

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

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|---|---|
| Device Generic Name: | Next generation sequencing oncology panel, somatic or germline variant detection system |
| Device Trade Name: | Oncomine™ Dx Target Test |
| Device Product Code: | PQP |
| Applicant's Name and Address: | Life Technologies Corporation 7305 Executive Way Frederick, MD 21704 |
| Date(s) of Panel Recommendation: | None |
| PMA Number: | P160045/S046 |
| Date of FDA Notice of Approval: | October 17, 2024 |

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

Subsequently, additional PMA supplements were approved for expanding the indications for use of the ODxT Test for detecting *RET* fusions in tumors from NSCLC and thyroid cancer (TC) patients, *RET* mutations in medullary thyroid cancer (MTC) patients, *EGFR* exon 20 insertions and *ERBB2/HER2* mutations in tumors from NSCLC patients, *IDH1* single nucleotide variants (SNVs) in cholangiocarcinoma (CC) patients, and identification of BRAF V600E mutations in anaplastic thyroid cancer (ATC) for treatment with the corresponding therapeutic products, since its original approval. The SSEDs to support the previously approved indications are available on the CDRH website.

The current panel-track supplement was submitted to expand the indications for use of the ODxT Test to include a companion diagnostic indication for the identification of *IDH1* and *IDH2* mutations in patients with astrocytoma (AC) and oligodendroglioma (OG) that may benefit from the targeted drug therapy, VORANIGO® (vorasidenib).

II. INDICATIONS FOR USE

The Oncomine™ Dx Target Test is a qualitative *in vitro* diagnostic test that uses targeted high-throughput, parallel-sequencing technology to detect single nucleotide variants (SNVs), deletions, and insertions in 23 genes from DNA and fusions in *ROS1* and *RET* from RNA

isolated from formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples from patients with non-small cell lung cancer (NSCLC), *IDH1* SNVs from FFPE tumor tissue samples from patients with cholangiocarcinoma (CC), *BRAF* V600E mutations from FFPE tumor tissue samples from patients with anaplastic thyroid cancer (ATC), *IDH1* and *IDH2* SNVs from FFPE tumor tissue samples from patients with astrocytoma (AC) and oligodendroglioma (OG), *RET* SNVs, multi-nucleotide variants (MNVs), and deletions from DNA isolated from FFPE tumor tissue samples from patients with medullary thyroid cancer (MTC) and *RET* fusions from RNA isolated from FFPE tumor tissue samples from patients with thyroid cancer (TC) using the Ion PGM™ Dx System.

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

Table 1. List of variants for therapeutic use by indication

| Tissue type | Gene | Variant | Targeted therapy |
|-------------|-------------------|--|---|
| NSCLC | <i>BRAF</i> | <i>BRAF</i> V600E mutations | TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib) |
| | <i>EGFR</i> | <i>EGFR</i> L858R mutation, <i>EGFR</i> exon 19 deletions | IRESSA® (gefitinib) |
| | <i>EGFR</i> | <i>EGFR</i> exon 20 insertions | RYBREVANT™ (amivantamab-vmjw) |
| | <i>ERBB2/HER2</i> | <i>ERBB2/HER2</i> activating mutations (SNVs and exon 20 insertions) | ENHERTU® (fam-trastuzumab deruxtecan-nxki) |
| | <i>RET</i> | <i>RET</i> fusions | GAVRETO™ (pralsetinib) RETEVMO® (selpercatinib) |
| | <i>ROSI</i> | <i>ROSI</i> fusions | XALKORI® (crizotinib) |
| CC | <i>IDH1</i> | <i>IDH1</i> R132C, <i>IDH1</i> R132G, <i>IDH1</i> R132H, <i>IDH1</i> R132L, and <i>IDH1</i> R132S mutations | TIBSOVO® (ivosidenib) |
| ATC | <i>BRAF</i> | <i>BRAF</i> V600E mutations | TAFINLAR® (dabrafenib) in combination with MEKINIST® (trametinib) |
| MTC | <i>RET</i> | <i>RET</i> mutations (SNVs, MNVs, and deletions) | RETEVMO® (selpercatinib) |
| TC | <i>RET</i> | <i>RET</i> fusions | RETEVMO® (selpercatinib) |
| AC and OG | <i>IDH1, IDH2</i> | <i>IDH1</i> R132C, <i>IDH1</i> R132G, <i>IDH1</i> R132H, <i>IDH1</i> R132L, <i>IDH1</i> R132S, <i>IDH2</i> R172M, <i>IDH2</i> R172K, <i>IDH2</i> R172W, <i>IDH2</i> R172S, and <i>IDH2</i> R172G mutations | VORANIGO® (vorasidenib) |

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

Results other than those listed in **Table 1** are indicated for use only in patients who have already been considered for all appropriate therapies (including those listed in **Table 1**).

Analytical performance using NSCLC specimens has been established for the variants listed in **Table 2**.

Table 2. List of Variants with Established Analytical Performance Only

| Gene | Variant ID/type | Amino acid change | Nucleotide Change |
|---------------|-----------------|-------------------|-------------------|
| <i>KRAS</i> | COSM512 | p.Gly12Phe | c.34_35delGGinsTT |
| <i>KRAS</i> | COSM516 | p.Gly12Cys | c.34G>T |
| <i>MET</i> | COSM707 | p.Thr1010Ile | c.3029C>T |
| <i>PIK3CA</i> | COSM754 | p.Asn345Lys | c.1035T>A |

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

III. **CONTRAINDICATIONS**

There are no known contraindications.

IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the Oncomine™ Dx Target Test labeling.

V. **DEVICE DESCRIPTION**

The Oncomine™ Dx Target Test is an *in vitro* diagnostic test that provides primer panels, assay controls and interpretative software [an Assay Definition File (ADF)] designed for use with the Ion PGM™ Dx System and the Ion PGM™ Dx Reagents for detection of alterations in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) isolated from NSCLC, CC, MTC, TC, ATC, AC and OG FFPE tumor specimens.

The Oncomine™ Dx Target Test consists of the following:

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

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

Ion Torrent™ Dx FFPE Sample Preparation Kit:

- Ion Torrent™ Dx Total Nucleic Acid Isolation Kit
- Ion Torrent™ Dx cDNA Synthesis Kit

- Ion Torrent™ Dx DNA Quantification Kit
- Ion Torrent™ Dx RNA Quantification Kit
- Ion Torrent™ Dx Dilution Buffer Kit

Ion PGM™ Dx Reagents / Chips:

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

Instrumentation and Software:

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

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

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

Nucleic Acid Extraction:

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

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

DNA. Following a series of washes to remove residual DNase and DNA degradation products, the purified RNA is eluted from the filter.

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

Quantification:

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

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

Reverse Transcription (RT) Step (RNA only):

RNA is enzymatically converted to cDNA using the Ion Torrent Dx cDNA Synthesis Kit. Ten nanograms (ng) of RNA is enzymatically converted to cDNA using an enzyme mix containing a proprietary engineered version of Moloney Murine Leukemia Virus (M-MLV) reverse transcriptase (Superscript III RT), an RNase inhibitor, a proprietary helper protein, and a buffer containing random primers, dNTPs, and MgCl₂.

Library Preparation Workflow:

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

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

preparation, the DNA and RNA libraries for all samples and controls may be blended for the templating reaction.

Data Analysis:

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

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are FDA approved companion diagnostic (CDx) alternatives for the detection of genetic alterations using FFPE tumor specimens, to those listed in **Table 1** of the ODxT Test intended use statement. These approved alternative CDx tests are listed in the **Table 3** below. Each alternative has its own advantages and disadvantages. A patient should fully discuss any alternative with his/her physician to select the most appropriate method. For additional details see FDA List of Cleared or Approved Companion Diagnostic Devices at:

<https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm?source=govdelivery>.

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

| Gene | Variant | Device | Company | Technology | Therapy |
|-------------|--|-------------------------------------|------------------------------|------------|---|
| <i>BRAF</i> | <i>BRAF</i> V600E | FoundationOne CDx | Foundation Medicine, Inc. | NGS | TAFINLAR [®] (dabrafenib) in combination with MEKINIST [®] (trametinib) |
| <i>EGFR</i> | <i>EGFR</i> L858R, exon 19 deletions | therascreen <i>EGFR</i> RGQ PCR Kit | Qiagen Manchester, Ltd. | PCR | IRESSA [®] (gefitinib) |
| <i>EGFR</i> | <i>EGFR</i> Exon 19 Deletions and Exon 21 L858R Substitution | O/RDx- LCCA | Pillar Biosciences, Inc. | NGS | <i>EGFR</i> Tyrosine Kinase Inhibitors |
| | | FoundationOne CDx | Foundation Medicine, Inc. | NGS | IRESSA [®] (gefitinib) |
| | | cobas <i>EGFR</i> Mutation Test v2 | Roche Molecular Systems, Inc | PCR | |
| <i>ROS1</i> | <i>ROS1</i> fusion | FoundationOne CDx | Foundation Medicine, Inc. | NGS | XALKORI [®] (crizotinib) |
| <i>RET</i> | <i>RET</i> fusion | FoundationOne CDx | Foundation Medicine, Inc. | NGS | RETEVMO [®] (selpercatinib) |

VII. MARKETING HISTORY

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

The expansion of the indications for use of the ODxT Test described above in Section II are not currently approved and have not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

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

No adverse events were reported in connection with the clinical studies used to support this PMA as the studies were performed retrospectively using banked samples.

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

IX. SUMMARY OF NONCLINICAL STUDIES

The indication for use was modified to include the *IDH1* and *IDH2* SNVs from FFPE tumor tissue samples from patients with astrocytoma (AC) and oligodendroglioma (OG) for treatment with VORANIGO® (vorasidenib). To support the AC and OG indication for *IDH1* and *IDH2* SNVs, non-clinical (analytical) validation studies were conducted using the ODxT Test. A summary of analytical validation studies demonstrating the performance of the ODxT Test to detect the *IDH1* and *IDH2* mutations are listed below.

A. Laboratory Studies

Analytical validation studies demonstrating the performance of the ODxT Test in detecting the *IDH1* and *IDH2* SNV mutations are listed below. These studies were performed using intended use specimens and sample blends across all validation studies. Studies evaluating analytical

accuracy/concordance, precision studies near the limit of detection (LoD), limit of blank (LoB), DNA input, tissue input, interference, guardbanding, and stability of assay intermediates were conducted to support the indication for *IDH1* and *IDH2* mutations.

1. Analytical Accuracy/ Concordance

An analytical accuracy study was performed using clinical specimens from 437 FFPE AC and OG clinical tumor samples using an orthogonal externally validated next generation sequencing test method (referred to as Ev-NGS assay hereafter) as a comparator. The AC and OG *IDH* positive clinical samples were obtained from the Servier Pharmaceuticals LLC., clinical trial (AG881-C-004) and *IDH1* and *IDH2* negative clinical samples were sourced from commercial vendors.

The 327 *IDH1* and *IDH2* mutation positive samples and 2 *IDH1* and *IDH2* negatives were derived from the clinical study (cohort 1). The remaining 108 negative samples were commercially procured AC and OG-staged matched *IDH1* and *IDH2* mutation negatives that were screened by a representative local test or the clinical trial assay (CTA) that was used for patient enrollment into the AG881-C-004 clinical trial. The concordance between the results from the ODxT Test and the Ev-NGS Assay evaluated for positive percent agreement (PPA), negative percent agreement (NPA), and overall percent agreement (OPA) is provided in **Table 4**, **Table 5**, **Table 6** and **Table 7**.

