primary objective of ORR as assessed by BIRC according to RECIST 1.1 in patients with *MET* exon 14 skipping positive tumors.

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. The analyses by BIRC assessment were similar to the analyses by investigator assessment. (Tables 14 and 15). Treatment with capmatinib was considered efficacious under the standard testing requirements in both Cohort 4 (second and third line) and Cohort 5b (treatment-naive) (36.7% (95% CI: 19.9, 56.1) and 78.6% (95% CI: 49.2, 95.3), respectively) and under the minimum testing requirements for both Cohort 4 and Cohort 5b (44.2% (95% CI: 30.5, 58.7) and 70% (95% CI: 45.7, 88.1), respectively) as demonstrated by an ORR per BIRC.

Table 14. Overall response per BIRC assessment in (CTA-positive, CDx-positive) and CTA-positive patients by cohort and CDx sample requirements (Cohort 4)

(CTA+, CDx+)

CDx sample requirements

	Standard N=30		Standard + Minimum N=52		CTA+ N=69	
	n (%)	95% CI (1)	n (%)	95% CI (1)	n (%)	95% CI (1)
Overall Response Rate (ORR: CR + PR)	11 (36.7)	(19.9, 56.1)	23 (44.2)	(30.5, 58.7)	28 (40.6)	(28.9, 53.1)

(1) The 95% CI calculated with the Clopper-Pearson Exact method.

Table 15. Overall response per BIRC assessment in (CTA-positive, CDx-positive) and CTA-positive patients by cohort and CDx sample requirements (Cohort 5b).

(CTA+, CDx+)

CDx sample requirements

	Standard N=14		Standard + Minimum N=20		CTA+ N=28	
	n (%)	95% CI (1)	n (%)	95% CI (1)	n (%)	95% CI (1)
Overall Response Rate (ORR: CR + PR)	11 (78.6)	(49.2, 95.3)	14 (70.0)	(45.7, 88.1)	19 (67.9)	(47.6, 84.1)

(1) The 95% CI calculated with the Clopper-Pearson Exact method.

c. Duration of Response

For the CTA selected patients, the responses in treatment-naïve (Cohort 5) *MET* exon 14 skipping positive NSCLC patients were durable with 68.4% of patients having responses of 6 months or longer and 47.4% of patients having responses of 12 months or longer (median DOR of 12.58 months (95% CI: 5.55, 25.33)) by BIRC assessment. The responses in previously treated (Cohort 4) *MET* exon 14 skipping positive NSCLC patients were also durable with 64.3% of patients having responses of 6 months or longer and 32.1% of patients having responses of 12 months or longer (median DOR of 9.72 months (95% CI: 5.55, 12.98)) by BIRC assessment. In both *MET* exon 14 skipping positive cohorts, the onset of response occurred within 7 weeks of treatment in the majority of patients (68.4% of treatment-naïve patients and 82.1% of previously treated patients) as assessed by BIRC.

Duration of response (DOR) data are captured in Table 16 for (CTA+, CDx+) patients that experienced complete or partial response. The data captures DOR

per BIRC assessment for patients by cohort for both standard and standard + minimum sample requirements.

Table 16 Summary of duration of response (CR + PR) per BIRC assessment

	Previously Treated (Cohort 4)	Treatment-Naïve (Cohort 5b)
Duration of Response (DOR) - CINC280A2201[a]		
Total number of patients with confirmed PR or CR	N = 28	N = 19
Median (months) (95% CI)[b]	9.7 (5.5, 13.0)	12.6 (5.5, 25.3)
Patients with DOR ≥ 12 months	32%	47%
Duration of Response (DOR) - CTA+/CDx+ population (Standard + Minimum)		
The total number of patients with confirmed PR or CR in (CTA+, CDx+)	N= 23	N= 14
Median (months) (95% CI) [b]	9.72 (4.27, 12.98)	12.58 (5.55, 25.33)
Patients with DOR > 12 months	34.8%	50.0%
Duration of Response (DOR) - CTA+/CDx+ population (Standard)		
The total number of patients with confirmed PR or CR in (CTA+, CDx+)	N= 11	N= 11
Median (months) (95% CI) [b]	9.59 (4.27, 12.98)	12.58 (4.24, 25.33)
Patients with DOR > 12 months	27.3%	45.5%

