SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Next Gen Sequencing oncology panel, somatic or germline variant detection system
Device Trade Name:	FoundationOne®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: P170019/S015

Date of FDA Notice of Approval: May 19, 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, seven 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 Morrisville, 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. PMA supplement (P170019/S011) for adding an indication for TABRECTA® (capmatinib) in NSCLC patients with MET single nucleotide variants (SNVs) and indels that lead to MET exon 14 skipping was approved on May 6, 2020.

The current supplement was submitted to expand the intended use of F1CDx to include a companion diagnostic indication for homologous recombination repair (HRR) gene

alterations in patients with metastatic castrate resistant prostate cancer (mCRPC) who may benefit from treatment with Lynparza® (olaparib).

II. INDICATIONS FOR USE

FoundationOne® CDx is a next generation sequencing (NGS) 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 (CDx) 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 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

Tumor Type	Biomarker(s) Detected	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, H1047Y alterations	Piqray® (alpelisib)
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)
Prostate cancer	Homologous Recombination Repair (HRR) gene (*BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D and RAD54L*) alterations	Lynparza® (olaparib)

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 (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 will 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/precautions and limitations are included 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, insertion-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*	*PDCD1G2*	*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 a ncRNA gene.

ALK	*BRCA1*	*ETV4*	*EZR*	*KIT*	*MYC*	*NUTM1*	*RET*	*DLC34A2*
introns 18, 19	*introns 2, 7, 8, 12, 16, 19, 20*	*introns 5, 6*	*introns 9-11*	*intron 16*	*intron 1*	*intron 1*	*introns 7-11*	*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 test output 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
Beckman Biomek NXP Span-8 Liquid Handler
Thermo Fisher Scientific KingFisher™ Flex with 96 Deep-well Head
Illumina® cBot System
Illumina® HiSeq 4000 System

Test Process
All assay reagents included in the F1CDx assay process are qualified by FMI and are compliant with the medical device Quality Systems 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 ($\geq$ 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 a Covaris LE220 before purification using 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 a 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.

Quality Control for Hybrid Capture is performed by measuring dsDNA yield using a 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 dNTP's 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 is analyzed using proprietary software developed by FMI. Sequence data is mapped to the human genome (hg19) using Burrows-Wheeler Aligner (BWA) v0.5.9.[4] PCR duplicate read removal and sequence metric collection is 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 $\geq 5\%$ (MAF $\geq 1\%$ 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, for HD, CNA is zero) 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 (5) chimeric pairs [three (3) 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 F1CDx Assay are analyzed for length variability and compiled into an overall MSI score via principal components analysis. 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 is recorded. Principal components analysis (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 is displayed in the FMI custom-developed CATi software applications with sequence quality control 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 is 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. One hundred (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 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%.

I. Variant Classification

A clinical report is provided to the ordering physician for each F1CDx test performed at Foundation Medicine, Inc. Each report is generated and reviewed by an internal team consisting of clinical bioinformatics analysts, scientists, curators, and pathologists with mutations positive for therapy identified. Each sample is assessed for mutations in the 14 HRR genes *ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, and *RAD54L* (Table 5). For these genes, both deleterious and suspected deleterious mutations in short variant, copy number alteration, and rearrangement variant classes are determined by an in-house software pipeline. Alterations listed in the COSMIC database and homozygous deletions are considered deleterious. Suspected deleterious mutations include truncating events i.e., splice, frameshift, and nonsense alterations, as well as large rearrangements that disrupt the coding sequence. The COSMIC check is a second layer of check for HRR positive suspected deleterious alterations. All splice, nonsense, frameshift alterations in HRR genes are considered biomarker positive and would be considered as suspected deleterious mutations (or "likely" status in FMI reporting rules). If these mutations are additionally reported in COSMIC, they would be listed as deleterious mutations (or "known" status in FMI reporting).

The F1CDx assay is intended as an aid in selecting prostate cancer patients with deleterious or suspected deleterious HRR variants, identified by the rules below, and who may be eligible for treatment with Lynparza™ (olaparib).

Table 5: Mutation types identified in the HRR genes

Variant Class	Alteration type	Description*
Short Variant	Nonsense, frameshift, or splice site	Any deleterious nonsense, frameshift, or splicing event that spans or occurs within ±2 bases of the intron/exon junction.
	Missense or non-frameshift	Any of the mutations listed in Table 6 for *ATM*, *BRCA1*, and *BRCA2*
Copy Number Alteration	Homozygous copy number loss	Deleterious homozygous copy number loss of one or more exons.
Rearrangement	Rearrangement	Any rearrangement that disrupts protein function

*For *BRCA2*, truncating mutations must occur upstream of bases encoding amino acid 3326. Additionally, the frameshift mutation T367fs*13 is *FANCL* is ineligible. All short variants must occur in the canonical transcript.

The specific deleterious mutation (DM) and suspected deleterious mutation (SDM) missense mutations or non-frameshift mutations for *BRCA1*, *BRCA2* and *ATM* are

shown in Table 6 below. However, any missense or non-frameshift mutations in the other 12 genes would not be considered HRR positive.

Table 6: Eligible deleterious mutation in the *ATM, BRCA1* and *BRCA2* genes

ATM	***BRCA1***	***BRCA2***
M1T	M1V	M1R
R2032K	M1I	M1I
R2227C	C61G	V159M
R2547_S2549del	C64Y	V211L
G2765S	R71G	V211I
R2832C	R71K	R2336P
S2855_V2856delinsRI (annotated as S2855_V2856>RI)	R1495M	R2336H
R3008C	E1559K	
R3008H	D1692N	
8418+5_8418+8delGTGA or 8418+1_8418+4delGTGA	D1692H	
	R1699W	
	A1708E	
	G1788V	

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 7, 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 7 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 US since March 30, 2018. The following PMA supplements were approved by FDA for including additional indications for use to the originally approved Intended Use:

- P170019/S005 was approved on April 10, 2019
- P170019/S004 and P170019/S008 were approved on July 1, 2019
- P170019/S009 approved on August 21, 2019
- P170019/S006 approved on December 3, 2019
- P170019/S010 approved on December 16, 2019
- P170019/S013 approved on April 17, 2020
- P170019/S011 approved on May 5, 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 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 indicated therapy. For the specific adverse events related to the approved therapeutics, please see approved drug product labels.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Performance characteristics were established using DNA derived from FFPE tissue from both bone metastasis and soft tissue types from prostate cancer patients. The study included a broad range of alteration types (substitution, insertion-deletion, copy number alterations, rearrangements) across a number of genes. For various analytical validation studies 175 unique samples [(121 HRR positive samples (151 variants) for analytival concordance, 7 samples (17 variants) for limit of detection and 47 samples (99 variants)] for precision/reproducibility studies were used. Total number of variants observed across all 175 samples were 267. The tables below (Table 8 and 9) include a list of genes/variant types that were represented in all the

analytical validation studies to support performance of the assay for detection of all the variant types in the HRR genes.

Table: 8: Summary of samples across analytical validation studies

Gene	Total	HD	RE	ID	SUB
BRCA1	12	1	6	4	1
BRCA2	77	17	6	38	16
ATM	46	6	8	16	16
BARD1	10	0	2	3	5
BRIP1	14	1	2	4	7
CDK12	48	3	4	29	12
CHEK1	6	1	1	2	2
CHEK2	12	2	2	8	0
FANCL	4	0	0	4	0
PALB2	16	1	2	1	12
RAD51B	3	0	3	0	0
RAD51C	5	2	1	2	0
RAD51D	5	0	1	1	3
RAD54L	2	0	1	0	1
Total	267	37	40	115	75

SUB: Base Substitutions. Patients who have other variant types (non-sense, missense, splice site, etc.)
ID: Insertion/Deletion. Patients who have small insertions/deletions which lead to a frameshift
HD: Homozygous deletion (copy number alteration, CN=0). Patients who have homozygous gene loss; RE: Large Rearrangement. Patients who have exonic or multi-exon insertions or deletion

Table 9: Variants Used is Three Key Analytical Validation Studies

	LoD				Precision				Accuracy			
	HD	RE	ID	SUB	HD	RE	ID	SUB	HD	RE	ID	SUB
BRCA1	0	1	0	0	1	2	1	1	0	2	3	0
BRCA2	1	0	0	0	1	3	11	7	15	3	27	9
ATM	0	1	0	1	4	4	4	3	2	3	12	12
BARD1	0	0	0	0	0	1	1	4	0	1	2	1
BRIP1	0	0	0	1	1	2	2	4	0	0	2	2
CDK12	0	1	1	0	0	0	7	3	3	3	21	9
CHEK1	0	0	0	0	1	1	0	2	0	0	2	0
CHEK2	0	1	0	0	1	0	2	0	1	1	6	0
**FANCL*	0	0	1	0	0	0	3	0	0	0	0	0
PALB2	0	0	1	1	0	1	0	9	1	0	0	2
RAD51B	0	1	0	0	0	2	0	0	0	0	0	0
**RAD51C*	0	0	0	0	1	0	1	0	1	1	1	0
RAD51D	0	1	0	0	0	0	0	2	0	1	1	1
RAD54L	0	1	0	0	0	0	0	1	0	0	0	0

*Not enrolled in the clinical trial

1. Analytical Accuracy/Concordance

a. Comparison to an Orthogonal Method

An analytical accuracy study was performed to demonstrate the concordance between F1CDx and an externally validated NGS assay (evNGS) for the detection of HRR gene alterations. This study evaluated a set of 230 specimens including 120 HRR positive clinical specimens (151 total variants observed) and 110 HRR negative specimens. The positive variants cover a range of variant types including nonsense mutations, frameshift indels, mutations in the consensus splice donor and acceptor sequence, rearrangements, and homozygous deletions (copy number = 0).