When excluding the ODxT Test Unknown results (UNK), the percent agreement of PPA, NPA, and OPA were 100%, 96.2%, and 99.0% respectively, with the 95% Score CI of 98.8%-100% for PPA, 90.5%-98.5% for NPA, and 97.6%-99.6% for OPA. Unknown (UNK) is defined as insufficient samples and sample quality control (QC) sequencing failures resulting in an invalid result or No Call for the variant. When including the ODxT Test Unknown results (UNK), the percent agreement of PPA, NPA, and OPA were 100%, 90.1%, and 97.4% respectively, with the 95% Score CI of 98.8%-100% for PPA, 83.1%-94.4% for NPA, and 95.5%-98.6% for OPA (**Table 5**). All 317 samples that were *IDH1* and *IDH2* mutation positive by both ODxT Test and the Ev-NGS Assay also agreed at the variant level.

Table 4. Concordance between ODxT Test and Ev-NGS Assay for *IDH1* and *IDH2*

| ODxT Test | Ev-NGS Assay | | | Total |
|-----------|--------------|----------|----------|-------|
| | Positive | Negative | Unknown* | |
| Positive | 317 | 4 | 6 | 327 |
| Negative | 0 | 100 | 3 | 103 |
| Unknown* | 0 | 7 | 0 | 7 |
| Total | 317 | 111 | 9 | 437 |

*Unknown samples are defined as values due to insufficient sample, or sample QC sequencing failure resulting in an invalid result or No Call for the variant.

Table 5. Unadjusted Agreements between ODxT Test and Ev-NGS Assay for *IDH1* and *IDH2*

| Agreement Parameter | Excluding Unknown* | | Including Unknown* | |
|---------------------|--------------------|---------------|--------------------|----------------|
| | Percent Agreement | 95% CI | Percent Agreement | 95% CI |
| PPA | 100% (317/317) | (98.8%, 100%) | 100% (317/317) | (98.8%, 100%) |
| NPA | 96.2% (100/104) | (90.5, 98.5) | 90.1% (104/111) | (83.1%, 94.4%) |

* Unknown samples are defined as values due to insufficient sample, or sample QC sequencing failure resulting in an invalid result or No Call for the variant.

Table 6: Unadjusted Agreements between ODxT Test and Ev-NGS Assay for *IDH1*

| Agreement Parameter | Excluding unknowns* | | Including unknowns* | |
|---------------------|---------------------|----------------|---------------------|----------------|
| | Percent agreement | 95% CI | Percent agreement | 95% CI |
| PPA | 100% (301/301) | (98.7%, 100%) | 100% (301/301) | (98.7%, 100%) |
| NPA | 96.7% (118/122) | (91.9%, 98.7%) | 92.9% (118/127) | (87.1%, 96.2%) |

* Unknown samples are defined as values due to insufficient sample, or sample QC sequencing failure resulting in an invalid result or No Call for the variant.

Table 7: Unadjusted Agreements between ODxT Test and Ev-NGS Assay for *IDH2*

| Agreement Parameter | Excluding unknowns* | | Including unknowns* | |
|---------------------|---------------------|---------------|---------------------|----------------|
| | Percent agreement | 95% CI | Percent agreement | 95% CI |
| PPA | 100% (16/16) | (80.6%, 100%) | 100% (16/16) | (80.6%, 100%) |
| NPA | 100% (398/398) | (99.0%, 100%) | 96.6% (398/412) | (94.4%, 98.0%) |

* Unknown samples are defined as values due to insufficient sample, or sample QC sequencing failure resulting in an invalid result or No Call for the variant.

The analytical concordance between ODxT Test vs Ev-NGS for *IDH1/IDH2* mutation was adjusted to account for patient selection in which 327 ODxT Test+ samples, 69 ODxT Test- samples, 4 ODxT Test *IDH* unknown samples and 37 reference Ev-NGS Assay samples were evaluated in the accuracy study. The updated concordance is included in **Table 8**.

Table 8. Adjusted Agreements between ODxT Test and Ev-NGS Assay for *IDH1* and *IDH2*

| Parameter | Excluding Unknowns | Including Unknowns |
|-----------|--------------------|--------------------|
| | Percent Agreement | Percent Agreement |
| PPA* | 100% | 100% |
| NPA* | 93.2% | 89.7% |

*Adjusted for ODxT Test and Ev-NGS test enrolment in this study.

2. Limit of Detection (LoD)

A study was conducted to establish the LoD of the ODxT Test for the detection of the *IDH1* and *IDH2* mutations using FFPE astrocytoma and oligodendroglioma samples. For three rare *IDH2* variants, where samples were not available, 2 non-glioma (adenocarcinoma) and 1 cell line blend were used. DNA from *IDH1* and *IDH2* variant-positive glioma cancer samples was blended with DNA from *IDH1* and *IDH2* WT glioma samples and used as input DNA for the test. A total of 10 FFPE samples, including five (5) *IDH1* variant-positive and five (5) *IDH2*-variant positive samples, were tested at six (6) dilution levels with 20 replicates per level (10 replicates per lot). This resulted in 120 replicates generated per sample and 120 data points per *IDH* variant. The final estimated LoD results for each *IDH1* and *IDH2* mutation is based upon the results from both reagent lots combined and are summarized in **Table 9** below.

Table 9. Summary of Final LoD Estimates for *IDH1* and *IDH2* SNVs

| Gene | COSMIC ID | Variant ID | Variant Amino Acid Change | Est. LoD ¹ (Allelic Frequency) |
|------|-----------|------------|---------------------------|--|
| IDH1 | COSM28746 | R132H | c.395G>A | 7.0% |
| | COSM28747 | R132C | c.394C>T | 5.5% |
| | COSM28748 | R132S | c.394C>A | 5.4% |
| | COSM28749 | R132G | c.394C>G | 4.6% |
| | COSM28750 | R132L | c.395G>T | 5.6% |
| IDH2 | COSM33731 | R172G | c.514A>G | 5.7% |
| | COSM33732 | R172M | c.515G>T | 5.1% |
| | COSM33733 | R172K | c.515G>A | 5.8% |
| | COSM34039 | R172W | c.514A>T | 4.1% |
| | COSM34090 | R172S | c.516G>T | 5.0% |

¹Clinical specimens were tested for 5 *IDH1* variants and 2 *IDH2* variants. For 3 rare *IDH2* variants, 2 adenocarcinoma and 1 cell line blends were used.

3. Contrived sample functional equivalency study

Contrived sample functional equivalency study was performed to show that the

performance of the ODxT Test in the detection of representative *IDH1* and *IDH2* SNVs from contrived FFPE cell line samples is comparable to the detection of these SNVs in clinical glioma FFPE samples. A contrived cell line sample was used in the glioma LoD study due to the rarity of clinical *IDH2* variant-positive glioma samples. Contrived sample functional equivalency was determined by comparing ODxT Test LoD sequencing results from contrived cell line FFPE blocks with results using clinical FFPE samples.

To establish equivalency, the study used DNA extracted from two *IDH1* (R132C and R132H) variant-positive contrived FFPE cell lines, one *IDH2* (R172K) variant-positive contrived FFPE cell line, and two WT glioma clinical samples. The DNA extracted from the contrived cell line FFPE samples was blended with DNA from WT samples at 6 dilution levels of varying allele frequencies with 20 replicates/level (10 replicates/reagent lot) resulting in 120 replicates/sample and 120 datapoints/*IDH* variant to estimate the LoD of the targeted variants.

The estimates were made using the empirical result of hit rate at each sample dilution level, where the LoD was determined as the lowest mean value among the 6 dilution levels at which at least 95% of the replicates yield a positive result. The final LoD for each *IDH1* or *IDH2* variant, as estimated by Probit analysis or empirical results, was then based on the results from both reagent lots combined. For each variant, the average allelic frequency (AF) associated with each test blend was computed, and the corresponding proportion of correct calls was determined. All differences in C25, C50, C75 and C95 estimates between the two sample types fell between 1.04% and 0.51% for each variant tested. The comparable C25, C50, C75 and C95 estimates between sample types support the functional equivalency of contrived cell line samples and clinical samples for *IDH1* and *IDH2* variants.

4. Limit of Blank (LoB)

To ensure that the ODxT Test does not generate a signal that might be classified as an *IDH1* and *IDH2* mutation positive result (false positive result), 4 WT glioma FFPE clinical samples for the *IDH1* and *IDH2* SNV variants were included in this study and tested using two (2) different lots of the ODxT Test reagents and two (2) operators. For each sample, a total of 36 library replicates were made using two (2) lots which is 18 library replicates per reagent lot. All sample replicates were sequenced. Results from this study showed that the false positive rate of the ODxT Test was zero (0) for *IDH1* and *IDH2* SNV variants since there were no positive calls at any of the variant locations analyzed by the test.

5. DNA Input Study

To define the tolerance around the amount of input DNA required for the ODxT Test to accurately detect *IDH1* and *IDH2* mutation variants, five (5) DNA input levels were tested: two (2) levels below the standard input of 10 ng (5 and 7.5, ng), one at 10 ng (standard input), and two (2) above 10 ng input (12.5 and 15 ng).

In this study, two (2) FFPE clinical samples harboring the most prevalent *IDH1* (R132H)

and *IDH2* (R172K) variants were blended using wild-type (WT) material to achieve an allelic frequency (AF) to a level near 1-1.5x LoD. The resulting DNA blend was adjusted to appropriate levels and used for library preparation. A total of 40 DNA libraries, including the controls, were made, and a single reagent lot was used for this study. Positive call rates were determined at different input levels of DNA tested for each sample.

The data generated from the study were analyzed using an analysis of variance (ANOVA) to determine the relationship of input level to AF. The study showed no statistically significant difference in AF between input level.

6. Tissue Input Study

This study was performed to verify that the number of slides used for extraction of glioma FFPE tissue samples provide adequate nucleic acid concentrations to meet the DNA and RNA input criteria for the ODxT Test. The test requires DNA at 10ng. A total of 17 clinical glioma FFPE tissue samples including 7 resection samples with $\geq 20\%$ tissue content (TC), 5 resection samples with $< 20\%$ TC, 2 stereotactic biopsies (STB) and 3 derived core needle biopsies (CNB) blocks were used in the study.

DNA was extracted with the Ion Torrent Dx FFPE Sample Preparation Kit using the recommended number of FFPE slides from the User Guides. Resections with Tumor Content $\geq 20\%$ were processed with 2 slides, STB and CNB samples were extracted with 9 slides and samples with $< 20\%$ tumor content were macrodissected with 2 (or more) slides based on surface section area.

The results from the study showed that when tissue input requirements for the glioma samples are met (2 x 5 μm sections for resection, 9 x 5 μm sections for CNB samples, and 9 x 5 μm sections for STB samples), 100% of samples extracted using the Ion Torrent Dx FFPE Sample Preparation Kit yielded DNA at a concentration of ≥ 0.83 ng/ μL . The study also demonstrated that when assay DNA input requirements (≥ 0.83 ng/ μL) and sample QC metrics are met, ODxT Test can provide *IDH1* and *IDH2* variant calls from DNA extracted from clinical glioma resection. The validation of the use of derivative CNB samples and STB samples on the ODxT Test to support inclusion of these type of samples has not been performed.

