SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: PDGFRB FISH for Gleevec in MDS/MPD

Device Trade Name: *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD)

Device Procode: PMI

Applicant's Name and Address: ARUP Laboratories, Inc.
500 Chipeta Way
Salt Lake City, UT 84108
www.aruplab.com

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H140005

Humanitarian Use Device (HUD) Designation Number: HUD # 10-0248

Date of HUD Designation: November 4, 2011

Date of Notice of Approval to Applicant: December 18, 2015

II. INDICATIONS FOR USE

The PDGFRB FISH for Gleevec Eligibility in Myelodysplastic Syndrome/ Myeloproliferative Disease (MDS/MPD) is an in vitro diagnostic test intended for the qualitative detection of PDGFRB gene rearrangement from fresh bone marrow samples of patients with MDS/MPD with a high index of suspicion based on karyotyping showing a 5q31~33 anomaly. The PDGFRB FISH assay is indicated as an aid in the selection of MDS/MPD patients for whom Gleevec®(imatinib mesylate) treatment is being considered. This assay is for professional use only and is to be performed at a single laboratory site.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for use in both peripheral blood and bone marrow specimens. It was modified for the HDE approval to indicate that only fresh bone marrow samples may be used.

III. CONTRAINDICATIONS

There are no known contraindications for performing the PDGFRB FISH assay.

IV. WARNINGS AND PRECAUTIONS

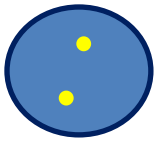
Precautions relating to procedure and interpretation can be found in the *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) under "Limitations of the Procedure".

V. DEVICE DESCRIPTION

The *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome / Myelo-proliferative Disease (MDS/MPD) is performed on fresh bone marrow aspirate samples collected in a heparin tube and received in the laboratory within 4 days of collection. Cultured and fixed bone marrow cells are analyzed using the FISH probe to detect the 5q31~33 rearrangement. At least 2 technicians score the same case and at least 200 cells are evaluated.

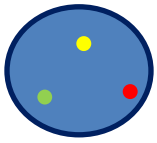
The Platelet-derived Growth Factor Receptor Beta (PDGFRB) FISH assay utilizes a break-apart probe to detect rearrangement of PDGFRB at chromosome locus 5q31~33. If the PDGFRB locus is intact, the probe will appear as adjacent (touching) red and green signals or as a fused (overlapping) yellow signal. Each normal cell will display two fusion "2F" (yellow) signals. If the PDGFRB locus is rearranged, the probe will most often appear as one red and one green signal separated by at least two signal distances. In the most common form of PDGFRB rearrangement, the abnormal cell will display an "RGF" signal, with one fusion (yellow), one red, and one green signal. Rarely, both PDGFRB loci are rearranged to generate the "2G2R" signal, resulting in two red and two green signals separated by at least two signal distances. Another rare signal pattern that can result from a PDGFRB rearrangement is called "FR", which is generated when one red signal is rearranged and one green signal is lost. The diagram shown below illustrates the normal 2F signal pattern and the three abnormal signal patterns indicative of PDGFRB rearrangement.

NORMAL SIGNAL PATTERNS INDICATIVE OF NO PDGFRB REARRANGEMENT

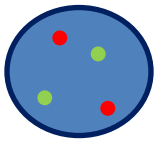


NORMAL 2F: 2 Fused (adjacent red and green appear yellow)

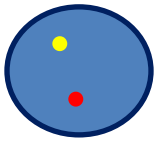
ABNORMAL SIGNAL PATTERNS INDICATIVE OF A PDGFRB REARRANGEMENT



COMMON RGF: 1 Red, 1 Green, 1 Fused

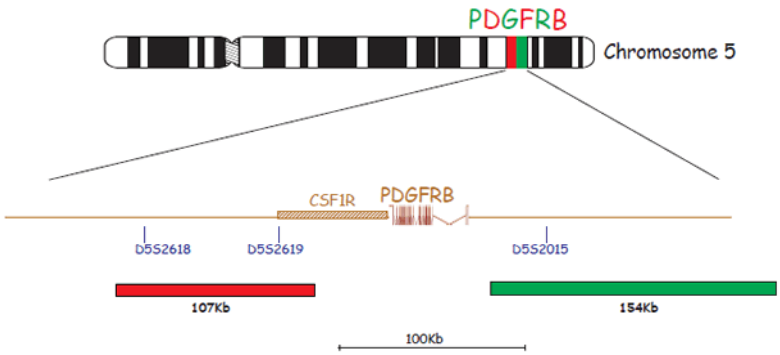


RARE 2G2R: 2 Green, 2 Red



RARE FR: 1 Red, 1 Fused (green signal lost due to rearrangement)