A summary of the Positive Percent Agreement (PPA) and Negative Percent Agreement (NPA) and corresponding 95% two-sided exact confidence intervals (CIs) is provided in Table 10, below.

Table 10: Concordance Summary for HRR alterations

Variant Types	F1CDx+ /evNGS+	F1CDx- /evNGS+	F1CDx+ /evNGS-	F1CDx- /evNGS-	PPA% [95% CI]	NPA [95%CI]
SUB	35	1	1	8243	97.22% [85.47%, 99.93%]	99.99% [99.93%, 100.00%]
ID	75	6	2	17627	92.59% [84.57%, 97.23%]	99.99% [99.96%, 100.00%]
RE	10	1	5	1824	90.91% [58.72%, 99.77%]	99.73% [99.36%, 99.91%]
HD	20	1	3	1356	94.02% [88.06%, 97.56%]	99.78% [99.36% , 99.95%]
Total	140	9	11	29050	93.96% [88.84, 97.20]	99.96% [99.93%, 99.98%]

SUB: Base Substitutions. Patients who have other variant types (non-sense, missense, splice site, etc.); ID: Insertion/Deletion. Patients who have small insertions/deletions which lead to a frameshift; HD: Homozygous deletion (copy number alteration, CN=0). Patients who have homozygous gene loss; RE: Large Rearrangement. Patients who have exonic or multi-exon insertions or deletion. PPA/NPA may be biased due to differential sampling.

Since the PPA and NPA were calculated without adjusting for the distribution of samples selected using F1CDx, positive predictive value (PPV) and negative predictive value (NPV) were also estimated conditional on F1CDx. The total number of alterations detected across all 120 samples by either F1CDx and/or evNGS was used to determine NPV. The observed PPV for short variants was 97.22% [95% confidence interval (CI): 85.83% - 99.86%], indels 97.40% [95%

confidence interval (CI): 91.01%, 99.28%], rearrangements 66.67% [95% confidence interval (CI): 8.38%, 88.18%], and homozygous deletions 86.96% [95% confidence interval (CI): 66.41%, 97.22%]. The NPV for all variants was 99.97% [95% confidence interval (CI): 99.94%, 99.98%].

Differences in alteration calls between the two assays were noted. These differences were primarily due to differences in filtering employed by F1CDx and evNGS. With F1CDx as the screening assay, evNGS failed to detect 11 HRR variants that were detected by F1CDx. Nine variants were detected by evNGS but not by F1CDx. Seven of the nine were short variants (indels) that were just below the analytical detection threshold. The threshold for indel detection is higher for F1CDx assay as compared to the evNGS assay. The F1CDx variant calling pipeline imposes a filter (higher MAF threshold) for indels in homopolymer regions to reduce the likelihood of calling false positives resulting from artifacts introduced by the technology. As such, the difference observed was due to varying filter thresholds between the two platforms. In addition, three genes, *FANCL, RAD51B, or RAD54L,* were excluded from the analysis as these gene could not be evaluated by the evNGS.

b. Comparison of variant concordance between soft tissue vs bone metastasis
Of the 230 patient samples, six were bone metastasis and 193 were soft tissue. A summary of the analysis is provided in Table 11, below.

Table 11: Soft tissue and bone metastasis concordance

Soft Tissue			
	evNGS +	evNGS -	
F1CDx +	114	9	PPV: 92.68% (89.56%, 96.60%)
F1CDx -	1	24383	NPV: 99.98% (99.95%, 99.99%)
	PPA: 95.80% (90.47%, 98.62%)	NPA: 99.96% (99.93% , 99.98%)	
Bone Metastasis			
	evNGS +	evNGS -	
F1CDx +	6	0	PPV: 100.00% (54.07%, 100.00%)
F1CDx -	1	755	NPV: 99.87% (99.27%, 100.00%)
	PPA: 85.71% (42.13%, 99.64%)	NPA: 100.00% (99.51%, 100.00%)	

2. Analytical Sensitivity

a. Limit of Detection (LoD) – Allele Fraction

The LoD was evaluated in FFPE-derived DNA from seven prostate tumor specimens (both soft tissues and bone metastases) at lowest DNA input level (52 ng). The LoD for short variants of CDx biomarkers representing *ATM* (substitution), *CDK12* (indel), *PPP2R2A* (7 bp indel), *BRIP1* (substitution), *PALB2* (substitution and indel), and *FANCL* (indel) are summarized in Table 12.

Table 12: Summary of LoD for Alterations Associated with CDx Claims

Alteration	LoD* Allele Fraction (%)
HRR base substitutions	5.44% - 6.33%
HRR indels	5.22% - 12.74%

*LoD calculations for the CDx variants were based on the 95% hit rate approach.

Additional results for F1CDx estimating the LoD by allele fraction were included in PMA P170019

b. Limit of Blank (LoB)

The limit of blank (LoB) of zero was confirmed by demonstrating that percentage of false-positive results did not exceed 5% (type I error risk α=0.05). Six HRR-biomarker negative samples were evaluated in 12 replicates each for the LoB assessment. Of the 72 aliquots, three failed prior to sequencing and 69 replicates were available for LoB analysis. The positive call rate is 0/69 (0%), confirming the LoB = zero.

c. Analytical Sensitivity – Tumor Purity and Average Reads

Using seven samples, LoD was determined for nine HRR rearrangements (two samples had multiple rearragements) and one homozygous deletion based on tumor purity level. For each sample, five levels of tumor purity with 14 replicates for 20% tumor purity and 20 replicates for 15 – 2.5% tumor purity levels, were evaluated (total of 94 replicates per sample). LoD calculations were based on the empirical hit rate approach, and are summarized in Table 13. LoD values were determined to be 20.1% tumor purity for HRR gene rearrangements and 23.9% tumor purity for HRR gene homozygous deletions.

Table 13: LoD by empirical hit rate based on tumor purity and average reads

Alteration	LoD Tumor Purity (%)	LoD Average Reads
HRR rearrangements	20.1%	39.3
HRR homozygous deletions	23.9%	N/A

Please refer to the Summary of Safety and Effectiveness Data P170019 (Section IX.A.2) for additional F1CDx platform-level F1CDx LoD data.

3. Analytical Specificity

a. Interfering Substances

Please see the Summary of Safety and Effectiveness Data P160018 and P710019 for F1CDx platform validation of analytical specificity, including interfering substances and *in silico* hybrid capture bait specificity.

4. Carryover/Cross-Contamination

Please see the Summary of Safety and Effectiveness Data P160018 and P170019 for F1CDx platform validation of carryover/cross-contamination.

5. Precision and Reproducibility

An intermediate precision study was performed for alterations in the 14 HRR genes. This study evaluated two aspects: repeatability and reproducibility. Repeatability (intra-run) and reproducibility (inter-run) were assessed in replicates of two, per two runs (plates), with three sequencers and two reagent lots as full factorial. A total of 24 replicates per sample were processed. Samples were selected close to LoD and up to 2-3X LoD.

A set of 47 unique FFPE samples from both soft tissue (38) and bone metastases (9) tumors carrying different variant types (62 alterations in HRR genes) were evaluated in the primary analysis. The primary analysis included 62 alterations at a range of MAF, chimeric read counts, and tumor purities. Several samples in the primary analysis included alterations that were very close to LoD and Variant Analysis Pipeline (VAP) thresholds. Some of these samples, the samples with rearrangements (RE) in particular, did not meet the acceptance criteria of ≥ 90%. Eight (8) of 15 RE samples were tested at 1x or just below 1x LoD. Five of those samples had up to 83% concordance for reproducibility and up to 80% concordance for repeatability. Three (3) other samples at 1x LoD and remaining seven (7) samples at 2–3x LoD had close to 100% concordance for both reproducibility and repeatability. Of the 11 samples with copy number alterations (CNA), 10 had homozygous deletion (HD, CNA =0) and one had copy number amplification. Of the 10 HD samples, five (5) samples were tested at 0.84 –1.8x LoD and four (4) samples were tested at 1.85 –2. 7x LoD and one sample was tested at 3.5x LoD. Except for one sample (0.84x LoD), all samples had 100% concordance for both reproducibility and repeatability. A summary results and corresponding 95% two-sided exact confidence intervals (CIs) is provided below (Table 14).