[a] Based on capmatinib USPI.
[b] Based on Kaplan-Meier estimate.

d. Clinical Efficacy Results in the CDx-positive Population

In Tables 12 and 13, all patients who were found to be negative for *MET* exon 14 skipping by the CTA were also tested negative by the F1CDx (i.e., NPA = 100%) for Cohorts 4 and 5b. Therefore, the conditional probability of being CTA positive in the F1CDx positive population is 100% (i.e., Pr(CTA+|CDx+) = 100%), regardless of the prevalence of *MET* exon 14 skipping as determined by the CTA. Thus, the final estimated drug efficacy (ORR) for F1CDx positive patients in the intended use population equals to the estimated drug efficacy of the (CTA+ and CDx+) patients observed in the GEOMETRY-mono 1 clinical trial. Table 17 shows the efficacy results in F1CDx-positive patients for Cohorts 4 and Cohort 5b using standard and minimum DNA input requirements.

Table 17. Estimated Clinical efficacy results for F1CDx positives

	Cohort 4 ORR with 95% CI	Cohort 5b ORR with 95% CI
CDx (Standard)	36.7% (19.9 – 56.1%)	78.6% (49.2 –95.3%)
CDx (Standard + Minimum)	44.2% (30.5 – 58.7%)	70% (45.7 – 88.1%)

Sensitivity analysis, using the multiple imputation methods was performed to evaluate the robustness of the clinical efficacy estimate against the 24 patients who tested positive by the CTA but were missing from the F1CDx results, which includes 19 patient samples that were not retested by F1CDx due to failing to meet the F1CDx minimum tissue sample requirements and/or due to lab error or also due to not meeting quality control metric, and five (5) patients who were tested by F1CDx but received invalid results.

Multivariate logistic regression analyses were performed to identify the clinically relevant covariates that are associated with the device outputs and clinical outcomes, respectively. Given that the sample size is limited in each cohort, a significance level of 0.2 was used as the criteria to select covariates in the logistic regression models. Covariate imbalances were assessed between F1CDx-evaluable and F1CDx non-evaluable sets within all enrolled CTA-positive patients. The distribution of the propensity scores among the group of patients with CDx results and the group without CDx results were assessed. Missing F1CDx results were imputed for Cohort 4 and Cohort 5b separately. The sensitivity analysis results demonstrated that the drug efficacy in F1CDx positive population is robust to missing F1CDx results.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric population since it is not applicable for the NSCLC indication.

E. Financial Disclosure

The bridging study was conducted retrospectively at a single testing site in Cambridge, MA and exempt from the requirements for Investigational Device Exemption as defined in Title 21 of the Code of Federal Regulations (21 CFR), 812.2(c)(3). The investigational product was not used in the diagnosis or treatment of patients. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

XII. 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 supplement 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.

XIII. 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 F1CDx 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 F1CDx 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 F1CDx.

B. Safety Conclusions

The risks of the device are based on data collected in the analytical studies conducted to support PMA approval as described above. The F1CDx assay is an *in vitro* diagnostic test, which involves testing of DNA extracted from FFPE tumor tissue. The assay can be performed using DNA extracted from existing (archival) tissue samples routinely collected as part of the diagnosis and patient care.

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently, inappropriate patient management decisions in cancer treatment. Patients with false positive results may undergo treatment with one of the therapies listed in Table 1 of the intended use statement without clinical benefit and may experience adverse reactions associated with the therapy. Patients with false negative results may not be considered for treatment with the indicated therapy. There is also a risk of delayed results, which may lead to delay of treatment with the indicated therapy.