The *PDGFRB* FISH probe is a mixture of a 107Kb red-labeled probe, located centromeric to the *PDGFRB* gene, and a 154Kb green-labeled probe located telomeric to the *PDGFRB* gene. The probes are pre-mixed in hybridization buffer.



The assay procedure is summarized briefly below:

- Live cells from patient bone marrow are either directly fixed or grown in culture and subsequently fixed.
- The fixed cells are dropped onto slides and pre-treated chemically to remove proteins that block DNA access.
- The DNA is denatured to its single-stranded form and subsequently allowed to hybridize with the PDGFRB probes described above.
- Following hybridization the unbound probe is removed by a series of washes, and the cell nuclei are counterstained with DAPI (4, 6 diamidino-2-phenylindole), a DNA specific stain that fluoresces blue.
- Hybridization of the *PDGFRB* probe is viewed using a fluorescence microscope equipped with appropriate filters allowing visualization of the red and green fluorescent signals.
- Detection of signals is conducted by manual microscopic examination of the nucleus.

All instruments required to perform this assay are qualified for their use by the single laboratory performing this assay.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are no cleared or approved alternatives to the *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) assay.

VII. MARKETING HISTORY

The *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) has not been has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Failure of the assay to perform as expected or failure to correctly interpret test results may lead to incorrect test results, and subsequently improper patient management decisions for these patients. Patients receiving a false-positive result may be treated with Gleevec and therefore subjected to the associated risks of treatment without the potential for benefit. Patients receiving a false-negative for Gleevec would be excluded from treatment with Gleevec.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1) Assay Cut-Off (Measuring Interval)

a) Objective: This study was designed to establish the reference range (measuring interval) and beta inverse cutoffs for the signal patterns obtainable with the assay to determine the assay cut-off. The assay cut-off is defined as the maximum number of scoreable interphase nuclei with a specific abnormal pattern at which the specimen is considered negative for that signal pattern. The cut-off value is expressed in terms of a percentage for the actual number of nuclear FISH patterns positive for rearrangement.

b) Testing: Twenty residual fixed cell pellets from normal bone marrow specimens were used. Slides were analyzed by 2 independent operators. A total of 250 cells were scored by each operator for each of the 20 specimens. Beta inverse cutoffs were generated and it was determined that a specimen would be determined to be PDGFRB rearranged if >4.4% (upper bound of the 95% CI) displayed the RGF signal pattern.

Table 1: Beta inverse cutoffs for the PDGFRB probe signals

# of cells	RGF	1F	3F	4F	FG	FR	2FR	2FG	2G2R	2FRG
200	4.4	5.1	4.4	4.4	2.3	1.5	2.3	2.3	2.3	2.3

Clinical support for the cut-off was demonstrated using 128 previously tested patient specimens. A total of 11 specimens (obtained from 8 patients) positive for the PDGFRB rearrangement, and 97 patients negative for the PDGFRB rearrangement were assessed using the current probe set. Results obtained from positive specimens (shown in yellow in Table 2 below) demonstrated a range from 5% to 88.5% (Table 2.). All test negative specimens were less than 1.5% (Figure 2).

