Pelabresib (CPI-0610) Monotherapy in Patients With Myelofibrosis – Update of Clinical and Translational Data from the Ongoing MANIFEST Trial

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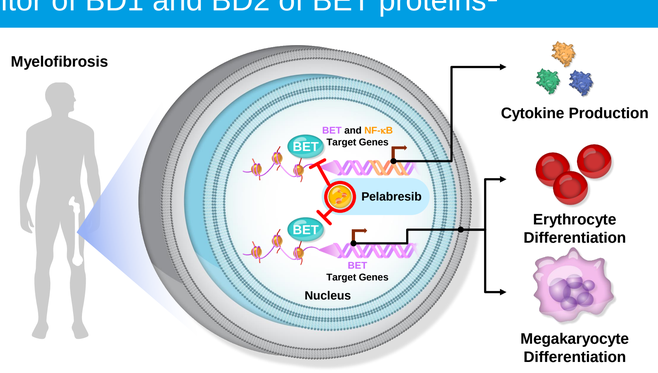
BSH22-PO27

Background, Design and Methods

Pelabresib, an investigational oral small molecule inhibitor of BD1 and BD2 of BET proteins[1]



[1]Albrecht et al. *J Med Chem.* 2016;59:1330−1339.
BET, bromodomain and extraterminal domain; NFkB, nuclear factor B.

Pelabresib monotherapy in myelofibrosis patients with unmet medical need

MANIFEST Arm 1: Refractory/resistant, intolerant or ineligible for JAKi treatment

Study Population

- No longer on ruxolitinib
- DIPSS Int-2 or higher*
- Platelet count ≥ 75 x 10^9/L
- TD cohort: ≥2 units of RBC transfusions/mo for 12 wks
- Non-TD cohort must have baseline spleen size of >450 cm^3

Arm/Cohort

Transfusion Dependent (TD) (Cohort 1A) N=36/60, **Ongoing**

Non-transfusion Dependent (Non-TD) (Cohort 1B) N=50, **Completed**

Endpoints

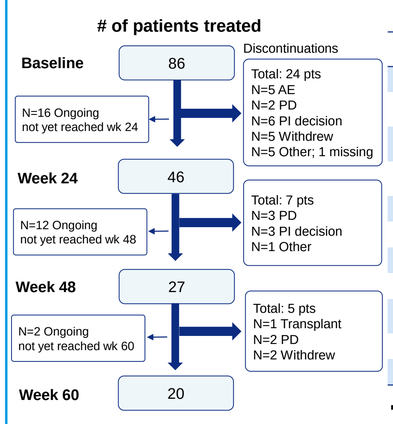
TD cohort (1A)	
Primary Endpoint	**Key Secondary**
TD to TI	SVR35, TSS50

Non-TD cohort (1B)	
Primary Endpoint	**Key Secondary**
SVR35	TSS50

*Patients with DIPSS Int-1 were allowed to enrol prior to the protocol amendment.
DIPSS, Dynamic International Prognostic Scoring System; SVR35: Spleen volume response defined as ≥35% reduction from baseline (MRI or CT) after 24 wk; TSS50, Total symptom score response defined as ≥50% total symptom score reduction from baseline after 24-wk
TD to TI: Conversion from Transfusion Dependent (TD) to Transfusion Independent (TI), defined as absence of RBC transfusions over any consecutive 12-wk period.
JAKi, Janus kinase inhibitor; MF, myelofibrosis; RBC, red blood cell; SVR35, ≥35% spleen volume reduction from baseline; TD, transfusion dependence; TI, transfusion independence; TSS50, ≥50% total symptom score reduction from baseline.

Disposition, Demographics and Disease Characteristics

Patient Disposition



	Cohort 1A TD*	Cohort 1B Non-TD	Overall*
Enrolled (n)	35	50	86
Ongoing with pelabresib monotherapy [n (%)]	15 (43)	24 (48)	40 (47)
Discontinued pelabresib treatment [n (%)]	20 (57)	26 (52)	46 (54)
Primary reason for pelabresib discontinuation [n (%)]			
PD	7 (20)	4 (8)	11 (13)
AE or lab abnormality	2 (6)	4 (8)	6 (7)
Withdrew consent	1 (3)	6 (12)	7 (8)
PI decision	5 (14)	7 (14)	12 (14)
Eligible for stem cell transplant	0	1 (2)	1 (1)
Other	3 (9)	3 (6)	6 (7)
Missing†	2 (6)	1 (2)	3 (3)

- Median duration of follow-up‡: 22 months (95% CI:10, 25)

*For one patient TD status unknown; †Pending data entry; ‡Reverse Kaplan Meier estimate.
AE, adverse event; CI, confidence interval; PD, progressive disease; PI, principal investigator; pts, patients; TD, transfusion dependence; wk, week.