7. Precision (Repeatability and Reproducibility)

Two reproducibility studies, an external sample processing reproducibility study and an external panel reproducibility study, were performed to evaluate precision and reproducibility of the ODxT Test. The external sample reproducibility study starts from the nucleic acid extraction step to determine the reproducibility and repeatability of sample processing.

a. Panel reproducibility

The external reproducibility study was conducted across 3 sites to demonstrate within-run precision performance (repeatability) and variability across sites, operators, days, and

instrument platforms (reproducibility).

Seven (7) FFPE glioma samples (5 *IDH1* and 2 *IDH2*-positive clinical glioma samples) and 3 contrived samples (2 adenocarcinoma and 1 cell line) representing rare variants were used in the study. The samples were tested across 3 sites and with 3 different reagent lots to demonstrate the ability of the ODxT Test to generate reproducible results in the presence of variability across sites, operators, and reagent lots. The DNA extracted from each of the *IDH1* and *IDH2* variant positive samples was blended with wildtype (WT) sample gDNA to a target AF of 0.9x – 1.3x and 1.8x – 2.5x of the estimated LoD. Extracted DNA from the *IDH1/IDH2*-negative samples were paired with the *IDH1/IDH2* positive sample blends to create 12 sample blends, additionally, one *IDH1/2* negative sample was also tested. In total 13 sample blends were tested in this study.

The study included 2 instrument systems and 2 operators per site. At each site, each operator was assigned to 2 instrument systems, and each tested all 13 samples on both instrument systems using 2 different lots of reagents. Each site performed 52 valid sequencing runs (26 runs per operator across 2 systems) for a total of 156 valid sequencing runs (72 replicates per sample) across all 3 sites. Testing was conducted with target amplification on non-consecutive days.

The number of valid results, number of positive calls, positive call rate, number of negative calls, negative call rate, number of no calls, no call rate, and the within-run repeatability for the *IDH1* and *IDH2* variants were calculated for all samples tested. The 95% two-sided exact confidence intervals (CIs) were calculated for the positive call rate, negative call rate, and within-run repeatability.

The overall positive call rate for *IDH1* variants was 100% including or excluding no calls (**Table 10**). For *IDH2* variants, the overall positive call rate was 97.5% including no calls, and 99.9% excluding no calls (**Table 11**). The negative call rate was 100% at all *IDH1* and *IDH2* variant locations (**Table 12**).

Table 10. Reproducibility Positive Call Rates (All *IDH1* Variants)

| Variant ID | IDH1 Variant | N of Valid Results | N of Positive calls | N of Negative calls | N of No Calls | Correct call rate (95% CI) | | Observed AF (xLOD) |
|------------|--------------|--------------------|---------------------|---------------------|---------------|----------------------------|--------------------|--------------------|
| | | | | | | Including no calls | Excluding no calls | |
| R132H | COSM28746 | 72 | 72 | 0 | 0 | 100% | 100% | 1.1x |
| R132H | COSM28746 | 72 | 72 | 0 | 0 | 100% | 100% | 1.9x |
| R132C | COSM28747 | 72 | 72 | 0 | 0 | 100% | 100% | 1.2x |
| R132C | COSM28747 | 72 | 72 | 0 | 0 | 100% | 100% | 2.1x |
| R132S | COSM28748 | 72 | 72 | 0 | 0 | 100% | 100% | 1.1x |
| R132S | COSM28748 | 72 | 72 | 0 | 0 | 100% | 100% | 2.1x |
| R132G | COSM28749 | 72 | 72 | 0 | 0 | 100% | 100% | 1.1x |
| R132G | COSM28749 | 72 | 72 | 0 | 0 | 100% | 100% | 2.2x |
| R132L | COSM28750 | 72 | 72 | 0 | 0 | 100% | 100% | 1.1x |

| Variant ID | IDH1 Variant | N of Valid Results | N of Positive calls | N of Negative calls | N of No Calls | Correct call rate (95% CI) | | Observed AF (xLOD) |
|------------|--------------|--------------------|---------------------|---------------------|---------------|----------------------------|--------------------|--------------------|
| | | | | | | Including no calls | Excluding no calls | |
| R132L | COSM28750 | 72 | 72 | 0 | 0 | 100% | 100% | 2.0x |

Table 11. Reproducibility Positive Call Rates (All IDH2 Variants)

| Variant ID | IDH2 Variant | N of Valid Results | N of Positive calls | N of Negative calls | N of No Calls | Correct call rate (95% CI) | | Observed AF (xLOD) |
|------------|--------------|--------------------|---------------------|---------------------|---------------|----------------------------|--------------------|--------------------|
| | | | | | | Including no calls | Excluding no calls | |
| R172G | COSM33731 | 72 | 72 | 0 | 1 | 98.6% | 100% | 1.1x |
| R172G | COSM33731 | 72 | 71 | 0 | 0 | 100% | 100% | 1.9x |
| R172M | COSM33732 | 72 | 70 | 0 | 2 | 97.2% | 100% | 1.1x |
| R172M | COSM33732 | 72 | 72 | 0 | 0 | 100% | 100% | 2.2x |
| R172K | COSM33733 | 72 | 72 | 0 | 0 | 100% | 100% | 1.1x |
| R127K | COSM33733 | 72 | 72 | 0 | 0 | 100% | 100% | 2.1x |
| R172S | COSM34090 | 72 | 69 | 0 | 3 | 95.8% | 100% | 1.1x |
| R172S | COSM34090 | 72 | 72 | 0 | 0 | 100% | 100% | 2.0x |
| R172W | COSM34039 | 72 | 60 | 1 | 11 | 83.3% | 98.4% | 0.9x |
| R172W | COSM34039 | 72 | 72 | 0 | 0 | 100% | 100% | 2.2x |

Table 12. Reproducibility Negative Call Rates

| Variant ID | IDH Variant | N of Valid Results | N of Positive calls | N of Negative calls | N of No Calls | Correct call rate (95% CI) | | Observed AF (xLOD) |
|------------|-------------|--------------------|---------------------|---------------------|---------------|----------------------------|--------------------|--------------------|
| | | | | | | Including no calls | Excluding no calls | |
| R132H | COSM28746 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R132C | COSM28747 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R132S | COSM28748 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R132G | COSM28749 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R132L | COSM28750 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R172G | COSM33731 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R172M | COSM33732 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R172K | COSM33733 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R172W | COSM34039 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |
| R172S | COSM34090 | 72 | 0 | 72 | 0 | 100% | 100% | 0.000 |

All 5 *IDH1* variants had a 100% positive call rate and there were no instances of No Calls observed across the study. In three of the *IDH2* variants, No Calls were observed at the near LoD level. Sample 3 (COSM33732), Sample 5 (COSM33731) and Sample 7 (COSM34090) each experienced at least 1 No Call by 1 or more operator. The positive

call rates including No Calls for these samples were above 95% with the exception of Sample 11 (COSM34039), which was 83.3% due to eleven (11) No Calls out of the 72 replicates. However, these No Calls were all below the LoD and close to the assay cutoff and met the acceptance criteria.

Estimates of within-run repeatability for each sample (10 variant-positive samples and 3 WT samples for each gene), calculated as the percentage of runs with concordant replicates, was 100% across all *IDH1* variants, including or excluding no calls (**Table 13 and 15** below). For *IDH2* variants, the repeatability estimates ranged from 95.8% to 100% with no calls excluded. Including no calls, repeatability estimates for most samples ranged from 87.5% to 100% except for sample R172W, which was lower due to no calls resulting from an AF that was below LoD (**Table 14 and 15** below).

Table 13. Within-Run Correct Call Rate by Variant (*IDH1*)

| Variant ID | Total Number of Runs | Repeatability Correct call rate (Including No Calls) | | | Repeatability Correct call rate (Excluding No Calls) | | |
|------------|----------------------|--|----------|-----------------|--|----------|-----------------|
| | | Number of Runs with Concordant Replicates | Estimate | 95% CI | Number of Runs with Concordant Replicates | Estimate | 95% CI |
| R132S | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132S | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132G | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132G | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132H | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132H | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132L | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132L | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132C | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R132C | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |

Table 14. Within-Run Correct Call Rate by Variant (*IDH2*)

| Variant ID | Total Number of Runs | Repeatability Correct call rate (Including No Calls) | | | Repeatability Correct call rate (Excluding No Calls) | | |
|------------|----------------------|--|----------|-----------------|--|----------|-----------------|
| | | Number of Runs with Concordant Replicates | Estimate | 95% CI | Number of Runs with Concordant Replicates | Estimate | 95% CI |
| R172K | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172K | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172M | 24 | 22 | 91.7% | (73.0%, 99.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172M | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172G | 24 | 23 | 95.8% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| R172G | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172S | 24 | 21 | 87.5% | (67.6%, 97.3%) | 24 | 100% | (85.8%, 100.0%) |
| R172S | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| R172W | 24 | 14 | 58.3% | (36.6%, 77.9%) | 23 | 95.8% | (78.9%, 99.9%) |
| R172W | 24 | 24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |

Table 15. Repeatability estimates for *IDH1* and *IDH2* variant calling by sample

| Gene | N of runs per sample | % Concordant runs excluding no calls | | % Concordant runs including no calls | |
|------|----------------------|--------------------------------------|--------------------|--------------------------------------|--------------------|
| | | Including no calls | Excluding no calls | Including no calls | Excluding no calls |
| IDH1 | 24 | 100% | 100% | 100% | 100% |
| IDH2 | 24 | 99.90% | 100% | 94.90% | 100% |

b. Sample reproducibility

The purpose of this study was to demonstrate that the processing of FFPE glioma samples as part of the ODxT Test workflow generated repeatable and reproducible results for the *IDH1* and *IDH2* variants when starting from the nucleic acid extraction step.

. Multiple sample replicates, operators, reagent lots, and days were included in the test design to evaluate within run repeatability and assay reproducibility with a 95% CI. Five (5) FFPE samples were tested (2 *IDH1*, 2 *IDH2*, and 1 WT sample). Each sample was tested at 3 sites using 3 different lots of the Ion Torrent Dx FFPE Sample Preparation Kit, with each of the sites receiving two of the three lots, and generating 4 replicates for each lot, for a total of 24 replicate data points across 3 sites per sample, 48 runs total across the four (4) *IDH1* and *IDH2* variants tested.

Within-run correct call rate repeatability was computed as the percentage of runs with concordant replicates (24 runs per sample). Including no calls, repeatability of correct call rate estimates ranged from 87.5% to 100%. Excluding no calls, repeatability estimates were 100% for all samples as summarized below in **Table 16** for *IDH1* and *IDH2* variants.