Figure 1: Percent RGF PDGFRB Rearranged Signal Pattern in Clinical Samples

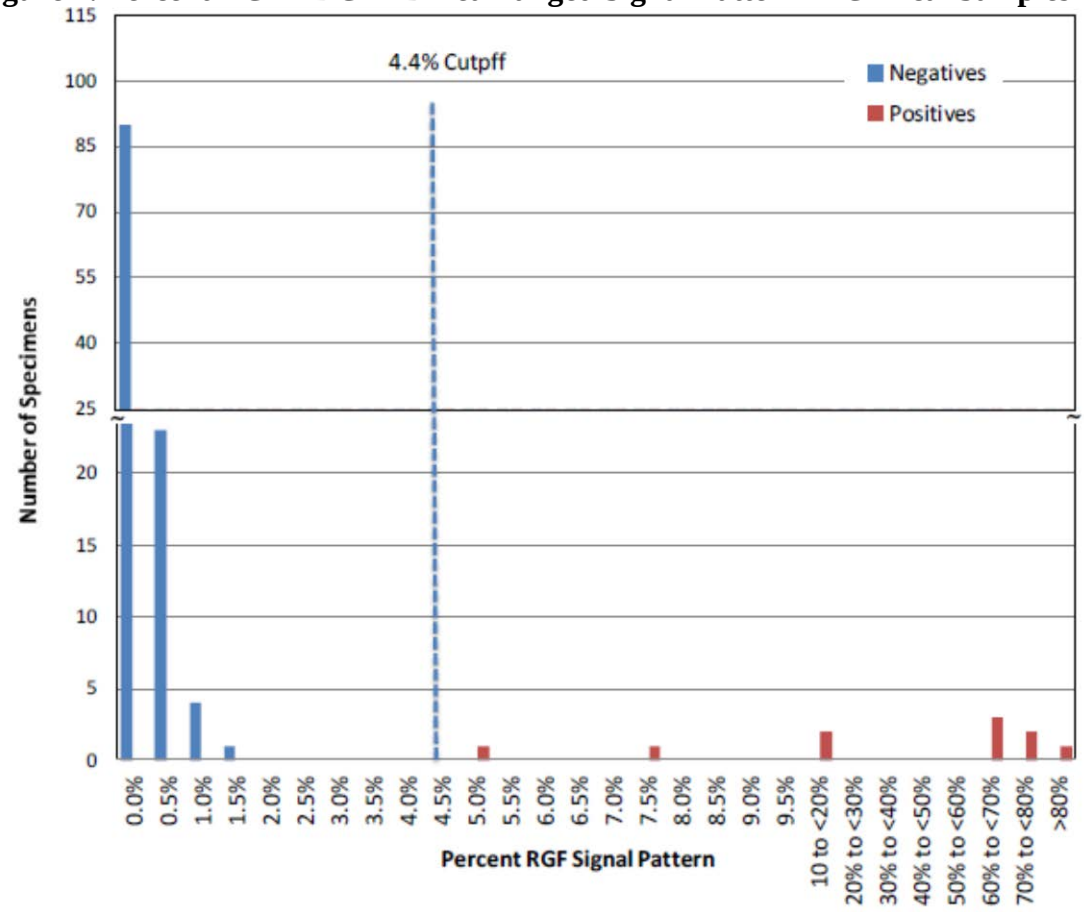


Table 2: Summary of PDGFRB Rearranged Clinical Samples

Patient	Date	Specimen Type	RFG (4.4%)	FR (1.5 %)	2G2R (2.3%)	Total PDGFRB rearranged (total of all 3)
1	4/10/13	Fixed cell pellet	63%	0	0	63%
	1/9/14	Prepared slides	63.5%	1%	0	64.5%
	7/16/14	Prepared slides	66.5%	14%	1%	81.5%
2	9/28/13	Bone marrow	76%	0	0	76%
	11/4/13	Bone marrow	13%[#]	0	0	13%[#]
3	1/13/13	Bone marrow	88.5%	0	0	88.5%
4	2/25/13	Bone marrow	5%*	0	0	5%*
5	10/13/13	Bone marrow	72%	0	0	72%
6	10/3/14	Peripheral blood	7.5%	0	0	7.5%
7	2/1/15	Peripheral blood	12.5%	1%	1.5%	15%
8	4/30/15	Peripheral blood	0	12.5 %	0	12.5%

*This sample was repeated due to the proximity to the cutoff value. The repeat result was 6% RGF signal.

[#] This sample was collected and tested 6 weeks after the patient was first tested. The reduction of the RGF signal pattern from 76% to 13% is suggestive of a response to therapy.

c) Conclusions: Taken together these data indicate that the PDGFRB rearrangement positive samples are distinguishable from the rearrangement negative samples and that the measuring interval (assay cut-off) is well-established.