An additional secondary analysis was performed to assess all somatic alterations in HRR genes (99 alterations in total for secondary analysis) at levels just upstream of the variant analysis pipeline (VAP) thresholds. The results of the secondary exploratory analysis are enumerated in Table 15. Alterations and variant categories exceeded the acceptance criteria, demonstrating ≥ 90% reproducibility and ≥ 90% repeatability.

Table 14: HRR Precision Primary Analysis Results

Variant	N	N Reps	N detected	Repro %	L 95%CI	U 95%CI	N pair	N pairs agree	Rep %	L 95%CI	U 95%CI
HD	11	259	242	93.4	89.7	96.1	129	122	94.6	89.1	97.8
Indel	26	610	597	97.9	96.4	98.9	302	293	97.0	94.4	98.6
RE	15	347	305	87.9	83.4	911	171	153	89.5	83.9	93.6
SUB	10	238	226	95.0	91.4	97.4	118	108	91.5	85.0	95.9
Total	**62**	**1454**	**1370**	**94.2**	**92.9**	**95.4**	**720**	**676**	**93.9**	**91.9**	**95.5**

Table 15: HRR Precision Secondary Analysis Results

Variant	N	N Reps	N detected	Repro %	L 95% CI	U 95% CI	N pair	N pairs agree	Rep %	L 95% CI	U 95% CI
HD	13	307	299	97.4	94.9	98.9	153	145	94.8	90.0	97.7
Indel	34	793	790	99.6	98.9	99.9	392	389	99.2	97.8	99.8
RE	16	371	366	98.7	96.9	99.6	183	178	97.3	93.7	99.1
SUB	36	846	840	99.3	98.5	99.7	417	412	98.8	97.2	99.6
Total	**99**	**2317**	**2295**	**99.1**	**98.6**	**99.4**	**1145**	**1124**	**98.2**	**97.2**	**98.9**

HD: homologous recombination (CNA = 0), Indel: insertion and deletions, RE: rearrangements, SUB: base substitutions

The variant component analysis was performed to assess the precision (mean, coefficient of variation, and standard deviation) using the underlying MAF for short variants (base subs and indels), TP (Tumor Purity) for HD/CNA and average reads for RE on the 62 alterations selected in the primary analysis. Of 62 alterations, three alterations (4.8%) were excluded from the variant component analysis due to reproducibility less than 50% (i.e., small number of positive call replicates for a reliable model). Based on the model, the mean, SD, and CV of repeatability and reproducibility were calculated for each alteration. The results of each short variant (base subs and indel), HD/CNA and RE assessed in the variant component analysis are summarized in Table 16, Table 17 and Table 18, respectively.

Table 16: Summary for base substitutions and indels component analysis results of each alteration

Gene	Variant Type	Average MAF%	Repeatability		Reproducibility	
			SD	CV	SD	CV
PALB2	SUB	35.1	0.03	0.08	0.02	0.08
CHEK2	ID	45.9	0.03	0.06	0.02	0.06
PALB2	SUB	6.9	0.01	0.18	0.01	0.24
CDK12	SUB	17.2	0.01	0.07	0.02	0.12
ATM	ID	13.5	0.01	0.09	0.01	0.11
CDK12	ID	38.8	0.02	0.06	0.02	0.07

Gene	Variant Type	Average MAF%	Repeatability		Reproducibility	
			SD	CV	SD	CV
BRCA2	ID	6.0	0.00	0.11	0.00	0.11
ATM	ID	6.9	0.03	0.04	0.03	0.04
ATM	ID	15.1	0.01	0.08	0.01	0.10
CDK12	ID	5.8	0.00	0.09	0.01	0.11
BARD1	ID	12.9	0.01	0.07	0.01	0.09
BRCA2	ID	10.8	0.01	0.09	0.01	0.11
CHEK1	SUB	31.6	0.02	0.07	0.02	0.07
BARD1	SUB	6.5	0.08	0.11	0.01	0.19
FANCL	ID	43.6	0.03	0.07	0.03	0.08
RAD51C	1D	57.3	0.01	0.03	0.01	0.03
BRCA1	1D	9.9	0.01	0.11	0.02	0.21
BRCA2	ID	59.9	0.02	0.04	0.02	0.04
ATM	ID	49.9	0.02	0.05	0.02	0.05
BRCA2	SUB	36.3	0.03	0.07	0.03	0.09
BRCA2	SUB	52.7	0.03	0.05	0.03	0.07
BRCA2	SUB	66.3	0.03	0.04	0.03	0.05
FANCL	ID	51.3	0.01	0.03	0.02	0.04
BRIP1	ID	16.1	0.02	0.09	0.01	0.10
CDK12	ID	15.4	0.01	0.07	0.01	0.12
CHEK2	ID	44.3	0.03	0.07	0.04	0.08
BRCA2	ID	48.3	0.02	0.05	0.03	0.05
BRCA2	ID	20.4	0.01	0.09	0.02	0.12
CDK12	ID	46.5	0.02	0.04	0.02	0.04
CDK12	ID	45.7	0.02	0.05	0.02	0.05
BRIP1	ID	46.0	0.01	0.03	0.04	0.09
RAD51D	SUB	6.3	0.01	0.15	0.01	0.25
FANCL	ID	42.9	0.02	0.05	0.02	0.06
BRIP1	SUB	19.1	0.01	0.07	0.01	0.08

Table 17. Summary of HD variant component analysis results of each alteration

Gene	Variant Type	TP%	Repeatability		Reproducibility	
			SD	CV	SD	CV
CHEK1	Amp	79.9	0.02	0.02	0.03	0.03
ATM	loss	82.2	0.06	0.07	0.07	0.08
BRCA1	loss	40.6	0.01	0.02	0.01	0.02
CHEK2	loss	55.9	0.03	0.06	0.05	0.09
RAD51C	loss	55.0	0.01	0.02	0.01	0.02
ATM	loss	65.4	0.16	0.25	0.16	0.25
ATM	loss	49.9	0.09	0.18	0.09	0.18
ATM	loss	43.6	0.09	0.20	0.09	0.22

Table 18: summary of RE variant component analysis results of each alteration

Gene	Variant Type	Average Reads	Repeatability		Reproducibility	
			SD	CV	SD	CV
ATM	RE	153.1	17.26	0.11	27.64	0.18
BRCA1	RE	73.6	9.64	0.13	9.88	0.13
BRCA1	RE	12.7	2.90	0.22	2.92	0.22
BRCA2	RE	23.8	4.89	0.20	5.82	0.24
BRCA2	RE	14.7	2.58	0.17	3.44	0.23
BRCA2	RE	17.1	5.03	0.29	5.19	0.30
BRIP1	RE	169.7	16.54	0.09	20.89	0.12
PALB2	RE	38.6	6.60	0.17	7.82	0.20
RAD51B	RE	236.9	20.84	0.08	32.68	0.13
ATM	RE	75.8	13.27	0.17	14.71	0.19
RAD51B	RE	12.5	3.06	0.24	3.06	0.24
CHEK1	RE	65.5	8.85	0.13	9.37	0.14
BRIP1	RE	68.2	10.3	0.15	14.70	0.21

Site-to-site reproducibility for the North Carolina site:
A two-site reproducibility study including the second site in Morrisville, North Carolina was not conducted. Site-to-site reproducibility will be provided in a post-market study.

6. Reagent Lot Interchangeability

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDx_{BRCA} assay and F1CDx. For reagent lot interchangeability performance data, see the Summary of Safety and Effectiveness Data for P160018.

7. <u>Stability Studies</u>

a. Reagent Stability

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDx_{BRCA} Assay and F1CDx. For reagent stability performance data, see the Summary of Safety and Effectiveness Data for P160018. The claimed reagent stability is 4 months for the LC and HC kits, and 3 months for the sequencing kits at manufacturer's recommended storage condition.

b. **DNA Stability**

Please refer to the Summary of Safety and Effectiveness Data for P160018 and P170019 for results on DNA stability.

c. **FFPE Slide Stability**

Please refer to the Summary of Safety and Effectiveness Data for P160018 and P170019 for data on the stability of FFPE slides.

8. General Lab Equipment and Reagent Evaluation

a. DNA Amplification

Identical reagents with the same specifications are used following the same protocols for both the FoundationFocus CDx_{BRCA} assay and F1CDx. For DNA amplification performance data, see the Summary of Safety and Effectiveness Data for P160018.

b. DNA Extraction

An additional study was conducted to evaluate the quality of DNA extracted by F1CDx assay when processing prostate soft tissue and bone metastases samples. A total of 24 FFPE prostate bone metastasis specimens and 23 FFPE prostate soft tissue specimens were procured for evaluation in the study. Each of the 47 blocks were processed in duplicate from extraction through sequencing.