Table 16. Repeatability and Call Rates

| Sample ID | Gene | Variant ID | COSMIC ID | Repeatability Correct Call Rate (Including No Calls) | | | Repeatability Correct Call Rate (Excluding No Calls) | | |
|-----------|------|------------|-----------|--|----------|-----------------|--|----------|-----------------|
| | | | | Total Runs with Concordant Replicates/ Total Runs | Estimate | 95% CI | Total Number of Runs with Concordant Replicates/Total Runs | Estimate | 95% CI |
| S1 | IDH1 | R132H | COSM28746 | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| | IDH2 | N/A | WT | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| S2 | IDH1 | N/A | WT | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| | IDH2 | R172W | COSM34039 | 21/24 | 87.50% | (67.6%, 97.3%) | 24 | 100% | (85.8%, 100.0%) |
| S4 | IDH1 | R132C | COSM28747 | 24/24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| | IDH2 | WT | WT | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| S5 | IDH1 | WT | WT | 24/24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| | IDH2 | R172K | COSM33733 | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |
| S6 | IDH1 | WT | WT | 24/24 | 100% | (85.8%, 100.0%) | 24 | 100% | (85.8%, 100.0%) |
| | IDH2 | WT | WT | 23/24 | 95.80% | (78.9%, 99.9%) | 24 | 100% | (85.8%, 100.0%) |

Table 17. Reproducibility for Correct Call Rate by Sample

| Sample | Variant ID | COSMIC ID | Total Replicates (N) | Number of Positives | Number of Negatives | Number of No Calls | Reproducibility Correct Call Rate (Including No calls) | | Reproducibility Correct Call Rate (excluding No calls) | |
|--------|------------|-----------|----------------------|---------------------|---------------------|--------------------|--|-----------------|--|-----------------|
| | | | | | | | Estimate | 95% CI | Estimate | 95% CI |
| S1 | IDH1 R132H | COSM28746 | 48 | 47 | 0 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |
| | IDH2 WT | WT | 48 | 0 | 47 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |
| S2 | IDH1 WT | WT | 48 | 0 | 47 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |
| | IDH2 R172W | COSM34039 | 48 | 45 | 0 | 3 | 93.8% | (82.8%, 98.7%) | 100% | (92.1%, 100.0%) |
| S4 | IDH1 R132C | COSM28747 | 48 | 48 | 0 | 0 | 100% | (92.6%, 100.0%) | 100% | (92.6%, 100.0%) |
| | IDH2 WT | WT | 48 | 0 | 47 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |
| S5 | IDH1 WT | WT | 48 | 0 | 48 | 0 | 100% | (92.6%, 100.0%) | 100% | (92.6%, 100.0%) |
| | IDH2 R172K | COSM33733 | 48 | 47 | 0 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |
| S6 | IDH1 WT | WT | 48 | 0 | 48 | 0 | 100% | (92.6%, 100.0%) | 100% | (92.6%, 100.0%) |
| | IDH2 WT | WT | 48 | 0 | 47 | 1 | 97.9% | (88.9%, 99.9%) | 100% | (92.5%, 100.0%) |

Between-run correct call rate reproducibility was computed for each gene and sample. Including no calls, correct call rate ranged from 93.8% to 100%. Excluding no calls, correct call rate was 100% for all samples as summarized in **Table 17** above.

8. Interference Study

To evaluate the potential impact of endogenous (necrotic tissue and hemoglobin) and exogenous interferences (paraffin, xylene, ethanol, Proteinase K, and wash buffer) on the performance of the ODxT Test in detecting *IDH1* and *IDH2* mutations, this study evaluated 3 clinical FFPE samples [one *IDH1* (R132H), one *IDH2* (R172K), and one WT] in 6 replicates per sample for 7 different conditions (6 with interfering substances and one control) taken through the entire test workflow, in the presence of endogenous or exogenous potential interferences. The interferent concentration tested was determined based on the CLSI EP07-3rd edition.

The study evaluated concordance of ODxT Test results. Concordance refers to agreement in ODxT Test variant call (positive, negative or no calls result), between experimental samples (samples with interferences) and control samples (samples without interferent).

a. Endogenous

Potential interference of necrotic tissue was evaluated in the clinical study (subject of this PMA). To evaluate the potential impact of tumor necrosis on *IDH1* and *IDH2* SNVs on variant calling, analysis based on tumor necrosis (0%,

0.1 – 10%, 10 – 20%, 20-40%5 and > 40%) was performed using ODxT Test. The analysis of the clinical study showed that among the range of tumor necrosis (0 to 70%) observed for the 437 clinical samples tested in this study there was no impact to the *IDH1* or *IDH2* SNV variant detection or overall concordance.

Additionally, two blends were tested to investigate the impact of necrosis on *IDH1* and *IDH2* variant detection near LoD. One 70% necrotic tissue containing WT glioma sample was blended with either a *IDH1* or *IDH2* variant positive sample near LoD such that the % of necrotic sample in the blends was 38.5% and 31.9%. There was no interference noted at that level from the necrotic sample.

For hemoglobin interference, the positive concordance with the control condition (with no calls being excluded) across all samples, and the overall concordance with the control condition across all samples were calculated. The concordance with the control condition across all samples was 100%.

b. Exogenous

Results from this study show that acceptance criteria of $\geq 95\%$ with respect to PPA (no calls excluded), NPA (no calls excluded), and OPA (no calls excluded) across all samples were achieved as results were reported at 100%. The data demonstrated that the presence of potentially interfering substances does not impact the performance of the assay to detect *IDH1* and *IDH2* mutations in FFPE samples.

9. Guard Banding Study

The purpose of the guard banding study was to evaluate tolerability of ODxT Test workflow to detect *IDH1* and *IDH2* mutations for 9 critical assay steps that include Panel volume, HiFi mix volume, FuPa reagent volume, switch solution volume, barcode adapter volume, incubation time, bubble formation after adding AMPure, residual ethanol and thermal cycling temperature offset. The study was conducted using the test conditions as previously described in Section IX. A.9.a. of the P160045 SSED.

To evaluate the workflow tolerance, two (2) blends were made from five (5) FFPE glioma clinical samples. Blend one was made from two (2) variant-positive FFPE clinical specimens containing *IDH1* R132H [COSM28746 (c.395G>A)], and *IDH2* R172K [COSM33733 (c.515G>A)] and one WT sample and was prepared at 1-1.5x LoD. Blend two was made with *IDH1* R132H [COSM28746 (c.395G>A)] variant positive derivative stereotactic biopsy (STB) glioma FFPE sample and one WT glioma sample and was prepared at 1-1.5x LoD.

An analysis of variance (ANOVA) was conducted to analyze the results. No significant differences between the high and low conditions, relative to the standard operating procedure (SOP), were observed. The AF was not significantly different from the AF observed when testing using the SOP condition, and no statistically significant difference in percent AF was observed in any resulting *IDH1* and *IDH2* data.

10. Stability of Assay Intermediates

The purpose of the study was to determine if the ODxT Test workflow allows for partially completed reactions (or intermediates) to be held at defined storage conditions prior to proceeding to the next step in the workflow. The stability of the intermediate products was evaluated by incorporating all of the pre-defined hold times specified in the User Guide.

The hold time studies were conducted with two (2) FFPE clinical glioma samples containing variant-positive *IDH1*(R132H) and *IDH2* (R132K) samples. Each sample was tested under three different test conditions (**Table 18** below).

This study used one DNA blend sample for all conditions. The DNA blend was composed of DNA extracted from FFPE clinical samples. The blend contained the WT and most prevalent clinical *IDH1*(R132H) and *IDH2* (R132K) variants. The blend used had an observed allelic frequency of 1-1.5x LoD.

Table 18. Designated Hold Time Test Conditions

| Condition | Eluted Library Hold Time |
|--|--------------------------|
| A) Nominal hold | No hold |
| B) Library hold | 30 days hold |
| C) Combo hold ¹ | No hold |
| ¹ Includes steps 1-2, and steps 4-9 (refer to the ODxT Test user guide) | |

For each hold condition investigated in this study, the relative percentage change in mean DNA variant AF from the corresponding mean AF at the nominal condition was used as a metric to evaluate stability. There were no statistically significant differences in AFs between each test condition when compared to the reference condition. These results demonstrated that assay workflow intermediates are stable for the periods tested when held at their defined storage conditions with respect to the assay's ability to report *IDH1* and *IDH2* variants.

11. Stability Studies

The purpose of the stability studies described below was to establish the tissue block/cut slide stability, and stability of DNA extracted from FFPE clinical samples when tested with the ODxT Test. The reagent stability studies are ongoing, and a minimum stability of 5 months has been established.

a. Tissue Slide Stability

The purpose of this study was to establish the stability of un-dipped slide mounted sections from FFPE glioma tissue blocks stored at room temperature from 15°C to 30°C for 12 months when tested with the ODxT Test. Three clinical samples were included in the study to represent both *IDH1* and *IDH2* SNVs

(Table 19). These samples were positive for an *IDH1* or *IDH2* SNV and were each tested at T0 (baseline), T1 (3 months+1 week), T2 (6 months+1 week), T3 (9 months+1 week), and T4 (12 months+1 week), see Table 20 below.

Table 19. Samples Tested

| Sample # | Sample ID | Gene | COSMIC ID | Variant |
|----------|-----------|------|-----------|---------|
| 1 | AD4168 | IDH1 | COSM28746 | R132H |
| 2 | AN2638 | IDH2 | COSM33733 | R172K |
| 3 | DES1012 | IDH1 | COSM28746 | R132H |

Table 20. Timepoints Tested

| Timepoint | Months | Weeks | Days |
|-----------|--------|-------|------|
| T0 | 0 | 0 | 0 |
| T1 | 3 | 12 | 84 |
| T2 | 6 | 24 | 168 |
| T3 | 9 | 36 | 252 |
| T4 | 12 | 48 | 336 |

Based on data from all timepoints, all FFPE glioma slides yielded DNA that resulted in *IDH1/2* SNV positive results with the ODxT Test, satisfying the study acceptance criteria. At the 12-month timepoint, DNA extracted from *IDH1* and *IDH2* positive FFPE tissue slides stored at room temperature met the acceptance criterion for maximum drift from baseline of $\leq 30\%$ for allele frequency for DNA variants. In this study, the stability of the slides was very consistent across all timepoints. There was no significant difference between the AFs at each timepoint for the clinical samples. The data supports stability of *IDH1* and *IDH2* positive FFPE slides stored at room temperature for 12 months.

b. Block Stability

The purpose of this study was to establish the stability of FFPE glioma *IDH1* and *IDH2* positive tissue blocks stored at 15°C to 30°C for 12 months when tested with the ODxT Test.

This study was performed to establish the stability of FFPE glioma tissue blocks using the Ion Torrent Dx FFPE Sample Preparation Kit for use in the ODxT Test. The data was generated from baseline through 4 time points (T0-T4) for each block to show stability of FFPE glioma tissue blocks stored at room temperature. Two (2) replicates per time point over a minimum of 5 time points were performed to achieve a minimum 80% power to detect a relative change in slope of 30% or more over the course of the study when

testing at a one-sided significance level $\alpha = 0.05$ (Table C1, CLSI-EP25-A). Three (3) clinical positive samples were used for an *IDH1* or *IDH2* SNV, each tested at baseline (0), 3 months+1 week (T1), 6 months+1 week (T2), 9 months+1 week (T3) and 12 months+1 week (T4). See **Table 21** for samples tested and **Table 22** for timepoints tested.