2) Analytical Sensitivity and Analytical Specificity

a) Objective: These studies were designed to assess the analytical sensitivity and specificity of the PDGFRB probe. Analytical sensitivity was defined as the percentage of interphase chromosome targets (2 per nucleus) with the expected normal probe signal. Analytical specificity was defined as the percentage of probe signals that hybridized to the correct location (total signals minus false positives).

b) Testing: The sponsor assessed analytical specificity with a single pool of 5 normal male

peripheral blood specimens. Two operators each scored 100 metaphase cells for a total of 200 cells. The analytical specificity was determined to be 99.5% (199/200) for each probe (Table 3). The studies met the sponsor's pre-determined acceptance criteria of >95% specificity.

Table 3. Analytical Specificity

	Number of Metaphase Chromosome Signals			**Specificity**	
Probe	**Total False Positives Observed**	**Total True Positives Observed**	**Total Observed**	**Point Estimate (%)**	**95% Confidence Interval (%)**
***PDGFRB* Centromeric - Red**	1	199	200	99.5	(97.25, 99.99)
***PDGFRB* Telomeric Green**	1	199	200	99.5	(97.25, 99.99)

Analytical sensitivity was calculated using the 5 normal peripheral blood specimens presented above and an additional 20 normal samples The analytical sensitivity was calculated to be 97.2% (4081/4200) (Table 4). The summary of this combined data set is presented below.

Table 4: Analytical Sensitivity

	No. of Cells		**Sensitivity**	
Signal Pattern	**Total True Positives Observed**	**Total Expected**	**Point Estimate (%)**	**95% Confidence Interval (%)***
2 - PDGFRB Red – Green fusion (2F)	4081	4200	97.2%	(96.7, 97.7)

**Confidence intervals calculated using the Exact method (Clopper and Pearson, Biometrika 26:404-413, 1934).*

b) Conclusions: Both analytical sensitivity and specificity met the criteria for interphase FISH probes of ≥ 95% sensitivity and ≥ 95% specificity.

3) Reproducibility and Precision

a) Objective: These studies were designed to assess the reproducibility and precision of the PDGFRB FISH assay.

b) Testing: Three operators each processed 3 sets of 9 slides (3 separate bone marrow pools each containing marrow from 2 donors, run in triplicate) on non-consecutive 3 days. Two independent operators scored 100 cells per slide.

Acceptance criteria for this study were as follows:

- Each operator completes 3 non-consecutive batches of 9 slides within 21 days
- 95% NPA and no greater than 5% CV for Intra-operator
- 95% NPA and no greater than 10% CV for Inter-operator

Concordance for all intra-operator comparisons was 100% NPA. CVs for signal pattern ranged from 0.17-0.77% CV.

There was 100% NPA for inter-operator comparisons. CVs for signal pattern for inter-operator comparisons ranged from 0.10-0.51% CV.

Table 5: Reproducibility and Precision

Normal Bone Marrow Sample Pool	Day	Operator	Replicate Mean # of Normal Signals	Inter-Operator Mean	Inter-Operator Standard Deviation	Concordance
Pool A	1	A	198.33	198.56	0.69	100% PPA, NPA, OPA 0.35% CV
		B	199.33			
		C	198.00			
	2	A	199.00	198.56	0.77	100% PPA, NPA, OPA 0.39% CV
		B	199.00			
		C	197.67			
	3	A	196.33	196.56	0.69	100% PPA, NPA, OPA 0.35% CV
		B	197.33			
		C	196.00			
Pool B	1	A	199.00	198.67	0.33	100% PPA, NPA, OPA 0.17% CV
		B	198.33			
		C	198.67			
	2	A	198.33	198.55	0.19	100% PPA, NPA, OPA 0.10% CV
		B	198.67			
		C	198.67			
	3	A	197.67	197.67	0.33	100% PPA, NPA, OPA 0.17% CV
		B	198.00			
		C	197.33			
Pool C	1	A	199.67	199.33	0.33	100% PPA, NPA, OPA 0.17% CV
		B	199.00			
		C	199.33			
	2	A	198.67	198.56	0.51	100% PPA, NPA, OPA 0.26% CV
		B	198.00			
		C	199.00			
	3	A	196.67	197.67	1.00	100% PPA, NPA, OPA 0.51% CV
		B	197.67			
		C	198.67			

c) Conclusions: The PDGFRB FISH assay is suitably reproducible and precise for its intended

use. The assay meets the predetermined acceptance criteria of 95% NPA for both intra- and inter-operator comparisons. The coefficients of variation (CV) also meet the predetermined acceptance criteria of 5% and 10% for intra- and inter-operator comparisons, respectively.