It is known that prostate bone metastasis specimens are challenging for DNA extraction. Of the 94 (47x2) samples, 19 samples (1 bone met and 18 soft tissue) failed pathology review. Of the 75 samples (47 bone mets and 28 soft tissues), 22 bone mets (47%) and all 28 soft tissues (100%) passed the DNA extraction QC yielding $\geq$ 55 ng DNA. For the samples that passed the DNA extraction yield requirement, the success rate was 100% for LC, 96.0% for HC and 94% for sequencing. There is no significant difference between processing success rates for bone mets and soft tissue samples (Table 19).

Table 19: Post-DNA extraction success rate

Process Steps	Over all % 95% CI	Bone mets % 95% CI	Soft Tissue % 95% CI
LC	100% [92.9%, 100%]	100% [84.6%, 100%]	100% [87.7%, 100%]
HC	96% [86.3%, 99.5%]	91% [70.8%, 98.9%]	100% [87.7%, 100%]
Sequencing	94% [82.8%, 98. 7%]	95% [75.1%, 99.9%]	93% [76.5%, 99.1%]

Additionally, the overall, positive and negative agreements between duplicates were determined to be 100% with corresponding exact 2-sided 95% CI of [98%, 100%], [72%, 100%] and [98%, 100%], respectively. In the 47 FFPE tissues, 11 HRR positive variants and 205 negative variants were identified. In the 11 HRR variants identified, the concordance was 100% for each variant type [substitutions (1), indels (7), rearrangements (1) and homozygous deletions (2)].

Please refer to the Summary of Safety and Effectiveness Data for P160018 and P170019 for additional DNA extraction performance data.

9. Guard banding/Robustness

Please see the Summary of Safety and Effectiveness Data for P160018, P170019 and P160018/S001 for guardbanding /robustness results..

10. Tissue Comparability

Please see the Summary of Safety and Effectiveness Data for P160018 and P170019 for tissue comparability study.

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 PROfound study is a Phase III, randomized, open-label, multicenter trial to assess the efficacy and safety of olaparib monotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC) that have qualifying homologous recombination repair (HRR) gene alterations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) and who have failed prior treatment with a new hormonal agent (NHA).

The safety and effectiveness of F1CDx for detecting HRR gene alterations in mCRPC patients who may benefit from treatment with Lynparza® (olaparib) was demonstrated based on results from the PROfound trial. Patients were selected into the trial by FMI's Clinical Trial Improvement Amendments (CLIA) HRR clinical trial assay (CTA). The CLIA HRR CTA uses the same classification rules as the F1CDx test with an expanded curated mutation list determined for all 14 HRR genes including *BRCA1* and *BRCA2* prior to the start of the PROfound study.

Since enrollment was based on FMI's F1CDx-based CLIA HRR assay, which is identical to the production F1CDx assay except some minor updates to the shared production analysis pipeline, the efficacy results are based on patients enrolled by the CLIA HRR assay (please see section D.2, below). The wet lab workflow (including reagents, equipment and QC) and the post-sequencing analysis pipeline are common between the CLIA HRR assay and production F1CDx assay.

A summary of the clinical study is presented below.

A. Study Design

The PROfound study was an international multicenter study conducted in 206 study centers in 20 countries (of these, 139 centres randomized patients): Argentina (6 sites), Australia (10 sites), Austria (5 sites), Brazil (14 sites), Canada (12 sites),

Denmark (1 site), France (13 sites), Germany (15 sites), Israel (6 sites), Italy (10 sites), Japan (30 sites), Netherlands (6 sites), Norway (1 site), South Korea (9 sites), Spain (7 sites), Sweden (2 sites), Taiwan (9 sites), Turkey (8 sites), United Kingdom (5 sites) and United States (37 sites). First patient was enrolled in 6 February 2017 and the last was patient enrolled in 18 September 2018. The original protocol (v.1; 19 October, 2016) was amended 4 times (v.4; final version was dated 7 March, 2019) across all study sites to modify study procedures or patient eligibility criteria.

All patients were required to have a qualifying HRR mutation assessed using the FMI CLIA HRR CTA to be randomized. Qualifying HRR gene alterations including alterations in *BRCA1*, *BRCA2* and *ATM* for Cohort A, and *BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and *RAD54L* for Cohort B. In addition, patients must have received a prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or castration-resistant prostate cancer (mCRPC) and, in the opinion of the investigator, progressed on this treatment. A total of 387 patients were enrolled based on the CTA. Patients were randomized in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets orally 300 mg bd
- Investigators choice of NHA with either enzalutamide 160 mg orally once daily (od) or abiraterone acetate 1000 mg orally qd with prednisone 5 mg orally bd (prednisolone was permitted for use instead of prednisone, if necessary)

The primary endpoint for the study was radiological progression-free survival (rPFS) of olaparib based on blinded independent central review (BICR) using RECIST 1.1 for soft tissue and prostate cancer working group 3 (PCWG3) for bone criteria in subjects with mCRPC with *BRCA1, BRCA2* or *ATM* qualifying mutations (Cohort A). The key secondary endpoints were objective response rate (ORR) by BICR assessment in subjects with measurable disease using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria (cohort A), rPFS by BICR using RECIST 1.1 (soft tissue) and PCWG3 (bone) criteria for (Cohort A+B) and overall survival (OS) for Cohort A.

1. Patient Information and Consent

In the PROfound study, written informed consent was obtained from each patient before enrollment according to the regulatory and legal requirements of the participating countries. The patients must provide informed consent for the genetic sampling and analyses as part of study inclusion criteria. As part of this procedure, the Investigator explained orally and in writing the information about the nature, purpose, possible risk and benefit of the study, information about alternative treatment with non-investigational drugs. The investigator(s) is responsible for ensuring that consent is given freely and that the Subject understands that they are free to discontinue from the study at any time. The patient received all information that was required by regulatory authorities and International Conference on Harmonization guidelines. The Investigator

provided the Sponsor with a copy of the IRB/IEC-approved Informed Consent Form (ICF) prior to the start of the study.
The ICF was signed and dated; one copy was given to the patient, and the Investigator retained a copy as part of the clinical study records. The Investigator did not undertake any investigation specifically required for the clinical study until written consent had been obtained.

2. Key Clinical Inclusion and Exclusion Criteria

Inclusion criteria:

Enrollment in the PROfound study was limited to patients who met the following inclusion criteria:

- Patients were to be male and at least 18 years of age.
- Patients must have provided written informed consent.
- Histologically confirmed diagnosis of prostate cancer.
- Subjects must have progressed on prior NHA (e.g., abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or CRPC.
- Radiographic progression at study entry while on androgen deprivation therapy (or after bilateral orchiectomy).
- Qualifying HRR mutation in tumor tissue by the FMI CLIA HRR (Lynparza HRR) CTA Assay
    - Either archival or *de novo* biopsies are acceptable.
    - If subjects have a mutation in one of the 15 HRR genes based on prior prostate cancer tissue specimen testing by the commercially available FoundationOne assay, they must have the mutation confirmed as a qualifying mutation by FMI. Residual DNA (stored at FMI) from the original FoundationOne test will be used for confirmation. Subjects who do not have sufficient residual DNA from the original test will be analysed *in-silico* for qualifying HRR gene mutations based on their original FoundationOne test data, but these subjects must supply sufficient formalin fixed, paraffin embedded (FFPE) tumor sample to carry out retrospective central confirmation using the FMI CLIA HRR CTA Assay.
- Patients must have had normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:
    - Haemoglobin (Hb) ≥10.0 g/dL with no blood transfusions in the past 28 days
    - Absolute neutrophil count ≥1.5 x 109/L
    - Platelet count ≥100 × 109/L
    - Total bilirubin ≤1.5 × institutional upper limit of normal (ULN)
    - Aspartate aminotransferase (serum glutamic oxaloacetic transaminase) / alanine aminotransferase serum glutamic pyruvate

transaminase) ≤2.5 × institutional ULN unless liver metastases are present in which case they must be ≤5 × ULN

- Patients must have creatinine clearance (CrCL) estimated of ≥51 mL/min using the Cockcroft-Gault equation for males or based on a 24 hour urine test.
- Estimated CrCL = (140-age [years]) × weight (kg)
  serum creatinine (mg/dL) × 72
- ECOG PS 0-2.