Table 21. Samples Tested

| Sample # | Sample ID | Gene | COSMIC ID | Variant |
|----------|-----------|------|-----------|---------|
| 1 | AD4168 | IDH1 | COSM28746 | R132H |
| 2 | AN2638 | IDH2 | COSM33733 | R172K |
| 3 | DES1012 | IDH1 | COSM28746 | R132H |

Table 22. Timepoints Tested

| Timepoint | Months | Weeks | Days |
|-----------|--------|-------|------|
| T0 | 0 | 0 | 0 |
| T1 | 3 | 12 | 84 |
| T2 | 6 | 24 | 168 |
| T3 | 9 | 36 | 252 |
| T4 | 12 | 48 | 336 |

Based on data from all timepoints, all FFPE glioma blocks yielded DNA that resulted in *IDH1/2* SNV positive results with a 100% call rate using the ODxT Test, satisfying the acceptance criteria. At the 12 months+1 week (T4) timepoint and all prior timepoints, DNA extracted from FFPE glioma samples harboring an *IDH1* or *IDH2* SNV met the acceptance criteria for maximum drift from baseline, $\leq 30\%$ for allele frequency of DNA variants. The data supports stability of FFPE clinical sample blocks harboring SNVs stored at 15°C to 30°C (room temperature) for 12 months.

c. Extracted Nucleic Acid Stability

The purpose of this study is to establish the storage stability of the DNA extracted from FFPE glioma clinical samples harboring an *IDH1* or *IDH2* SNV when tested with the ODxT Test.

Three clinical samples positive for an *IDH1* or *IDH2* SNV, were tested at baseline (T0), 3 months+1 week (T1), 6 months+1 week (T2), 9 months+1 week (T3) and 12 months+1 week (T4) time points. The summary of samples tested is shown in **Table 23** and the timepoints tested is shown in **Table 24** below.

Table 23. Samples Tested

| Sample # | Sample ID | Gene | COSMIC ID | Variant |
|----------|-----------|------|-----------|---------|
| 1 | AD4168 | IDH1 | COSM28746 | R132H |
| 2 | AN2638 | IDH2 | COSM33733 | R172K |
| 3 | DES1012 | IDH1 | COSM28746 | R132H |

Table 24. Timepoints Tested

| Timepoint | Months | Weeks | Days |
|-----------|--------|-------|------|
| T0 | 0 | 0 | 0 |
| T1 | 3 | 12 | 84 |
| T2 | 6 | 24 | 168 |
| T3 | 9 | 36 | 252 |
| T4 | 12 | 48 | 336 |

At the 12-month timepoint, DNA extracted from IDH1 and IDH2 positive tissue blocks stored at -30°C to -10°C met the acceptance criterion for maximum drift from baseline of ≤30% for allele frequency for DNA variants. In this study the stability of the extracted material was consistent across all timepoints. There were no significant differences between the AFs at each timepoint for the clinical samples. The data supports stability of extracted nucleic acid harboring an *IDH1* and *IDH2* SNV stored at -30°C to -10°C for 12 months (48 weeks).

12. Cross-Contamination

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

13. Reagent Lot Interchangeability

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

B. Animal Studies

Not applicable.

X. SUMMARY OF PRIMARY CLINICAL STUDY

ODxT Test Clinical Study for *IDH1* and *IDH2*

The clinical validation study was conducted to provide evidence in support of the safety and effectiveness of the ODxT Test when used as an aid to determine *IDH1/IDH2* (+/-) status in

patients with astrocytoma and oligodendroglioma screened and enrolled for treatment with VORANIGO® (vorasidenib) in Servier Pharmaceuticals' clinical trial, AG881-C-004. This was demonstrated through testing of DNA in FFPE tissue specimens from patients enrolled into the Servier pivotal clinical trial (AG881-C-004) to support the efficacy of VORANIGO® (vorasidenib).

A. Study Design

The clinical validation of ODxT Test was performed by utilizing FFPE glioma specimens (AC and OG) with an *IDH1* or *IDH2* mutation obtained from the Servier pivotal clinical trial (AG881-C-004). AG881-C-004 was a phase 3, global, multicenter, double-blind, randomized, placebo-controlled clinical study to evaluate the efficacy and safety of VORANIGO® (vorasidenib) in patients with residual or recurrent Grade 2 oligodendroglioma or astrocytoma, with an *IDH1* or *IDH2* mutation. A total of 331 subjects out of 410 *IDH1/2* variant-positive patients were enrolled in the AG881-C-004 based on the central confirmation of mutation status by the CDx (ODxT Test) and randomized to either placebo (163 subjects) or VORANIGO®/vorasidenib (168 subjects). Out of the 410 IDH variant-positive, 79 were not enrolled in the AG881-C-004 clinical trial because they did not meet at least one inclusion criterion, or they met at least one exclusion criterion. Since negative samples were not collected for enrollment testing in the AG881-C-004, Thermo Fisher procured negative samples from commercial vendors and screened these negative samples with an assay representative of the local prescreening tests (henceforth referred to as the representative LLT). The negative samples screened with representative LLT were then blinded, combined, randomized, and retested with ODxT Test. To minimize bias, operators were blinded during ODxT Testing of the negatives.

1. Inclusion Criteria:

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

- Be at least 12 years of age and weigh at least 40 kg
- Be able to understand and willing to sign informed consent (for subjects ≥18 years of age) or assent (for subjects <18 years of age) and willing to comply with scheduled visits, treatment plans, procedures, and laboratory tests, including serial peripheral blood sampling and urine sampling, during the study. A legally authorized representative may consent on behalf of a subject who is otherwise unable to provide informed consent, if acceptable to and approved by the site and/or site's institutional review board/independent ethics committee. A parent or legal guardian must sign informed consent for subjects <18 years of age.
- Have Grade 2 oligodendroglioma or astrocytoma per WHO 2016 criteria.
- Have had at least 1 prior surgery for glioma (biopsy, sub-total resection, gross-total resection), with the most recent surgery having occurred at least 1 year and not more than 5 years before the date of randomization, and no other prior anticancer therapy, including chemotherapy and radiotherapy.

- Have confirmed IDH1 (IDH1 R132H/C/G/S/L mutation variants tested) or IDH2 (IDH2 R172K/M/W/S/G mutation variants tested) gene mutation status disease by central laboratory testing during the prescreening period and available 1p19q status by local testing (e.g., fluorescence in situ hybridization, comparative genomic hybridization array, sequencing) using an accredited laboratory.
- Have MRI-evaluable, measurable, non-enhancing disease, as confirmed by the BIRC, assessed at Screening on 2D T2-weighted or 2D T2-weighted fluid-attenuated inversion recovery MRI with ≤ 4 mm slice thickness and no interslice gap. Measurable non-enhancing disease is defined as a least 1 target lesion measuring ≥ 1 cm \times ≥ 1 cm (bidimensional). Centrally confirmed, minimal, non-nodular, non-measurable enhancement that has not changed between the 2 most recent scans (including screening scan) will be permitted.
- Have Karnofsky performance status (KPS) $\geq 80\%$
- Have expected survival of ≥ 12 months
- Have adequate bone marrow function as evidenced by:
 - Absolute neutrophil count $\geq 1,500$ mm³ or $\geq 1.5 \times 10^9/L$
 - Hemoglobin ≥ 9 g/dL
 - Platelets $\geq 100,000$ mm³ or $\geq 100 \times 10^9/L$
- Have adequate hepatic function as evidenced by:
 - Serum total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN) unless considered due to Gilbert's disease after approval by the Medical Monitor, and
 - Aspartate aminotransferase at or below ULN and alanine aminotransferase at or below ULN, and
 - Alkaline phosphatase $\leq 2.5 \times$ ULN
- Have adequate renal function as evidenced by:
 - Serum creatinine $\leq 2.0 \times$ ULN, OR
 - Creatinine clearance > 40 mL/min based on the Cockcroft-Gault glomerular filtration rate estimation: $(140 - \text{Age}) \times (\text{Weight in kg}) \times (0.85 \text{ if female}) / 72 \times \text{Serum Creatinine}$
- Have recovered from any clinically relevant toxicities associated with any prior surgery for the treatment of glioma unless stabilized under medical management.
- Female subjects of childbearing potential must have a negative serum pregnancy test before the start of therapy. Women of childbearing potential are defined as having had onset of their first menstrual period and have not undergone a hysterectomy or bilateral oophorectomy or are not naturally postmenopausal (i.e., have not menstruated at all in the preceding 24 consecutive months). Women of childbearing potential as well as fertile men with partners who are women of childbearing potential must agree to abstain from sexual intercourse or to use 2 highly effective forms of contraception, at least one of which must be a barrier method, from the time of giving informed consent or assent, throughout the study,

and for 90 days after the last dose of VORANIGO®/vorasidenib. Abstinence is acceptable only as true abstinence when this is in line with the preferred and usual lifestyle of the subject; periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. Highly effective forms of contraception are defined as hormonal oral contraceptives, injectables, patches, intrauterine devices, intrauterine hormone release systems, bilateral tubal ligation, condoms with spermicide, or male partner sterilization.

2. Exclusion Criteria:

Patients were not permitted to enroll in the AG881-C-004 study if they met any of the following exclusion criteria:

- Have had any prior anticancer therapy other than surgery (biopsy, subtotal resection, gross-total resection) for treatment of glioma including systemic chemotherapy, radiotherapy, vaccines, small-molecules, IDH inhibitors, investigational agents, etc.
- Have high-risk features as assessed by the Investigator, including brainstem involvement either as primary location or by tumor extension, clinically relevant functional or neurocognitive deficits due to the tumor in the opinion of the Investigator (deficits resulting from surgery are allowed), or uncontrolled seizures (defined as persistent seizures interfering with activities of daily life AND failed 3 lines of antiepileptic drug regimens including at least 1 combination regimen)
- Concurrent active malignancy except for a) curatively resected nonmelanoma skin cancer or b) curatively treated carcinoma in situ. Subjects with previously treated malignancies are eligible provided they have been disease-free for 3 years at Screening.
- Are pregnant or breastfeeding.
- Have an active infection that requires systemic anti-infective therapy or with an unexplained fever $>38.5^{\circ}\text{C}$ within 7 days of C1D1.
- Have a known hypersensitivity to any of the components of AG-881
- Have significant active cardiac disease within 6 months before the start of study treatment, including New York Heart Association Class III or IV congestive heart failure (Appendix 11.2), myocardial infarction, unstable angina, and/or stroke.
- Have left ventricular ejection fraction (LVEF) $<40\%$ by echocardiogram (or by other methods according to institutional practice) obtained within 28 days before the start of study treatment.
- Have a heart-rate corrected QT interval using Fridericia's formula (QTcF) ≥ 450 msec or other factors that increase the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome). Subjects with bundle branch block and prolonged QTcF are permitted with approval of the Medical Monitor.

- Are taking therapeutic doses of steroids for signs/symptoms of glioma. Subjects taking physiologic doses (defined as equivalent of ≤ 10 mg prednisone daily) for medical conditions not related to glioma will be permitted. Are taking any medications that are cytochrome P450 (CYP) 3A or CYP2C9 substrates with a narrow therapeutic index (Subjects should be transferred to other medications before receiving the first dose of study drug.)
- Have known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, known positive human immunodeficiency virus antibody results, or AIDS-related illness. Subjects with a sustained viral response to HCV treatment or immunity to prior HBV infection will be permitted. Subjects with chronic HBV that is adequately suppressed by institutional practice will be permitted.
- Have known active inflammatory gastrointestinal disease, chronic diarrhea, previous gastric resection or lap band dysphagia, short-gut syndrome, gastroparesis, or other condition that limits the ingestion or gastrointestinal absorption of drugs administered orally. Gastroesophageal reflux disease under medical treatment is allowed (assuming no drug interaction potential).
- Have any other acute or chronic medical or psychiatric condition, including recent (within 12 months of C1D1) or active suicidal ideation or behavior, or a laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the subject inappropriate for entry into this study.