4) Assay Robustness

a) Objective: These studies were undertaken to understand the extent of variation from the protocol that could still yield acceptable assay performance.

b) Testing:

(1) Probe/Target denaturation time: These studies were undertaken to understand the impact of variations in probe/target denaturation time. Three slides were prepared identically from a single sample of normal bone marrow but with different denaturation times [2 min (standard), 1 min, and 3 min]. Two independent operators then scored 100 cells each on the slides. Acceptance was based on 100% NPA for PDGFRB rearrangement as compared to standard condition. All slides passed acceptance criteria.

(2) Probe/Target denaturation temperature: These studies were undertaken to understand the impact of variations in probe/target denaturation temperature. Three slides were prepared identically from a single sample of normal bone marrow but with different denaturation temperatures [73˚C (standard), 72˚C, and 74˚C]. Two independent operators then scored 100 cells each on the slides. Acceptance was based on 100% NPA for PDGFRB rearrangement as compared to standard condition. All slides passed acceptance criteria.

(3) Hybridization time: These studies were undertaken to understand the impact of variations in probe/target hybridization time. Four slides were prepared identically from a single sample of normal bone marrow using 4 different hybridization times [11hrs, 12 hrs (standard minimum), 18 hrs (standard maximum and 19 hrs]. Two independent operators then scored 100 cells each on the slides. Acceptance was based on 100% NPA for PDGFRB rearrangement as compared to standard condition. All slides passed acceptance criteria.

(4) Hybridization temperature: These studies were undertaken to understand the impact of variations in probe/target hybridization temperature. Three slides were prepared identically from a single sample of normal bone marrow but with different hybridization temperatures [36˚C, 37˚C (standard), and 38˚C]. Two independent operators then scored 100 cells each on the slides. Acceptance was based on 100% NPA for PDGFRB rearrangement as compared to standard condition. All slides passed acceptance criteria.

(5) Slide wash temperature: These studies were undertaken to understand the impact of variations in slide wash temperature. Three slides were prepared identically from a single sample of normal bone marrow but with different slide wash temperatures [72˚C, 73˚C (standard), and 74˚C]. Two independent operators then scored 100 cells each on the slides. Acceptance was based on 100% NPA for PDGFRB rearrangement as compared to standard condition. All slides passed acceptance criteria.

(6) Pre-hybridization slide stability: These studies were undertaken to understand the stability of the slide samples prior to hybridization. The sponsor used cultured, fixed healthy bone marrow cells from a single donor and a single lot of probe for this experiment. Four identical slides were prepared and subjected to different times prior to hybridization [30 min (short), 2 hrs (standard), 1 day (long), 2 days (longest)]. Slides were hybridized according to standard protocol and 2 independent readers each scored 100 cells. All slides were enumerable and gave acceptable results.

(7) Post-hybridization signal/slide stability: These studies were undertaken to understand the stability of the slide samples after the hybridization step. This study used the standard conditions slide described above with a single lot of probe. A single slide was scored at the following times post-hybridization [7 days (standard), 0 days (shorter), 14 days (longer), 15 days (longest)]. The slide was stored in the dark between readings. Two independent readers scored 100 cells each. All slides were enumerable.

c) Conclusions: The PDGFRB FISH assay has acceptable robustness around the parameters described above. No false results were observed for these studies.

5) Interference Studies

a) Objective: This testing was performed to evaluate the effect of interfering substances on the PDGFRB FISH assay performance.

b) Testing: Two normal bone marrow samples were combined and placed into tubes containing ~20 million nucleated cells. One aliquot for each interfering substance per level was harvested while the other aliquot was cultured overnight. Two lots of probe were used and 2 slides were prepared for each interfering substance as listed in Table 5 for two concentrations each (high and low concentrations in accordance with CLSI guideline EP07-A2) and each cell harvest method (direct or overnight culture) for a total of 4 slides per interfering substance (but only 1 slide for each condition). Two slides with no interfering substances were used as a comparison, 1 for each harvesting method (direct or overnight culture). Two independent operators each scored 100 cells per slide. Acceptance criteria were 100% NPA for PDGFRB rearrangement. All slides met the acceptance criteria. The conditions tested are shown in Table 6 and results are shown in Table 7 below.