Exclusion criteria:
Patients were not permitted to enroll in the PROfound study if they met any of the following exclusion criteria:

- Any previous treatment with PARP inhibitor, including olaparib
- Patients who have any previous treatment with DNA-damaging cytotoxic chemotherapy, except if for non-prostate cancer indication and last dose >5 years prior to randomisation. For example, patients who received prior mitoxantrone or platinum-based chemotherapy for prostate cancer was excluded.
  - Prior estramustine was allowed.
- Other malignancy (including myelodysplastic syndrome [MDS] andmonoclonal gammopathy of undetermined significance) within the last 5 years except: adequately treated non-melanoma skin cancer or other solid tumours including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥5 years
- Patients with MDS/acute myeloid leukaemia (AML) or with features suggestive of MDS/AML
- Patients who were receiving any systemic anti-cancer therapy (except radiotherapy) within 3 weeks prior to study treatment.
- Persistent toxicities (>Grade 2, per the CTCAE) caused by previous cancer therapy, excluding alopecia or toxicities related to the use of LHRH agonist or antagonist
- Patients with known brain metastases. A scan to confirm the absence of brain metastases was not required.
- Patients inevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria:
- A bone scan referred to as a superscan showing an intense symmetric activity in the bones.
  - No soft tissue lesion (measurable or non-measurable) that can be assessed by RECIST.

3. Follow-up schedule

Safety follow-up
All randomised patients have a safety follow-up visit every 4 weeks post randomization until week 24. Following the week 24 visit, the safety follow-up

schedule switches to a follow-up visit every 8 weeks. Safety follow-up visits continue using this schedule until the final study dose. After final study dose the patient receives a study discontinuation visit 7 days after the final study dose) and a safety follow-up visit 30 days (+/- 7 days) after the final study dose

Efficacy follow-up

a. *From Enrolment to Radiographic Progression*

The baseline assessments of all imaging modalities should be performed as close as possible to the start of study treatment and no more than 4 weeks (-28 days) before randomization. Following the baseline assessment, subsequent assessments should be performed every 8 weeks (± 7 days), relative to the date of randomization, until objective radiological disease progression has been confirmed by BICR or by Investigator Assessment, irrespective of treatment decisions or dose interruptions.

b. *Post Radiographic Progression to 24 weeks following initiation of olaparib for patients who switch from NHA to olaparib post-progression*

Subjects who switch to olaparib post Radiographic Progression the visit schedule is every 4 weeks (±7 days) until 24 weeks following initiation of olaparib. Patients are then followed-up for efficacy every 12 weeks (±14 days) as part of survival follow-up.

Survival follow-up

In survival follow-up, patients are followed up every 12 weeks (+/- 14 days) for 2nd progression and death. Patients who discontinue study treatment switch to survival follow-up. Patients on the Investigators Choice of NHA arm, who switch to olaparib post-progression enter survival follow-up after 24 weeks of treatment.

Follow-up activities continue per the above schedules until the final data cut-off (DCO, last subject, last visit). Following final DCO, sites should continue to follow visits as per general practice.

B. Accountability of PMA Cohort

Cohort A

A total of 4425 patients with mCRPC who had failed treatment with a prior NHA, were enrolled at 206 centers in 20 countries. Of these, 139 centres randomized patients. Of these, 139, 111 centers in 20 countries randomized patients into Cohort A. Patients with an available FFPE tumor sample were screened for qualifying HRR gene mutations using the FMI CLIA HRR CTA. Of the 245 patients with qualifying HRR gene mutations (*BRCA1*, and/or *BRCA2* and/or *ATM*) that were randomized into Cohort A, 162 patients received olaparib and 83 patients received investigators choice of NHA.

Of the 245 patients randomized onto Cohort A, 224 patients had single mutations and 21 had co-occurring mutations. Of the 224 patients, 13 patients (5.8%) had a *BRCA1* mutation, 127 patients (56.7%) had a *BRCA2* mutation, and 84 patients (37.5%) had a *ATM* mutation alone.

Of the 21 patients that had co-occurring mutations; 1 patient was *BRCA1+ATM*, 1 patient was *BRCA1+RAD54L*, 2 patients were *BRCA2+ATM*, 2 patients were *BRCA2+BARD1*, 4 patients were *BRCA2+CDK12*, 1 patient was *BRCA2+CDK12+CHEK2*, 2 patients were *BRCA2+CHEK2*, 1 patient was *BRCA2+CHEK2+RAD51D*, 3 patients were *BRCA2+PPP2R2A*, 1 patient was *BRCA2+RAD51B*, 1 patient was *ATM+CHEK2*, 1 patient *ATM+ PP2R2A*, and 1 patient was *ATM+RAD51B*. Note: patients with co-occurring mutations (*BRCA1, BRCA2, or ATM* plus a Cohort B gene) were assigned to Cohort A.

Cohort B

Of these, 139 of these centers randomized patients with 85 centers in 18 countries randomizing patients into Cohort B. Patients with an available FFPE tumor sample were screened for qualifying HRR gene mutations using the FMI CLIA HRR CTA. Of the 142 patients with qualifying HRR gene mutations (*BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D* and/or *RAD54L*) that were randomized into Cohort B, 94 patients received olaparib and 48 patients received investigators choice of NHA.

Of the 142 patients randomized onto Cohort B, 135 patients had single mutation and 7 patients had co-occurring mutations. Of the 135 patients, 89 patients (65.9%) had a *CDK12* mutations and 31.9% of patients had a single mutation in 1 of 9 HRR genes (*BARD1, BRIP1, CHEK1, CHEK2, PALB2, PPP2R2A, RAD51B, RAD51D* and *RAD54L*). No patients in Cohort B had a *FANCL* or *RAD51C* mutation alone and thus, not enrolled in the trial.

For Cohort B, 7 patients had co-occurring mutations; 1 patient was *BRCA2m+ CDK12m*, 1 patient was *BARD1+CDK12*, 1 patient was *BRIP1+PALB2*, 1 patient was *CDK12+CHEK1*, 2 patients were *CDK12 +PALB2* and 1 patient was *PALB2+PPP2R2A*.

The majority (97.2%) of the PROfound trial patients (FAS; N=387) were confirmed as positive according to the testing criteria and mutation classification rules approved for the F1CDx test (N=376). This subgroup is refered to as confirmed FMI F1CDx subgroup (N=376). The efficacy of olaparib was studied in 376 patients with HRR mutations in mCRPC in the PROfound trial. A break-down by FAS (N=387) and confirmed FMI F1CDx subgroup (N=376) is shown in Table 20.

Table 20: Break-down of FAS and and confirmed FMI F1CDx subgroup by Cohort

	FAS						Confirmed FMI F1CDx subgroup					
	Number of patients (N)		Variant Status				Number of patients (N)		Variant Status			
Gene**	Cohort A (245)	Cohort B (142)	HD	LR	ID	SUB	Cohort A (240)	Cohort B (136)	HD	LR	ID	SUB
BRCA1	15	0	0	5	5	5	14	0	0	5	5	4
BRCA2	143	2	27	15	73	36	140	2	27	14	73	34
ATM	90	2	10	8	39	41	88	2	10	8	38	40
BARD1	2	2	0	0	2	2	1	1	0	0	1	1
BRIP1	0	4	0	0	3	1	0	4	0	0	3	1
CDK12	5	94	5	5	68	39	5	89	5	5	65	36
CHEK1	0	3	0	0	2	1	0	3	0	0	2	1
CHEK2	5	12	1	0	15	1	5	12	1	0	15	1
*FANCL**	0	0	0	0	0	0	0	0	0	0	0	0
PALB2	0	8	0	0	6	3	0	7	0	0	6	2
RAD51B	2	5	2	2	0	3	2	5	2	2	0	3
*RAD51C**	0	0	0	0	0	0	0	0	0	0	0	0
RAD51D	1	1	0	1	1	0	1	1	0	1	1	0
RAD54L	1	5	0	1	1	4	1	5	0	1	1	4

HD: Homozygous deletion. Patients who have homozygous gene loss
LR: Large Rearrangement. Patients who have exonic or multi-exon insertions or deletion
ID: Insertion/Deletion. Patients who have small insertions/deletions which lead to a frameshift
SUB: Base Substitutions. Patients who have other variant types (non-sense, missense, splice site, etc.)
*These two genes were not enrolled in the trial. **Patients harboring *PPP2R2A* were also enrolled in the trial, [FAS subgroup (*PPP2R2A* Cohort A 4, Cohort B 11); Confirmed FMI F1CDx subgroup (*PPP2R2A* Cohort A 4, Cohort B 10)]..

C. Study Population Demographics and Baseline Parameters

In the safety population, the median age was 65 years (range: 29 to 91 years), and 13.4% of patients were ≥75 years of age. Most patients were White (85.1%); 57.7% had an ECOG performance status of 0 at study entry, and 42.3% had an ECOG performance status of 1 at study entry. In the biomarker-defined population, the median age was 63 years (range: 39 to 91 years), and 10.2% of patients were ≥75 years of age. Most patients were White (81.6%); 59.2% had an ECOG performance status of 0 at study entry, and 40.8% had an ECOG performance status of 1 at study entry. Demographics for the overall safety population and for the biomarker-defined

population are summarized in Table 21 and 22. Overall, 421 (90.9%) patients were treated at US sites and 42 (9.1%) patients were treated at Canadian sites.