3. Follow-up Schedule

The AG881-C-004 study is ongoing for the safety and Overall survival patient follow-up assessments.

4. Clinical Endpoints

The key clinical efficacy endpoints were analyzed based on subjects who are randomized to the trial AG1881-C-004 and *IDH1/IDH2* positive by the ODX_T Test. The primary efficacy endpoint was Progression-Free Survival (PFS) per Blinded Independent Review Committee (BIRC). The hazard ratio between vorasidenib treatment and placebo was estimated by a Cox's proportional hazard model stratified by the randomization strata.

Refer to the Drugs@FDA database for the most recent therapeutic product labeling.

B. Accountability of PMA Cohort

Sample accountability for all randomized samples is presented in **Figure 1** and **Figure 2**

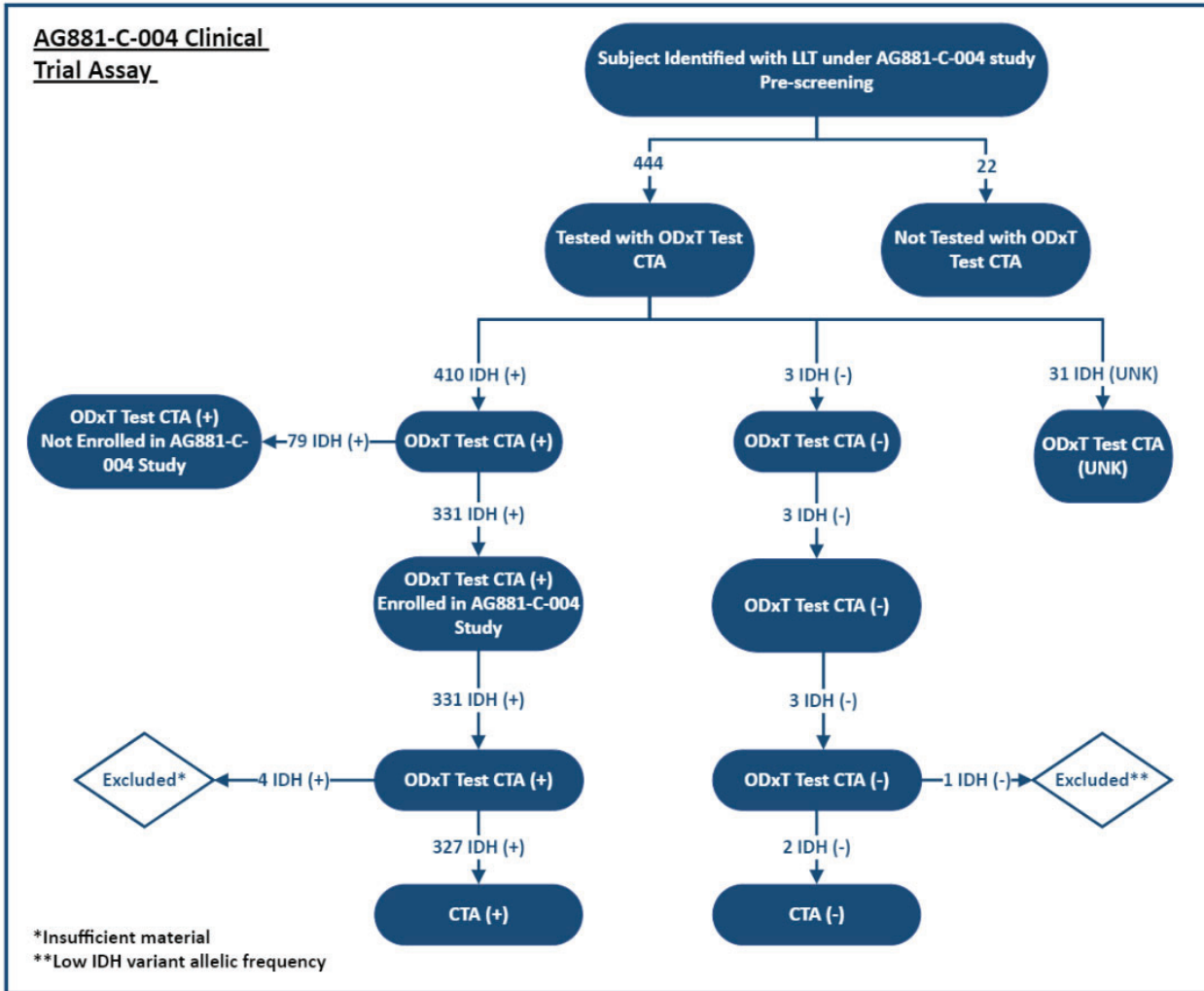
below.

Prescreened positives tested with LLT were retested and centrally confirmed for enrollment by the ODxT Test; therefore, the clinical trial enrolled ODxT Test and LLT double positive patients. A total of 444 samples were evaluated for this study. Out of these 444 samples, 410 were identified as IDH variant-positive, 3 were identified as IDH variant-negative, and 31 were identified as unknown by the enrolling CTA (ODxT Test). Out of the 410 IDH variant-positive, 79 were not enrolled in the AG881-C-004 clinical trial. Therefore, a total of 331 CTA *IDH*-variant positive subjects were enrolled in the AG881-C-004 clinical trial. The sample accountability chart for the CTA is provided in **Figure 1**. Out of these 331, samples from 4 subjects were not included (randomized) for this study due to insufficient material.

To supplement the negative population, 108 commercially procured stage-matched variant-negative samples were identified using two different NGS-based screening assays representative of local prescreening tests. Ultimately 71 of the commercially procured samples included in the clinical bridging were excluded due to prescreening bias leaving 37 evaluable samples (out of the 131 samples screened with one of the representative screening assays) in the negative cohort.

The clinical concordance sample accountability chart is provided in **Figure 2**. A total of 366 samples were included to evaluate the concordance between the NGS LLT assay and ODxT Test. Out of these, 329 samples (327 *IDH* variant-positive and 2 *IDH* variant-negative) were from the clinical enrollment population and the remaining 37 samples were commercially procured.

Figure 1. Sample Accountability Chart for CTA Testing



•≥65 years: 1 subject (0.6%) and 2 subjects (1.2%)

The proportion of males and females in the placebo arm was balanced; in the vorasidenib arm, more males (60.1%, n=101) were enrolled than females (39.9%, n=67). To be eligible for this study, adolescent subjects had to be at least 12 years of age and weigh at least 40 kg.

Table 25: Summary of Demographic Characteristics and Physical Measurements at Baseline

| | Placebo N=163 | Vorasidenib N=168 |
|---|--------------------------|------------------------------|
| Age (years) | | |
| n | 163 | 168 |
| Mean (StD) | 39.8 (9.53) | 40.9 (10.51) |
| Median (Q1, Q3) | 39.0 (34.0, 45.0) | 40.5 (34.0, 46.5) |
| Min, max | 16, 65 | 21, 71 |
| Age category (years), n (%) | | |
| <16 ^a | 0 | 0 |
| 16 - <18 | 1 (0.6) | 0 |
| 18 - <40 | 87 (53.4) | 76 (45.2) |
| 40 - <65 | 74 (45.4) | 90 (53.6) |
| ≥65 | 1 (0.6) | 2 (1.2) |
| Sex, n (%) | | |
| Male | 86 (52.8) | 101 (60.1) |
| Female | 77 (47.2) | 67 (39.9) |
| Race, n (%) | | |
| American Indian or Alaska Native | 0 | 1 (0.6) |
| Asian | 8 (4.9) | 5 (3.0) |
| Black or African American | 1 (0.6) | 2 (1.2) |
| Native Hawaiian or other Pacific Islander | 0 | 0 |
| White | 132 (81.0) | 125 (74.4) |
| Other | 1 (0.6) | 2 (1.2) |
| Not reported | 21 (12.9) | 33 (19.6) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 9 (5.5) | 9 (5.4) |
| Not Hispanic or Latino | 135 (82.8) | 122 (72.6) |
| Not Reported | 19 (11.7) | 37 (22.0) |
| BMI (kg/m²) | | |
| n | 162 | 166 |
| Mean (StD) | 26.52 (5.887) | 26.81 (5.748) |
| Median (Q1, Q3) | 25.48 (22.32, 29.10) | 25.91 (23.29, 29.20) |
| Min, max | 17.7, 48.9 | 17.6, 60.3 |

Abbreviations: BMI = body mass index; N = number of subjects in the FAS within each treatment arm; n = number of subjects in the FAS within each treatment arm in each category; Q1 = first interquartile range; Q3 = third interquartile range; StD = standard deviation.

Baseline Disease Characteristics

The main disease characteristics at enrollment for subjects are summarized by treatment arm in **Table 26**. The proportions of subjects with oligodendroglioma and astrocytoma, and median time from initial diagnosis were consistent between the treatment arms.

Table 26: Summary of Baseline Disease Characteristics and Prior Surgeries

| | Placebo N=163 n (%) | Vorasidenib N=168 n (%) |
|--|------------------------------------|--|
| Time from last surgery for Glioma to randomization (year) | | |
| n | 163 | 168 |
| Mean (StD) | 2.60 (1.285) | 2.66 (1.139) |
| Median (Q1, Q3) | 2.21 (1.50, 3.68) | 2.52 (1.61, 3.52) |
| Min, Max | 0.9, 5.0 | 0.2, 5.2 |
| >1-2 | 71 (43.6) | 56 (33.3) |
| >2-4 | 57 (35.0) | 88 (52.4) |
| >4 | 34 (20.9) | 22 (13.1) |
| Laterality at initial diagnosis, n (%) | | |
| Left | 77 (47.2) | 89 (53.0) |
| Right | 84 (51.5) | 79 (47.0) |
| Bilateral | 2 (1.2) | 0 |
| IDH1 positive | 152 (93.3) | 163 (97.0) |
| R132C | 7 (4.3) | 8 (4.8) |
| R132G | 1 (0.6) | 5 (3.0) |
| R132H | 138 (84.7) | 146 (86.9) |
| R132L | 4 (2.5) | 2 (1.2) |
| R132S | 2 (1.2) | 2 (1.2) |
| IDH2 positive | 11 (6.7) | 5 (3.0) |
| R172G | 0 | 2 (1.2) |
| R172K | 10 (6.1) | 3 (1.8) |
| R172M | 0 | 0 |
| R172S | 0 | 0 |
| R172W | 1 (0.6) | 0 |
| MGMT promoter status, n (%) | | |
| Methylated | 52 (31.9) | 39 (23.2) |
| Unmethylated | 18 (11.0) | 14 (8.3) |

| | Placebo N=163 n (%) | Vorasidenib N=168 n (%) |
|------------------------------------|------------------------------------|--|
| Unknown | 3 (1.8) | 3 (1.8) |
| Not reported | 90 (55.2) | 112 (66.7) |
| TERT promoter status, n (%) | | |
| Yes | 24 (14.7) | 34 (20.2) |
| No | 18 (11.0) | 18 (10.7) |
| Unknown | 0 | 1 (0.6) |
| Not reported | 121 (74.2) | 115 (68.5) |
| ATRX mutation status, n (%) | | |
| Yes | 64 (39.3) | 60 (35.7) |
| No | 51 (31.3) | 61 (36.3) |
| Unknown | 2 (1.2) | 3 (1.8) |
| Not reported | 46 (28.2) | 44 (26.2) |
| P53 mutation status, n (%) | | |
| Yes | 65 (39.9) | 58 (34.5) |
| No | 46 (28.2) | 47 (28.0) |
| Unknown | 2 (1.2) | 7 (4.2) |
| Not reported | 50 (30.7) | 56 (33.3) |

ATRX= α -thalassemia/mental-retardation-syndrome-X-linked gen; IDH = isocitrate dehydrogenase; IWRS = interactive web response system; Max = maximum; MGMT= O6 methylguanine-DNA-methyltransferase.