Table 6: Interfering substances tested and pre-specified acceptance criteria

Interfering Substance	Final Concentration	Amount Added	# Samples	Acceptance Criteria
NONE	N/A	N/A	2	-
Hemoglobin (high)	2 g/L	18.7 µL	2	100% NPA
Hemoglobin (low)	1 g/L	9.3 µL	2	100% NPA
Bilirubin (unconj) (high)	342 µmol/L	20 µL	2	100% NPA
Bilirubin (unconj) (low)	171 µmol/L	10 µL	2	100% NPA
Intralipid (high)	37 mmol/L	150 µL	2	100% NPA
Intralipid (low)	18.5 mmol/L	75 µL	2	100% NPA
EDTA (high)	3.6 mg/mL	3 mL BM to 6mL tube	2	100% NPA
EDTA (low)	1.8 mg/mL	6 mL BM to 6mL tube	2	100% NPA
Heparin (high)	30 USP units/mL	3 mL BM to 6mL tube	2	100% NPA
Heparin (low)	15 USP units/mL	6 mL BM to 6mL tube	2	100% NPA

Note: Percentages represent point estimates and not the lower bound of 95% confidence intervals.

Table 7: Interference study results

Interfering Substance	Harvest Method	2F	RGF	1F	3F	4F
None	**Direct**	**196**	**1**	**3**	**0**	**0**
	Overnight	**195**	**0**	**2**	**1**	**2**
Hemoglobin.High	**Direct**	**194**	**0**	**6**	**0**	**0**
	Overnight	**197**	**0**	**2**	**1**	**0**
Hemoglobin/Low	**Direct**	**194**	**1**	**4**	**0**	**1**
	Overnight	**196**	**0**	**1**	**0**	**3**
Bilirubin (unconj)/high	**Direct**	**197**	**0**	**2**	**0**	**1**
	Overnight	**198**	**0**	**2**	**0**	**0**
Bilirubin (unconj)/low	**Direct**	**196**	**0**	**3**	**1**	**0**
	Overnight	**195**	**1**	**3**	**0**	**1**
Intralipid high	**Direct**	**196**	**1**	**3**	**0**	**0**
	Overnight	**197**	**0**	**2**	**0**	**1**
Intralipid low	**Direct**	**195**	**0**	**4**	**0**	**0**
	Overnight	**195**	**0**	**4**	**0**	**1**
EDTA high	**Direct**	**197**	**0**	**3**	**0**	**0**
	Overnight	**194**	**0**	**5**	**0**	**1**
EDTA low	**Direct**	**199**	**0**	**1**	**0**	**0**
	Overnight	**198**	**0**	**0**	**0**	**2**
Heparin high	**Direct**	**198**	**0**	**2**	**0**	**0**
	Overnight	**196**	**1**	**2**	**0**	**1**
Heparin low	**Direct**	**195**	**1**	**2**	**1**	**1**
	Overnight	**196**	**0**	**3**	**0**	**1**

c) Conclusions: The assay is robust to the inclusion of hemoglobin, bilirubin, intralipid, EDTA, and heparin in the concentrations indicated.

6) Probe Stability

a) Objectives: The objective of these studies was to demonstrate the PDGFRB probe stability under normal laboratory conditions.

b) Testing:

(1) Freeze/thaw stability: This testing was performed to determine the maximum number of freeze/thaw cycles that should be allowed for each tube of probe mix. Testing was performed on healthy donor bone marrow. A single tube of probe stored at -20˚C was dispersed into 4 tubes and subjected to different numbers of freeze-thaw cycles (0, 5, 10, 15, or 20). One slide was prepared for each tube tested and 100 cells were scored by 2 independent operators per slide. The acceptance criteria were based on the NPA for PDGFRB rearrangement compared to normal cells and probe which had undergone no freeze-thaw cycles. The results are shown below in Table 8.