Table 21: Demographic characteristics (FAS; Cohort A)

		Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)	Total (N=245)
Age (years)	Mean	68.0	68.1	68.1
	Standard deviation	8.23	7.36	7.93
	Median	68.0	67.0	68.0
	Min	47	49	47
	Max	86	86	86
Age group (years), n (%)	<65	54	23	77
	≥65	108	60	168
Race, n (%)	White	109	55	164
	Black or African	2	1	3
	Asian	43	19	62
	Other	1	1	2
	Missing	7	7	14
Ethnic group, n (%)	Hispanic or Latino	12	9	21
	Not Hispanic or	145	69	214
	Missing	5	5	10

Table 22: Demographics Characteristics (FAS; Cohort B)

		Olaparib 300 mg bd (N=94)	Investigators choice of NHA (N=48)	Total (N=142)
Age (years)	Mean	69.2	70.3	69.6
	Standard deviation	8.79	7.83	8.46
	Median	69.0	69.5	69.0
	Min	48	51	48
	Max	91	87	91
Age group (years), n (%)	<65	28 (29.8)	11 (22.9)	39 (27.5)
	≥65	66 (70.2)	37 (77.1)	103 (72.5)
Race, n (%)	White	54 (57.4)	30 (62.5)	84 (59.2)

		Olaparib 300 mg bd (N=94)	Investigators choice of NHA (N=48)	Total (N=142)
	Black or African American	5 (5.3)	0	5 (3.5)
	Asian	26 (27.7)	17 (35.4)	43 (30.3)
	Other	1 (1.1)	0	1 (0.7)
	Missing	8 (8.5)	1 (2.1)	9 (6.3)
Ethnic group, n (%)	Hispanic or Latino	5 (5.3)	3 (6.3)	8 (5.6)
	Not Hispanic or Latino	83 (88.3)	43 (89.6)	126 (88.7)
	Missing	6 (6.4)	2 (4.2)	8 (5.6)

Baseline disease characteristics, including site of the primary tumor, histologic subtype, and duration, are provided for the safety population and the biomarker-defined population in Table 23 and 24.

Table 23: Baseline Disease Characteristics at baseline (FAS, cohort A)

	Number (%) of patients		
	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)	Total (N=245)
Time from CRPC to randomisation (months)			
Median	24.2	23.7	24.1
Min, max	-6[a], 189	1, 175	-6, 189
Time from mCRPC to randomisation (months)			
Median	23.3	22.5	23.1
Min, max	-6[a], 121	1, 105	-6, 121
Histology type at diagnosis			
Adenocarcinoma	160 (98.8)	80 (96.4)	240 (98.0)
Small cell carcinoma	0	0	0
Other	0	2 (2.4)	2 (0.8)
Missing	2 (1.2)	1 (1.2)	3 (1.2)
Total Gleason Score at diagnosis			
2	1 (0.6)	0	1 (0.4)
3	0	0	0
4	2 (1.2)	0	2 (0.8)
5	2 (1.2)	1 (1.2)	3 (1.2)
6	6 (3.7)	3 (3.6)	9 (3.7)
7	41 (25.3)	22 (26.5)	63 (25.7)

	Number (%) of patients		
	Olaparib 300 mg bd (N=162)	Investigators choice of NHA (N=83)	Total (N=245)
8	36 (22.2)	12 (14.5)	48 (19.6)
9	59 (36.4)	35 (42.2)	94 (38.4)
10	10 (6.2)	7 (8.4)	17 (6.9)
Missing	5 (3.1)	3 (3.6)	8 (3.3)
Sites of disease at baseline[b]			
Total	162 (100)	83 (100)	245 (100)
Prostate	27 (16.7)	12 (14.5)	39 (15.9)
Locoregional lymph	35 (21.6)	17 (20.5)	52 (21.2)
Distant lymph nodes	59 (36.4)	35 (42.2)	94 (38.4)
Bone	140 (86.4)	73 (88.0)	213 (86.9)
Respiratory	30 (18.5)	11 (13.3)	41 (16.7)
Liver	18 (11.1)	13 (15.7)	31 (12.7)
Other distant sites	34 (21.0)	15 (18.1)	49 (20.0)
Bone only	42 (25.9)	25 (30.1)	67 (27.3)
Lymph node only	13 (8.0)	5 (6.0)	18 (7.3)
Bone and lymph node	26 (16.0)	14 (16.9)	40 (16.3)
ECOG performance status at baseline			
(0) Fully active	84 (51.9)	34 (41.0)	118 (48.2)
(1) Restricted in	67 (41.4)	46 (55.4)	113 (46.1)
(2) Ambulatory and	11 (6.8)	3 (3.6)	14 (5.7)
Missing	0	0	0
Baseline pain (BPI-SF worst pain [Item 3]) score			
0 to <2	83 (51.2)	37 (44.6)	120 (49.0)
2 to 3	17 (10.5)	9 (10.8)	26 (10.6)
>3	56 (34.6)	34 (41.0)	90 (36.7)
Missing	6 (3.7)	3 (3.6)	9 (3.7)
Baseline PSA (µg/L)			
n	160	81	241
Median	62.180	112.920	74.570
Min, max	0.20, 7240.74	1.85, 7115.00	0.20, 7240.74
Baseline haemoglobin (g/L)			
n	162	83	245
Mean (standard deviation)	122.6 (12.87)	122.5 (13.95)	122.6 (13.22)

Baseline ALP (U/L)			
n	162	83	245
Mean (standard deviation)	172.2 (201.75)	182.7 (203.14)	175.7 (201.86)
Baseline LDH (U/L)			
n	160	80	240
Mean (standard	268.0 (254.07)	267.3 (185.02)	267.7 (232.94)
Patient positive by F1 CDx test			
Yes	157 (96.9)	83 (100)	240 (98.0)
No	5 (3.1)	0	5 (2.0)
Patient positive by Myriad germline test			
Yes	43 (26.5)	19 (22.9)	62 (25.3)
No	119 (73.5)	64 (77.1)	183 (74.7)
Measurable disease at baseline[c]			
Yes	95 (58.6)	46 (55.4)	141 (57.6)
No	67 (41.4)	37 (44.6)	104 (42.4)
Received prior taxane therapy[c]			
Yes	106 (65.4)	52 (62.7)	158 (64.5)
No	56 (34.6)	31 (37.3)	87 (35.5)
Personal history of second malignancy apart from prostate cancer			
Yes	14 (8.6)	10 (12.0)	24 (9.8)
No	148 (91.4)	73 (88.0)	221 (90.2)
Family history of prostate cancer			
Yes	33 (20.4)	16 (19.3)	49 (20.0)
No	129 (79.6)	67 (80.7)	196 (80.0)
Family history of other cancers			
Yes	88 (54.3)	40 (48.2)	128 (52.2)
No	74 (45.7)	43 (51.8)	117 (47.8)

Table 24: Disease characteristics at baseline (FAS; Cohort B)

	Number (%) of patients		
	Olaparib 300 mg bd (N=94)	**Investigators choice of NHA (N=48)**	**Total (N=142)**
Time from CRPC to randomisation (months)			
Median	26.2	24.8	26.2
Min, max	1, 125	2, 177	1, 177
Time from mCRPC to randomisation (months)			
Median	23.0	18.5	22.2

	Number (%) of patients		
	Olaparib 300 mg bd (N=94)	**Investigators choice of NHA (N=48)**	**Total (N=142)**
Min, max	1, 125	2, 70	1, 125
Histology type at diagnosis			
Adenocarcinoma	93 (98.9)	47 (97.9)	140 (98.6)
Small cell carcinoma	0	0	0
Other	1 (1.1)	1 (2.1)	2 (1.4)
Missing	0	0	0
Total Gleason Score at diagnosis			
6	0	1 (2.1)	1 (0.7)
7	16 (17.0)	5 (10.4)	21 (14.8)
8	25 (26.6)	16 (33.3)	41 (28.9)
9	42 (44.7)	21 (43.8)	63 (44.4)
10	11 (11.7)	4 (8.3)	15 (10.6)
Missing	0	1 (2.1)	1 (0.7)
Sites of disease at baseline[a]			
Total	93 (98.9)	48 (100)	141 (99.3)
Prostate	14 (14.9)	9 (18.8)	23 (16.2)
Locoregional	19 (20.2)	14 (29.2)	33 (23.2)
Distant lymph	40 (42.6)	16 (33.3)	56 (39.4)
Bone	78 (83.0)	40 (83.3)	118 (83.1)
Respiratory	13 (13.8)	4 (8.3)	17 (12.0)
Liver	7 (7.4)	5 (10.4)	12 (8.5)
Other distant sites	23 (24.5)	16 (33.3)	39 (27.5)
Bone only	23 (24.5)	11 (22.9)	34 (23.9)
Lymph node only	5 (5.3)	4 (8.3)	9 (6.3)
Bone and lymph	20 (21.3)	5 (10.4)	25 (17.6)
ECOG performance status at baseline			
(0) Fully active	47 (50.0)	21 (43.8)	68 (47.9)
(1) Restricted in physically strenuous activity	45 (47.9)	25 (52.1)	70 (49.3)
(2) Ambulatory and	2 (2.1)	1 (2.1)	3 (2.1)
Missing	0	1 (2.1)	1 (0.7)
Baseline pain (BPI-SF worst pain [Item 3]) score			