D. Safety and Effectiveness Results

1. Safety Results

Safety was evaluated by the incidence, severity, and type of adverse events (AEs), and by evaluation of vital signs, KPS, clinical laboratory results, ECGs, and LVEF data (as clinically indicated).

All safety data with respect to treatment with vorasidenib are listed by subject and summarized by treatment arm in the original NDA 218784. Refer to VORANIGO[®] (vorasidenib) labeling for approved NDA 218784 for more information. No adverse events were reported in connection with the concordance study used to support this PMA supplement, as the study was performed retrospectively using banked samples.

2. Effectiveness Results

a. Clinical Concordance

To evaluate the impact of pre-screening due to the usage of LLT during the patient enrollment, the concordance between the ODxT Test and the NGS LLT assay for *IDH1/IDH2* mutations were determined. The concordance results and agreement estimates are outlined in **Table 27** and **Table 28**, respectively.

Table 27. Concordance between ODxT Test and NGS LLT Assay for *IDH1/IDH2* mutation

| | Concordance of ODxT Test by NGS LLT Assay | | | |
|--------------------------------|---|----------|-----|-------|
| ODxT Test (<i>IDH1/IDH2</i>) | NGS LLT Assay (<i>IDH1/IDH2</i>) | | | |
| Frequency | Positive | Negative | Unk | Total |
| Positive | 306 | 0 | 21 | 327 |
| Negative | 1 | 34 | 1 | 36 |
| Unk | 0 | 3 | 0 | 3 |
| Total | 307 | 37 | 22 | 366 |

Table 28. Clinical Concordance of ODxT Test in reference to NGS LLT Assay for *IDH1/IDH2* mutation

| Parameter | Agreement of ODxT Test by NGS LLT Assay | |
|--------------|---|-----------------|
| | Estimate | 95% CI |
| PPA | 99.7% | (98.2%, 99.9%) |
| NPA | 100% | (89.8%, 100%) |
| Adjusted PPV | 100% | (98.8%, 100%) |
| Adjusted NPV | 100% | (89.8%, 100.0%) |

The NPA ($\Pr(\text{ODxT-}|\text{LLT-})$) is 100% when excluding ODxT Test unknown subjects ($n = 3$) and indicates that there are no discordant positive subjects ($\text{LLT-}/\text{ODxT+}$) in the ODxT+ intended use population. Therefore, the impact of LLT pre-screening is negligible in this case and the drug efficacy for the ODxT+ intended use population can be estimated from the drug efficacy of enrolled LLT+/ ODxT+ patients in the trial (see Section b below).

An additional postmarket study is planned to confirm the negative percent agreement (NPA, $\Pr(\text{ODxTT-} | \text{LLT-})$) and the clinical effectiveness of the ODxT Test as a companion diagnostic device for identification of patients with astrocytoma (AC) and oligodendroglioma (OG) with *IDH1/IDH2* mutations who may benefit from treatment with VORANIGO (vorasidenib) (See Section XIV).

b. Primary Clinical Efficacy Analysis Based on ODxT Test Results

In total, 331 out of 410 ODxT Test *IDH1/2* variant-positive patients identified during the CTA testing were enrolled in the AG881-C-004 clinical study and included in the full analysis set for the drug efficacy evaluation.

Patients were randomized in 1:1 ratio to receive vorasidenib (168 patients) or vorasidenib matched placebo (163 patients) with progression-free survival (PFS) as the primary endpoint; defined as the time from date of randomization to date of death or documented radiographic progressive disease (PD) as assessed by the BIRC per modified RANO-LGG. The hazard ratio (HR) was determined from the Cox regression model stratified by the randomization strata with placebo as the denominator (two-sided 95% CIs). The Kaplan-Meier survival rate (%) was calculated based on survival distribution function estimates from the product-limit method. Overall, 75/163 patients within the placebo group and 121/168 patients treated with vorasidenib were censored, majority due to ongoing without an event with placebo (70/75) or vorasidenib (115/121). The primary clinical efficacy analysis for the AG881-C-004 clinical trial is summarized in **Table 29** and **Table 30**.

The median patient age was comparable between the placebo (39.0 years, n=163) and the vorasidenib treated group (40.5 years, n=168). Other characteristics such as race, ethnicity, weight, etc., appeared comparable in both groups. Despite having slightly more male patients in the vorasidenib treated population (60.1% male vs 39.9% female) compared to the placebo group (52.8% male vs 47.2% female), the ratio seems to be aligned with the overall gender distribution of the study (56.5% male vs 43.5% female).

The median progression-free survival time was 27.7 months (95% CI: 17.0 months, NE) for patients treated with vorasidenib, versus 11.1 months (95% CI: 11.0 months, 13.7 months) for the placebo group. (NE: not estimable). The hazard ratio for patients treated with vorasidenib was 0.39 (95% CI: 0.27, 0.56). This indicates a 61% decrease in risk of progression or death compared with placebo. The Kaplan-Meier survival rate at cutoff readout (24 months) was 50.7% (95% CI: 36.2%, 63.5%) for patients treated with vorasidenib, versus 17.6% (95% CI: 7.1%, 31.9%) for the placebo group.

Table 29. Summary of Progression-Free Survival (PFS) per BIRC

| Efficacy Parameter | Placebo N=163 | Vorasidenib N=168 |
|--|------------------|----------------------|
| Progression-free survival (months)[1] | | |
| Number of events, n (%) | 88 (54.0) | 47 (28.0) |
| Progressive disease | 88 (54.0) | 47 (28.0) |
| Death | 0 | 0 |
| Number censored, n (%) [2] | 75 (46.0) | 121 (72.0) |
| Start of subsequent anticancer therapy | 1 (0.6) | 1 (0.6) |
| No adequate baseline assessment | 0 | 1 (0.6) |
| Withdrawal of consent | 4 (2.5) | 4 (2.4) |
| Ongoing without an event | 70 (42.9) | 115 (68.5) |

| Efficacy Parameter | Placebo N=163 | Vorasidenib N=168 |
|--|--------------------------|------------------------------|
| 25th percentile (95% CI) [3] | 8.2 (5.7, 8.4) | 11.9 (8.8, 16.6) |
| Median (95% CI) | 11.1 (11.0, 13.7) | 27.7 (17.0, NE) |
| 75th percentile (95% CI) | 19.4 (14.1, 25.3) | NE (27.7, NE) |
| Hazard ratio (95% CI) [4] | | 0.39 (0.27, 0.56) |
| (95% repeated confidence interval) [5] | 17.6 (7.1, 31.9) | (0.21, 0.73) |
| P-value [6] | NE (NE, NE) | 0.000000067 |

Table 30. Summary of Progression-Free Survival (PFS) per BRIC

| | Placebo (N = 163) | Vorasidenib (N = 168) |
|---|------------------------------|----------------------------------|
| Kaplan Meier survival rate (%) (95% CI) [7] | | |
| 3 months | 91.8 (86.4, 95.2) | 94.6 (89.8, 97.1) |
| 6 months | 80.1 (72.9, 85.6) | 89.6 (83.8, 93.4) |
| 12 months | 41.2 (32.1, 50.1) | 73.8 (65.3, 80.6) |
| 18 months | 26.7 (17.1, 37.4) | 60.4 (48.3, 70.5) |
| 24 months | 17.6 (7.1, 31.9) | 50.7 (36.2, 63.5) |
| 30 months | NE (NE, NE) | NE (NE, NE) |
| 36 months | NE (NE, NE) | NE (NE, NE) |
| 42 months | NE (NE, NE) | NE (NE, NE) |
| 48 months | NE (NE, NE) | NE (NE, NE) |

Progression-free survival (PFS) per BIRC refers to death or documented radiographic progressive disease (PD) as assessed by the BIRC per modified RANO-LGG.

[1] Progression-free survival (PFS) = (date of event or censoring – randomization date + 1) / 30.4375.

[2] Subjects with no adequate Baseline tumor assessment or with no adequate post-Baseline tumor assessments within 24 weeks after randomization will be censored on the date of randomization, unless the subject dies within 24 weeks after randomization, in which case, death will be an event on date of death; If a subsequent anticancer therapy is started prior to an event, the subject will be censored on the date of the last adequate tumor assessment that documented no PD prior to the start of the subsequent anticancer therapy; Subjects without an event or with an event after 2 or more inadequate or missing post-Baseline tumor assessments will be censored on the date of the last adequate tumor assessment that documented no PD; regardless, deaths within 24 weeks after randomization for subjects who did not initiate subsequent anticancer therapy will be considered an event; Ongoing without an event are censored at the last adequate post-Baseline assessment date.

[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals (CIs) are calculated from Brookmeyer and Crowley method with log-log transformation.

[4] Hazard ratio is calculated from the Cox regression model stratified by the randomization strata with placebo as the denominator, with two-sided 95% CIs.

[5] The 2-sided repeated confidence interval (RCI) for the hazard ratio is calculated for hazard ratio based on the method from Jennison and Turnbull (2000).

[6] P-value is calculated from the one-sided log-rank test stratified by the randomization factors (Chromosome 1p19q codeletion status and Tumor size at Baseline per local assessment per IWRS).

[7] Based on Survival Distribution Function estimates from product-limit method. * 5 subjects crossed over to receive vorasidenib did not have PD by BIRC. These subjects are censored as Ongoing without an event. NE: not estimable

The results support use of the OncoPrint™ Dx Target Test for the identification of *IDH1/IDH2* variant-positive AC and OG patients for treatment with vorasidenib.

3. Subgroup Analysis

Clinical efficacy data is provided for subjects with *IDH1* R132H mutation. Based on the low prevalence (frequency of <5%) of non-*IDH1*-R132H mutations in the clinical study, no prespecified subgroup analysis based on the allele types was performed. All non-*IDH1* R132H mutant tumors were combined into a single group, including those with *IDH2* alleles (**Table 31**). For all these *IDH1* and *IDH2* mutations ((i.e., *IDH1* R132C, R132G, R132S, R132L; *IDH2* R172K, R172G), data is provided by a subject listing of Progression Free Survival (PFS) by Blinded Independent Review Committee (BIRC), Time to Next Intervention (TTNI), and Best Overall Response (BOR) (**Table 32**).