Table 8: Probe freeze-thaw stability results

"Freeze-thaw" Cycles	2F	RGF	1F	3F	4F	Total
0	195	0	4	0	1	200
5	198	1	1	0	0	200
10	196	0	4	0	0	200
15	198	1	1	0	0	200
20	199	0	1	0	0	200

(2) Shelf-life stability: This testing is being performed to establish probe expiry dating under normal storage conditions. Probe shelf life stability is being tested on an ongoing basis using a single tube from 2 lots of probe tested at 3 month intervals out to 24 months (manufacturer's recommended expiration date). One additional time point at 1 month post expiration (25 months) will be included in the study. One slide of cells will be prepared for each time point, and 100 cells will be scored by 2 independent operators from a single healthy bone marrow specimen. The acceptance criterion was 100% NPA for PDGFRB rearrangement compared to the first time point based on the cutoff of 4.4% RGF signal patterns. To date, shelf life testing has reached 13 months and will continue to 25 months. Results to date show 100% agreement with the first time point.

(3) Open container stability: This testing was performed to establish the maximum number of permissible tube openings for the probe mix. Open container studies used 2 tubes per lot and 2 lots of probes. One tube from each lot underwent 1, 5, 20, 15, or 20 openings (defined as the tube being removed from -20˚C, having 5 µL removed, and returned to -20˚C for a minimum of 30 minutes). One slide was

prepared for each condition and 100 cells were scored by 2 independent operators using a single healthy bone marrow specimen. Acceptance criterion was based on 100% NPA for PDGFRB rearrangement as compared to the first tube opening (number of abnormal cells below the cutoff of 4.4%). Results are shown below in Table 9.

Table 9: Open container stability testing results

Probe exp. date	Openings	2F	RGF	1F	3F	4F	Total
November 2015	1	195	0	4	0	1	200
	5	196	1	1	1	1	200
	10	197	0	1	0	2	200
	15	196	1	3	0	0	200
	20	198	1	1	0	0	200
September 2015	1	195	0	4	0	1	200
	5	193	0	5	0	2	200
	10	196	0	0	0	4	200
	15	198	0	1	0	1	200
	20	195	0	4	0	1	200

a. Conclusions: The PDGFRB FISH probe is stable for up to 20 freeze-thaw cycles and for up to 20 tube openings. The shelf-life stability is currently demonstrated to be at least 13 months from the time of receipt and will be tested up to 25 months.

3) Specimen Stability

a. Objectives: This testing was designed to understand the time post collection over which the PDGFRB FISH assay will perform as expected.

b. Testing: Specimen stability was examined up to 6 days post collection (5 days transport/storage plus 1 day of culturing). Three slides per time point (4 time points) were assessed by 2 independent operators each counting 100 cells. Acceptance was based on 100% NPA for PDGFRB rearrangement. All slides examined fell below the cutoff for abnormal signal patterns. Specimens will only be accepted if they are received at ARUP within 4 days from the time of collection.

Table 10: Specimen stability study results

Time points	Days from collection prior to culture	Slide	2F	RGF	1F	3F	4F	Total	Avg %RGF
Direct harvest (1 day transit, 0 days storage, no culture)	N/A	PB 0-1	195	2	2	0	1	200	0.5%
		PB 0-2	196	0	2	0	2	200	
		PB 0-3	197	1	2	0	0	200	
Dav 2 (1 day transit, 0 days storage, 1 day culture)	1	PB 1-1	196	0	4	0	0	200	0%
		PB 1-2	196	0	4	0	0	200	
		PB 1-3	199	0	1	0	0	200	
Dav 4 (1 day transit, 2 days storage, 1 day culture)	3	PB 3-1	197	2	0	0	1	200	0.67%
		PB 3-2	197	1	2	0	0	200	
		PB 3-3	198	1	1	0	0	200	
Dav 6 (1 day transit, 4 days storage, 1 day culture)	5	PB 5-1	197	0	2	0	1	200	0.33%
		PB 5-2	197	1	2	0	0	200	
		PB 5-3	196	1	3	0	0	200	

c. Conclusions: Samples may be accepted for processing up to 4 days from the time of collection with no expected diminishment of assay performance.

B. Animal Studies

None

C. Additional Studies

None

X. SUMMARY OF CLINICAL INFORMATION

Gleevac® (imatinib; manufactured by Novartis) was approved in October 2006 through supplement 12 of NDA 21-588 for the treatment of patients with MDS/MPD positive for PDGFRB rearrangement as part of an open-label, multi-center, phase 2 clinical trial to evaluate Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases. The study included 7 patients with MDS/MPD. These patients were treated with Gleevec 400 mg daily. The ages of the enrolled patients ranged from 20 to 86 years. A further 24 patients with MDS/MPD aged 2 to 79 years were reported in 12 published case reports and a clinical study. These patients also received Gleevec at a dose of 400 mg daily with the exception of three patients who received lower doses.