0 to <2	42 (44.7)	20 (41.7)	62 (43.7)
2 to 3	14 (14.9)	4 (8.3)	18 (12.7)
>3	37 (39.4)	22 (45.8)	59 (41.5)
Missing	1 (1.1)	2 (4.2)	3 (2.1)
Baseline PSA (µg/L)			
Median	85.760	100.060	92.865
Min, max	2.32, 6450.50	2.24, 2365.80	2.24, 6450.50
Baseline haemoglobin (g/L)			
n	94	47	141
Mean (standard	121.6 (13.15)	117.6 (13.37)	120.3 (13.31)
Baseline ALP (U/L)			
n	94	47	141
Mean (standard	148.1 (175.22)	149.6 (141.93)	148.6 (164.36)
Baseline LDH (U/L)			
n	92	47	139
Mean (standard	241.1 (160.95)	251.3 (140.14)	244.6 (153.80)
Patient positive by F1CDx test			
Yes	91 (96.8)	45 (93.8)	136 (95.8)
No	3 (3.2)	3 (6.3)	6 (4.2)
Patient positive by Myriad germline test			
Yes	0	0	0
No	94 (100)	48 (100)	142 (100)
Measurable disease at baseline[b]			
Yes	54 (57.4)	26 (54.2)	80 (56.3)
No	40 (42.6)	22 (45.8)	62 (43.7)
Received prior taxane therapy[b]			
Yes	64 (68.1)	32 (66.7)	96 (67.6)
No	30 (31.9)	16 (33.3)	46 (32.4)
Personal history of second malignancy apart from prostate cancer			
Yes	10 (10.6)	3 (6.3)	13 (9.2)
No	84 (89.4)	45 (93.8)	129 (90.8)
Family history of prostate cancer			
Yes	23 (24.5)	7 (14.6)	30 (21.1)
No	71 (75.5)	41 (85.4)	112 (78.9)
Family history of other cancers			
Yes	42 (44.7)	21 (43.8)	63 (44.4)

No	52 (55.3)	27 (56.3)	79 55.6)

D. Safety and Effectiveness Results

1. Safety Results

The safety assessment based primarily on Cohort A+B data from PROfound, where 256 patients received olaparib, is used to provide the most robust assessment of safety in the mCRPC population. In addition, the underlying genetic mutations are not considered to affect the safety profile of olaparib. However, the safety with respect to treatment with olaparib is not comprehensively addressed in the SSED for the F1CDx. The evaluation of safety was based on the analysis of adverse events (AEs), clinical laboratory evaluations, physical examinations, and vital signs.

Overall, olaparib was well tolerated and the study did not result in the identification of any new safety signals. The most common AEs were fatigue (59.1%), nausea (59.1%), vomiting (37.2%), anaemia (32.9%), diarrhoea (27.2%), and abdominal pain (25.8%). A total of 162/298 (54.4%) patients reported at least 1 CTCAE Grade 3 or higher event. The most common CTCAE events of Grade 3 or higher were anaemia (17.4%), fatigue (6.4%), and abdominal pain (5.7%). Dose modifications due to AEs occurred in 120 (40.3%) patients; main events requiring dose modification were anaemia (9.7%), vomiting (7.0%), fatigue (5.0%), nausea (3.7%), thrombocytopenia (3.0%) and abdominal pain (3.0%). A small number of patients (11 [3.7%]) required permanent discontinuation from the study due to AEs, with 9 (3%) patients having events with a fatal outcome. The olaparib safety and tolerability profile in this study was consistent with that observed in previous studies of olaparib. Refer to Lynparza (olaparib) drug label for more information.

2. Effectiveness Results

a. Overall Efficacy

The PROfound study met its primary objective, demonstrating a statistically significant improvement in rPFS as assessed by BICR with olaparib compared with investigators choice of NHA in Cohort A. In addition, there was significant improvement in rPFS as assessed by BICR for cohort A+B. Specifically, the PROfound efficacy data with olaparib demonstrated:

- There was a statistically significant and clinically meaningful 66% reduction in the risk of radiological disease progression or death by BICR [HR=0.34; 95% confidence interval (CI: 0.25 to 0.47; p<0.0001)] with a median rPFS of 7.4 months for olaparib vs 3.6 months for investigators choice of NHA. This equates to a prolongation of median progression-free interval of 3.8 months with olaparib vs investigators choice of NHA. As shown in the table below (Table 25), the rPFS outcome in the confirmed FMI F1CDx

subgroup (N=376) (HR 0.33 (95% CI: 0.24, 0.46) was consistent with the Full Analysis Set (FAS) (HR 0.34, 95% CI: 0.25, 0.47).

Table 25: Summary of efficacy analysis of rPFS based on BICR (Cohort A)

Analysis group	Full Analysis Set		Confirmed FMI F1CDx Subgroup	
	Olaparib (N=162)	**NHA (N=83)**	**Olaparib (N=157)**	**NHA (N=83)**
n (%) of events[a]	106 (65)	68 (82)	101 (64)	68 (82)
Treatment effect				
Median rPFS (95% CI) [months]	7.4 (6.2, 9.3)	3.6 (1.9, 3.7)	7.4 (6.9, 9.3)	3.6 (1.9, 3.7)
HR (95% CI)[b]	0.34 (0.25, 0.47)		0.33 (0.24, 0.46)	
2-sided p-value[c]	<0.0001		<0.0001	

[a]Progression, as assessed by BICR, was defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomized therapy or received another anticancer therapy prior to progression.

[b]The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A).

[c] The analysis was performed using the log-rank test stratified by the variables selected in the primary pooling strategy (prior taxane use and measurable disease in Cohort A) using the Breslow method for handling ties.

BICR blinded independent central review; CI confidence interval; FAS full analysis set; HR hazard ratio; NHA new hormonal agent; PCWG-3 Prostate Cancer Working Group 3; RECIST Response Evaluation Criteria in Solid Tumours; rPFS radiological progression-free survival.

- The major efficacy outcome was supported by a statistically significant improvement in ORR based on BICR for patients with measurable disease at baseline in Cohort A. The ORR based on BICR for the full analysis set was 28% and ORR by BICR for the FMI F1CDx subgroup was 27% (Table 26).

Table 26: Confirmed radiological objective response rate (ORR) based on BICR (Cohort A)

Analysis group	Treatment group	N	ORR (N%) (95% CI)	p-value
Full Analysis Set	Olaparib	84	28 (33) (23, 45)	<0.0001
	NHA	43	1 (2) (0, 12)	
Confirmed FMI F1CDx Subgroup	Olaparib	84	27 (33) (23. 44)	<0.0001
	NHA	43	1 (2) (0, 12)	

* Due to the low numbers of responders in the comparator arm (N=1), the median DoR is difficult to interpret for the control arm and results should be interpreted with caution.

- For cohort A+B, there was a statistically significant and clinically meaningful 51% reduction in the risk of radiological disease progression or death by BICR (HR=0.49; 95% CI 0.38, 0.63; p<0.0001) and a median rPFS of 5.8 months for olaparib vs 3.5 months for investigators choice of NHA; this equates to a prolongation of median progression-free interval of 2.3 months with olaparib vs investigators choice of NHA. As shown in the table below (Table 27), the outcome by BICR in the confirmed FMI F1CDx subgroup (HR=0.49; 95% CI: 0.38, 0.63; p<0.0001; median rPFS 5.8 months vs 3.5 months, respectively) was consistent with the Full Analysis Set (FAS).

Table 27: Efficacy results of rPFS based on BICR (Cohort A+B)

Analysis group	Full Analysis Set		Confirmed FMI F1CDx Subgroup	
	Olaparib (N=256)	NHA (N=131)	Olaparib (N=248)	NHA (N=128)
n (%) of events	180 (70)	99 (76)	172 (69)	96 (75)
Treatment effect				
Median rPFS (months) (95% CI)	5.8 (5.5, 7.4)	3.5 (2.2, 3.7)	6.2 (5.5, 7.4)	3.5 (2.1, 3.7)
HR (95% CI)	0.49 (0.38, 0.63)		0.49 (0.38, 0.63)	
2-sided p-value	<0.0001		<0.0001	

- In Cohort A, the interim OS data (Table 28) indicate a trend for OS benefit in olaparib-treated patients compared with investigators choice of NHA-treated patients, with a median OS improvement of 3.4 months in

the olaparib arm vs the investigators choice of NHA arm (HR=0.64; 95% CI 0.43, 0.97; p=0.0173; median OS 18.5 months vs 15.1 months, respectively) for full analysis set. Similar OS improvement of 3.4 months in olaparib arm compared to the control arm was seen for F1CDx confirmed subgroup (HR=0.62; 95% CI 0.41, 0.95; p=0.0058).