C. Benefit-Risk Determination

GEOMETRY-mono 1 is a prospectively designed, multi-cohort, multicenter, non-randomized, open-label Phase II trial of oral cMET inhibitor (capmatinib) in adult patients with EGFR wild-type (wt), metastatic NSCLC. The primary endpoint was to assess overall response rate (ORR) and the key secondary endpoint was duration of response (DOR) by a blinded independent review committee (BIRC) assessment to determine the effectiveness of capmatinib in NSCLC patients. Patients have been enrolled into multiple cohorts of the study, out of which the bridging study was focused on the fully-enrolled MET exon 14 skipping positive Cohorts 4 and 5b. Cohort 4 only enrolled pretreated (second and third line) MET exon 14 skipping positive patients and Cohort 5b only enrolled treatment-naïve MET exon 14 skipping positive patients. Patients were screened for enrollment in Cohort 4 and 5b for MET exon 14 skipping status as detected using a MET exon 14 deletion a reverse-transcriptase PCR (RT-PCR) CTA. After initial patient screening, clinical samples were stored for retrospective testing.

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. 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.

The clinical utility of F1CDx based on patients with valid CDx results was demonstrated in the MET exon 14 skipping positive population for both the "Standard" and "Standard + Minimum" populations. For the double positive samples (CTA+, F1CDx+) that met "Standard + Minimum" sample requirements, ORR was determined as 44.2% by CDx with 95% CI (30.5 - 58.7%) for Cohort 4 and estimated 70% for Cohort 5b with 95% CI (45.7 -88.1%).

In terms of the bridging study, to determine the efficacy in the F1CDx positive population, it is important to note that all patients who were found to be negative for MET exon 14 skipping by the CTA also tested negative by the F1CDx (i.e., NPA = 100%) for Cohorts 4 and 5b. Therefore, the conditional probability of being CTA positive in the F1CDx positive population is 100% (i.e., Pr(CTA+|CDx+) = 100%), regardless of the prevalence of MET exon 14 skipping as determined by the CTA. Thus, the final estimated drug efficacy (ORR) for F1CDx positive patients in the intended use population equals the estimated drug efficacy for the double positives (CTA+, CDx+) observed in the GEOMETRY-mono 1 clinical trial, which maintains the efficacy in the ITT population. There is however, a degree of uncertainty regarding benefit due to the analytical studies for two site reproducibility, which will be performed as a conditions of approval.

There is potential risk associated with the use of this device, mainly due to 1) false positives, false negatives, and failure to provide a result and 2) incorrect interpretation of test results by the user. The performance of the accuracy study partially mitigates the risks associated with this device, however, there is a degree of uncertainty regarding risk due to the analytical studies for two site reproducibility, which were not performed pre-market.

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

Summary of Benefits
Treatment with capmatinib provides meaningful clinical benefit to NSCLC patients with MET exon 14 skipping, as measured by ORR demonstrated in the GEOMETRY-mono 1 trial. Given the available information, the data supports the conclusion that FoundationOne®CDx has probable benefit in selecting patients with SNVs and indels

that lead to MET exon 14 skipping for treatment with capmatinib in patients with NSCLC.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the clinical bridging study support the performance of F1CDx as an aid for the identification of SNVs and indels that lead to *MET* exon 14 skipping in NSCLC patients for whom TABRECTA® (capmatinib) may be indicated.

XIV. CDRH DECISION

CDRH issued an approval order on May 6, 2020. The final clinical conditions of approval cited in the approval order are described below.

The applicant will provide the following in a post-approval report:

- Provide the results of a site-to-site reproducibility study to include the second laboratory site in Morrisville, North Carolina using intended use specimens carrying MET exon 14 SNVs and indels that lead to MET exon 14 skipping, as was used in support of the Morrisville, North Carolina site approval (P170019/S010).

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

XV. 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.

XVI. REFERENCES

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