Of the total population of 31 patients treated for MDS/MPD, 14 (45%) achieved a complete hematological response and 12 (39%) a major cytogenetic response (including 10 with a complete cytogenetic response). Sixteen patients had a translocation, involving chromosome 5q33 or 4p12, resulting in a PDGFR gene rearrangement. All of these patients had a hematological response (13 completely). Cytogenetic response was evaluated in 12 out of 14 patients, all of whom responded (10 patients completely). Only 1 (7%) out of the 14 patients without a translocation associated with PDGFR gene re-arrangement achieved a complete hematological response and none achieved a major cytogenetic response. A further patient with a PDGFR gene re-arrangement in molecular relapse after bone marrow transplant responded molecularly.

The *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) assay demonstrated analytical validity using bone marrow specimens from the intended use population as described in the above clinical study. These data are supportive of the selection of patients with PDGFRB rearrangement to determine Gleevec eligibility. To date, no clinical studies have been conducted using this device.

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. No new clinical studies were conducted in support of this application, so no clinical investigator financial information was reviewed.

XII. RISK PROBABLE BENEFIT ANALYSIS

The PDGFRB FISH for Gleevec Eligibility in Myelodysplastic Syndrome/ Myeloproliferative Disease (MDS/MPD) is an in vitro diagnostic test intended for the qualitative detection of PDGFRB gene rearrangement from fresh bone marrow samples of patients with MDS/MPD with a high index of suspicion based on karyotyping showing a 5q31~33 anomaly. The PDGFRB FISH assay is indicated as an aid in the assessment of MDS/MPD patients for whom Gleevec (imatinib mesylate) treatment is being considered. Some adverse drug reactions that occurred in >10% of Gleevec treated patients included nausea, vomiting, musculoskeletal and joint pains, rash, diarrhea, headache, and fluid retention. Severe adverse reactions which occurred in <10% of the Gleevec treated patients included elevations in liver function tests, hemorrhage, and severe fluid retention, congestive heart failure and left ventricular dysfunction. In the open-label, multi-center, phase 2 clinical trial that was conducted testing Gleevec in diverse populations of patients suffering from life-threatening diseases associated with Abl, Kit or PDGFR protein tyrosine kinases, the adverse reactions regardless of relationship to study drug in > 10% of the patients included nausea, diarrhea, anemia, fatigue, muscle cramp, arthralgia and periorbital edema.

Failure of the assay to perform as expected or failure to correctly interpret test results may lead to incorrect test reporting, and subsequently improper patient management decisions for these patients. Patients receiving a false-positive result may be treated with Gleevec and therefore subjected to the associated risks of treatment without the potential for benefit. Patients receiving a false-negative for Gleevec would be excluded from treatment with Gleevec. If the test result is invalid and needs to be repeated, a patient who would be eligible for treatment with Gleevec might experience a delay in receiving treatment benefit. However if the patient eventually was found to be ineligible for Gleevec treatment due to the lack of detection of the *PDGFRB* rearrangement, there would be little or no risk of a delay in receiving treatment due to an invalid test result. Based on the risk assessment performed by the sponsor, the impact to a patient of a false negative result was deemed to be higher than the impact of a false positive or delayed result

because the patient might be incorrectly denied a potentially effective treatment. There is therefore a potential benefit in knowing *PDGFRB* gene rearrangement status in MDS/MPD patients so that clinicians can make more informed decisions to improve the overall management of their MDS/MPD patients.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Clinical Molecular Genetics Devices Panel because other marketing applications for FISH assays for similar indications with similar design have been reviewed by the Panel. It was determined, therefore, that the clinical issues raised by this HDE are similar to those previously reviewed.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the *PDGFRB* FISH for Gleevec Eligibility in Myelodysplastic Syndrome/Myeloproliferative Disease (MDS/MPD) will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on December 18, 2015.

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

Hazards to Health from Use of the Device: See indications, limitations and patient information in the labeling.

Post-approval Requirements and Restrictions: See approval order.