Table 28: Summary of overall survival (OS) based on BICR (Cohort A)

Analysis group	Full Analysis Set		Confirmed FMI F1CDx Subgroup	
	Olaparib (N=162)	**NHA (N=83)**	**Olaparib (N=157)**	**NHA (N=83)**
n (%) of events	54 (33)	39 (47)	51 (32)	39 (47)
Treatment effect				
Median rPFS (95% CI) [months]	18.5 (17.2, NR)	15.1 (11.3, 19.1)	18.5 (17.2, NR)	15.1 (11.3, 19.1)
HR (95% CI)	0.64 (0.43, 0.97)		0.62 (0.41, 0.95)	
2-sided p-value	0.0173		0.0158	

- For *RAD54L, CHEK2*, and *PPP2R2A*, results should be interpreted with caution due to the small number of events. HRs were not calculated for some of the Cohort B genes (*BARD1, BRIP1, CHEK1, PALB2, RAD51B,* and *RAD51D*) due to the small number of events (<5 across arms) in these subgroups. There were no patients enrolled with *FANCL* or *RAD51C* mutations. *Note: Although patients with PPP2R2A gene mutations were enrolled in the trial, Lynparza is not indicated for the treatment of patients with this gene mutation because of lack of response, and a numerical decrement in both rPFS and OS compared to enzalutamide or abiraterone.*

Since the CTA (FMI's CLIA HRR CTA) is identical to the CDx, the efficacy results are based on the patients enrolled by the CTA. Due to minor differences in the bioinformatics pipeline between the CTA and CDx, it is believed that there will be no significant impact on the efficacy results. See Benefit-Risk Determination section below. Based on the risk-based pre-postmarket balance, the degree of uncertainty due to the absence of the final CDx efficacy results is deferred to the postmarket setting. An *in-silico* bridging study will be performed postmarket to confirm that the efficacy results based on F1CDx is preserved despite minor bioinformatics pipeline changes.

3. Pediatric Extrapolation

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

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 225 principal investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). 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 of Medical Devices, 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

PROfound trial results demonstrated a positive benefit for olaparib monotherapy in patients with mCRPC that have qualifying HRR gene mutations that were predicted to be deleterious or suspected deleterious who have failed prior treatment with an NHA. This is evidenced by the following:

- PROfound study demonstrated clinically meaningful improvement in rPFS as assessed by BICR with olaparib compared with investigators choice of NHA in Cohort A, with a 66% reduction in the risk of BICR-confirmed radiological disease progression or death and a prolongation of median progression-free interval of 3.8 months with olaparib vs investigators choice of NHA (HR=0.34; 95% CI 0.25, 0.47; $p<0.0001$; median rPFS 7.4 months vs 3.6 months, respectively). The rPFS in the confirmed FMI F1CDx subgroup (HR 0.33; 95% CI 0.24, 0.46; <0.0001) was consistent with the Full Analysis Set.

- The improvement in median rPFS in Cohort A was further supported by the analysis of the key secondary endpoints in this cohort: confirmed radiological ORR and OS. There was a statistically significant and clinically meaningful improvement in confirmed radiological ORR for patients in Cohort A in the olaparib arm compared with the investigators choice of NHA arm.

- In addition to the positive results in Cohort A, there was also a statistically significant and clinically meaningful improvement in rPFS for olaparib-treated patients compared with investigators choice of NHA-treated patients in Cohort

A+B, with a 51% reduction in the risk of radiological disease progression or death and a prolongation of median progression-free interval of 2.3 months with olaparib vs investigators choice of NHA for both FAS and confirmed F1CDx subgroups.

In summary, the efficacy results in the PROfound study demonstrated clinically relevant and statistically significant benefit compared with enzalutamide or abiraterone acetate in men with mCRPC who have failed prior treatment with a new hormonal agent and have HRR gene mutations. An improvement was observed in overall health-related quality of life (HRQoL) in olaparib-treated patients compared with investigators choice of NHA-treated patients, indicating olaparib treatment provided clinically meaningful patient-centred benefit.

The performance of the next generation sequencing-based F1CDx was also supported by the analytical validation studies. As demonstrated in the analytical specificity study, the assay is highly specific to detect variants in the 14 HRR genes. The intended use to include HRR gene alterations in prostate cancer patients to determine eligibility for treatment with olaparib was demonstrated through a clinical study using specimens screened for the PROfound trial. The data from analytical and clinical studies support the reasonable assurance of safety and effectiveness of the F1CDx assay when used in accordance with the indication for use. Data from the PROfound trial demonstrate that patients who had qualifying HRR gene alterations received benefit from treatment with olaparib and supports the addition of the proposed CDx indication to F1CDx.

B. Safety Conclusions

The F1CDx is an *in vitro* diagnostic device, which involves testing formalin fixed paraffin embedded tumor tissues collected from patients with mCRPC. The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Risks of the F1CDx are associated with failure of the device to perform as expected or failure to correctly interpret test results and subsequently, inappropriate patient management decisions in cancer treatment.

Patients with false positive results may undergo treatment with Lynparza® (olaparib) without any clinical benefit and may experience adverse reactions associated with olaparib therapy. Patients with false negative results may not be considered for treatment with Lynparza® (olaparib), and therefore, may forgo potentially beneficial treatment with olaparib with a demonstrated rPFS benefit of about 4 months or may receive other treatment options. There is also a risk of delayed results, which may lead to a delay in treatment with Lynparza® (olaparib). The olaparib safety and tolerability profile observed in this study was consistent with that observed in previous studies of olaparib monotherapy. The most commonly reported AEs in the olaparib arm were anaemia, nausea, decreased appetite, fatigue and diarrhoea.

C. Benefit-Risk Determination

Treatment with olaparib provides meaningful clinical benefit to metastatic castration resistant prostate cancer patients with alterations in Homologous Recombination Repair

genes, as demonstrated in the PROfound trial. The probable benefits of the F1CDx device are based on data collected in the clinical study, showing improved rPFS in a defined population of patients with mCRPC, with a clinically meaningful overall response in patients with deleterious or suspected deleterious Homologous Recombination Repair gene alterations. Given the available information, the data supports the conclusion that FoundationOne®CDx has probable benefit in selecting patients with alterations in Homologous Recombination Repair genes, for treatment with olaparib in patients with metastatic castration resistant prostate cancer.

Additional factors to be considered in determining probable risks and benefits for F1CDx included: analytical performance of the device, representation of variants in the major effectiveness study, and the availability of alternative tests. Analytical accuracy of the device showed a high degree of agreement with the comparator.

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

The risks of the F1CDx for selection of prostate cancer patients with alterations in Homologous Recombination Repair genes, for treatment with olaparib are associated with the potential mismanagement of patient's treatment resulting from false results of the test. Patients who are determined to be false positive by the test may be exposed to a drug 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 erroneous results are partially mitigated by the analytical performance of the device.

The likelihood of false results was assessed by an analytical accuracy study that performed specifically to evaluate the concordance between the F1CDx assay and an externally validated NGS (evNGS). The comparison between the F1CDx assay and the evNGS based comparator assay evaluated 230 specimens that comprised of 120 HRR positive clinical specimens (151 total variants observed) and 110 HRR negative clinical specimens. The positive variants cover a range of variant types including nonsense mutations, frameshift indels, mutations in the consensus splice donor and acceptor sequence, rearrangements, and homozygous deletions (copy number = 0). The performance of the accuracy study partially mitigates the risks associated with this device.

Treatment with olaparib provides meaningful clinical benefit measured by overall magnitude of the response rate, with a moderate degree of uncertainty due to the small number of subjects in some of the subgroups.

In conclusion, given the available information above, the data support the use of the F1CDx test as an aid in identifying mCRPC patients with deleterious or suspected

deleterious HRR genes alterations for the treatment with olaparib, and the probable benefits outweigh the probable risks.

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

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 study support the utility of F1CDx as an aid in selecting patients with previously treated mCRPC who may be eligible for treatment with olaparib. Olaparib demonstrated improvement in radiological progression free survival and overall response in mCRPC patients who have failed prior treatment with a New Hormonal Agent and who have deleterious or suspected deleterious homologous recombination repair (HRR) gene mutations, as identified with F1CDx.

In summary, considering all factors including conditions of approval (postmarket actions), the benefits of the use of F1CDx in patients with HRR gene mutations are judged to outweigh the risks.

XIII. CDRH DECISION

CDRH issued an approval order on May 19, 2020. The final conditions of approval cited in the approval order are described below.

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

- Provide results from an *in-silico* bridging study to confirm that the final efficacy results of the CDx remain unaltered when compared to the enrolling assay, FMI's CLIA HRR CTA. This information should be provided within 3 months of the approval of this PMA supplement.

- 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 HRR gene alterations from patients with prostate cancer, as was used in support of the Morrisville, North Carolina site approval (P170019/S010). This information should be submitted within 1 year of the PMA approval date.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.