Table 31. Summary of Progression-Free Survival (PFS) per BIRC by *IDH1/IDH2* Mutation Type

| Efficacy Parameter | Subjects with <i>IDH1</i> R132H mutation | | Subjects with non-R132H mutation | |
|---|--|----------------------|----------------------------------|----------------------|
| | Placebo N=138 | Vorasidenib N=146 | Placebo N=25 | Vorasidenib N=22 |
| Progression-free survival (months) [1] | | | | |
| Number of events, n (%) | 86 (62.3) | 42 (28.8) | 18 (72.0) | 12 (54.5) |
| Progressive disease | 86 (62.3) | 42 (28.8) | 18 (72.0) | 12 (54.5) |
| Death | 0 | 0 | 0 | 0 |
| Number censored, n (%) [2] | 52 (37.7) | 104 (71.2) | 7 (28.0) | 10 (45.5) |
| Start of subsequent anticancer therapy | 1 (0.7) | 3 (2.1) | 1 (4.0) | 1 (4.5) |
| No adequate baseline assessment | 0 | 1 (0.7) | 0 | 0 |
| Withdrawal of consent | 4 (2.9) | 5 (3.4) | 0 | 0 |
| Ongoing without an event | 47 (34.1) | 95 (65.1) | 6 (24.0) | 9 (40.9) |
| | | | | |
| 25th percentile (95% CI) [3] | 8.2 (5.7, 8.4) | 16.9 (11.0, 19.4) | 8.7 (5.5, 11.1) | 8.3 (2.8, 16.6) |
| Median (95% CI) | 11.4 (11.1, 14.0) | NE (27.7, NE) | 11.2 (8.7, 17.1) | 16.6 (8.3, NE) |
| 75th percentile (95% CI) | NE (17.2, NE) | NE (NE, NE) | 25.3 (13.9, 30.3) | NE (18.5, NE) |
| Hazard ratio (95% CI) [4] | | 0.33 (0.23, 0.48) | | 0.66 (0.28, 1.58) |

Table 32. Summary of Time To Next Intervention (TTNI) by *IDH1/IDH2* Mutation Type

| Efficacy Parameter | Subjects with <i>IDH1</i> R132H mutation | | Subjects with non-R132H Mutation | |
|--|--|----------------------|----------------------------------|---------------------|
| | Placebo N=138 | Vorasidenib N=146 | Placebo N=25 | Vorasidenib N=22 |
| Time to next intervention (months) [1] | | | | |
| Number of events, n (%) | 64 (46.4) | 19 (13.0) | 14 (56.0) | 9 (40.9) |
| First subsequent anticancer therapy (except crossover) | 6 (4.3) | 19 (13.0) | 2 (8.0) | 9 (40.9) |
| Crossover to Vorasidenib | 58 (42.0) | 0 | 12 (48.0) | 0 |
| Death | 0 | 0 | 0 | 0 |
| Number censored, n (%) [2] | 74 (53.6) | 127 (87.0) | 11 (44.0) | 13 (59.1) |
| Ongoing without an event | 70 (50.7) | 122 (83.6) | 11 (44.0) | 13 (59.1) |
| Withdrawal of consent | 4 (2.9) | 5 (3.4) | 0 | 0 |
| 25th percentile (95% CI) [3] | 12.0 (9.3, 12.9) | NE (28.8, NE) | 12.0 (6.2, 16.2) | 15.4 (4.9, 26.0) |
| Median (95% CI) | 20.1 (17.5, NE) | NE (NE, NE) | 18.2 (12.3, NE) | 26.0 (15.4, NE) |
| 75th percentile (95% CI) | NE (NE, NE) | NE (NE, NE) | 27.1 (18.2, NE) | NE (26.0, NE) |

Percentages are based on the number of subjects in the Full Analysis Set in each column (denominator). Time to next intervention is the time from randomization to the initiation of first subsequent anticancer therapy (including Vorasidenib for subjects randomized to placebo who subsequently crossover to Vorasidenib) or death due to any cause.

[1] Time to next intervention (TTNI) = (date of event or censoring – randomization date + 1) / 30.4375.

[2] Subjects with no event and (EOS date >= date of randomization when reason for EOS=Withdrawal by Subject) are censored at withdrawal of consent date; No event and lost to follow-up in any disposition page or survival follow-up page are censored at lost to follow-up date; No event and none of the conditions in the prior hierarchy are met are considered as ongoing without an event.

[3] Quartile estimates from product-limit (Kaplan-Meier) method. Confidence intervals (CIs) from Brookmeyer and Crowley method with log-log transformation.

[4] Hazard ratio is calculated from the Cox regression model stratified by the randomization strata with placebo as the denominator, with two-sided 95% CIs.

NE: not estimable.

4. Pediatric Extrapolation

In this premarket application, existing clinical data from clinical trial AG881-C-004 were leveraged to support reasonable assurance of safety and effectiveness of the proposed device in the pediatric sub-population age 18-22 years old. While limited subjects were tested in the pediatric population, no tangible clinical differences are expected between a patient diagnosed at the age of 12-21 and a patient diagnosed at the age of 22 or older, except for the age at which the tumor was discovered, which can be due to incidental finding, development of seizure or other unspecific symptoms (e.g., headache). In gliomas, according to the 2021 WHO classification of CNS tumors, pediatric-type diffuse

glioma frequently harbor abnormalities in the MAPK pathway such as fusions and mutations involving BRAF and are distinct entities compared with adult-type gliomas that are defined by the presence of *IDH* mutation (Louis, et al 2021). However, adult-type diffuse gliomas that harbor *IDH* mutation can also occur in pediatric patients (Louis, et al 2021). Given the natural course of these tumors, it is believed that these adult-type diffuse gliomas can arise during the early adolescent years and manifest during adulthood. As such there is no expected difference in the behavior of these tumors whether diagnosed at late adolescents or early adulthood. Given the epidemiology of low-grade gliomas, and the expected biological similarities in the behavior and response of adult-type diffuse gliomas that occur in patients between 12 to 18 years of age and older patients, as well as data that support similar drug exposures in adolescent and adult patients, subjects at least 12 years of age were permitted in Study AG881-C-004. Notably, this multi-institutional study included patients between 18 and 21 years of age in the evaluation of pediatric *IDH*-mutant gliomas given the known resemblance between patients diagnosed at this age and patients younger than 18. In the pivotal study for vorasidenib, Study AG881-C-004, subjects younger than 25 at the time of enrollment who were randomized to vorasidenib (N=5), were originally diagnosed between 17 and 21 years of age, reflecting the natural course and resemblance of these tumors to those diagnosed at a younger age. Additionally, data generated in adult population is considered generalizable to younger subjects.

XI. 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 two investigators of which none were full-time or part-time employee of the sponsor, and none had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

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

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

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Molecular and Clinical

Genetics Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For the intended use to identify the *IDH1* or *IDH2* mutation in astrocytoma or oligodendroglioma patients to be treated with vorasidenib, the effectiveness of the ODxT Test was demonstrated through analytical studies using patient samples from the intended use population and a clinical validation study using specimens from patients enrolled in the AG881-C-004 study. The data from the analytical validation and clinical studies support the reasonable assurance of safety and effectiveness of the ODxT Test when used in accordance with the indications for use. Data from the AG881-C-004 study show that patients *IDH1* or *IDH2* mutations received benefit from treatment with vorasidenib and support the addition of the CDx indication to the ODxT Test.

B. Safety Conclusions

The risks of the device are based on data collected in the analytical studies conducted to support sPMA approval as described above. The ODxT Test is an *in vitro* diagnostic test, which involves testing of DNA and RNA extracted from FFPE tumor tissue.

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

C. Benefit-Risk Determination

The probable benefit of the ODxT Test for the identification of eligible *IDH1/IDH2* mutations in patients with glioma (astrocytoma or oligodendroglioma) for the treatment with vorasidenib was established using results from the Servier clinical trial AG881-C-004 (Phase 3, global, multicenter, double-blind, randomized, placebo-controlled clinical study). The ODxT Test served as the central confirmatory test in this trial. The key clinical efficacy endpoints were analyzed based on subjects who are randomized to the trial AG1881-C-004 and *IDH1/IDH2* positive by the ODxT Test. The primary efficacy endpoint was Progression-Free Survival (PFS) per Blinded Independent Review Committee (BIRC). The hazard ratio between vorasidenib treatment and placebo was estimated by a Cox's proportional hazard model stratified by the randomization strata. The hazard ratio for patients treated with vorasidenib was 0.39 (95% CI: 0.27, 0.56). This indicates a 61% decrease in the risk of progression or death compared with placebo. The Kaplan-Meier survival rate at the cutoff readout (24 months) was 50.7% (95% CI: 36.2%, 63.5%) for patients treated with vorasidenib, versus 17.6% (95% CI: 7.1%, 31.9%) for the placebo group, indicating a meaningful clinical benefit in *IDH1/IDH2* CDx biomarker positive patient treated with vorasidenib. In addition, the clinical concordance of the ODxT Test to the representative

NGS local test, indicated a PPA of 99.7% and an NPA of 100%, when excluding unknown results; this data indicates that this test is highly accurate in ascertaining *IDH1/IDH2* CDx mutation status. In addition, the totality of the analytical data and the clinical data, discussed above, indicates that there is a meaningful clinical benefit of the ODxT Test in identifying *IDH1/IDH2* CDx mutation positive patients for the selection of patients for treatment with vorasidenib.

There is 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 ODxT Test are associated with the potential mismanagement of patients resulting from false results of the test. Patients who are determined to be false positive by the test may be exposed to a drug (vorasidenib) that is not beneficial to the patient that does not carry these eligible *IDH1/IDH2* alterations, and this may lead to adverse events or delayed access to treatments that could be more beneficial. A false negative result may prevent a patient from accessing a vorasidenib, which is potentially beneficial drug.

The clinical and analytical performance of the device included in this submission demonstrate that the assay is expected to perform with reasonable accuracy, partially mitigating the risks of false results. In addition, to supplement the premarket data, a post-market study is planned as summarized in Section XIV below, to further confirm the benefits observed herein.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that for the ODxT Test, and the indications noted in the intended use statement and discussed above, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the clinical validation study support the performance of the ODxT Test as an aid for the identification of *IDH1* and *IDH2* mutations in patients with AC and OG that may benefit from the targeted drug therapy, VORANIGO® (vorasidenib).

XIV. CDRH DECISION

CDRH issued an approval order for the PMA (P160045/S046) on 10/17/2024.

Additional non-clinical study is requested as condition of approval cited in the approval order and is described below.

The following data should be provided as a separate report, which may be followed by a PMA supplement, where applicable. The study data and conclusions should be submitted within 1 year of the PMA approval date, unless otherwise specified.

1. Life Technologies Corporation must provide data from additional *IDH1* and *IDH2* negative/wild type glioma and glioblastoma samples screened with a representative local

immunohistochemistry (IHC) assay, to identify an additional negative population for inclusion into the clinical concordance evaluation between the LLT and the final CDx ODxT Test. This information must be provided to confirm the negative percent agreement (NPA, $\Pr(\text{ODxTT-} \mid \text{LLT-})$) and the clinical effectiveness of the ODxT Test as a companion diagnostic device for identification of patients with astrocytoma (AC) and oligodendroglioma (OG) with IDH1/IDH2 mutations who may benefit from treatment with VORANIGO (vorasidenib).

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order and Section XIV above.

XVI. REFERENCES

1. Louis, DN., Perry, A., Wesseling, P., et al., The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.*, 2021: 23(8):1231-125.