Baseline Demographics and Disease Characteristics

Characteristic		Cohort 1A: TD*	Cohort 1B: Non-TD	Overall*
		N=35	N=50	N=86
Age (years)	Mean (SD)	73 (8)	69 (9)	70 (9)
Gender	Male, n (%)	23 (66)	23 (46)	47 (55)
DIPSS	Int-1, n (%)	0	7 (14)	7 (8)
	Int-2, n (%)	22 (63)	31 (62)	54 (63)
	High, n (%)	12 (34)	10 (20)	22 (26)
MF subtype	Primary MF, n (%)	21 (60)	33 (66)	54 (63)
	Post PV MF, n (%)	5 (14)	10 (20)	15 (17)
	Post ET MF, n (%)	7 (20)	5 (10)	12 (14)
	Missing†, n (%)	2 (6)	2 (4)	5 (6)
# of prior lines of therapy	Median (Min-Max)	2 (1, 9)	2 (1, 7)	2 (1, 9)
Haemoglobin (g/dL)	Median (Min-Max)	9 (6, 10)	9 (6, 15)	9 (6, 15)
	<10 g/dL, n (%)	31 (89)	34 (68)	65 (76)
Platelet (x10^9/L)	Median (Min-Max)	163 (79, 1262)	185 (68, 895)	168 (68, 1262)
Spleen volume (cc)	Median (Min-Max)	1356 (281, 8352)	2046 (525, 9155)	1837 (281, 9155)
TSS	Median (Min-Max)	16 (1, 56)	25 (8, 52)	21 (1, 56)
Mutations	HMR‡, n (%)	21 (60)	18 (36)	39 (45)
	ASXL1, n (%)	16 (46)	14 (28)	30 (35)
	JAK2 V617F, n (%)	22 (63)	30 (60)	52 (61)
	CALR, n (%)	7 (20)	11 (22)	19 (22)
	MPL, n (%)	4 (11)	3 (6)	7 (8)
	Triple negative, n (%)	1 (2.9)	2 (4.0)	3 (4)

*For one patient TD status unknown; †Pending data entry; ‡HMR: High molecular risk mutations; *ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*.
DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; HMR, high-molecular risk; Int-1, intermediate-1; Int-2, intermediate-2; MF, myelofibrosis; PV, polycythaemia vera; QD, once daily; SD, standard deviation; TD, transfusion dependent; TSS, tumour symptom score.

Patient Population

Patient Subgroups (Cohort 1A TD and 1B Non-TD)	N=86
JAKi ineligible not received any prior JAKi therapy*	14 (16%)
JAKi intolerant received at least one prior JAKi therapy and discontinued due to AE†	21 (24%)
JAKi refractory/resistant received at least one prior JAKi therapy and had suboptimal response or progression	48 (56%)
Subgroup unknown	3 (3%)

*i.e., due to anaemia, thrombocytopenia, history of severe infections or other considerations by the treating investigator; †i.e., due to anaemia, thrombocytopenia.
AE, adverse event; JAKi, Janus kinase inhibitor; TD, transfusion dependent.

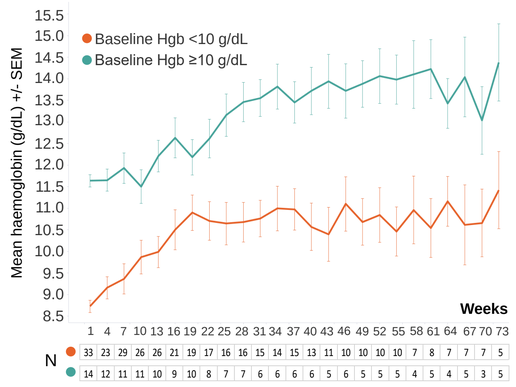
Results

Anaemia Improvement

Arm 1A TD cohort: TD to TI conversion	
TD to TI conversion*	16% (4/25)
Median TI duration	41 wks (range 31, 53)
Median time to TI conversion	32 wks

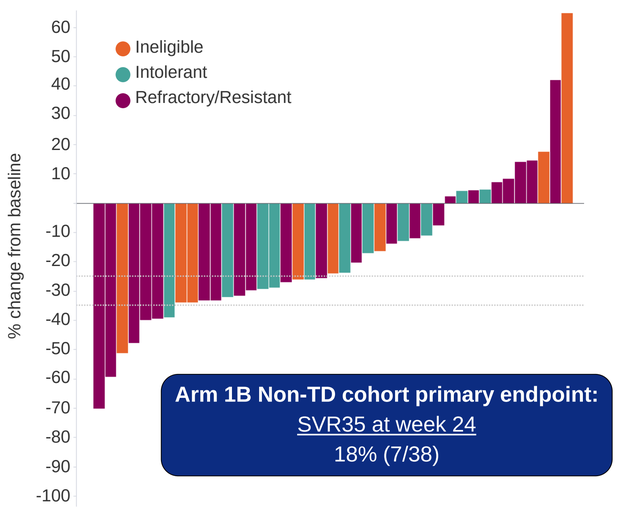
Arm 1B Non-TD cohort: Haemoglobin response	JAKi R/R	JAKi IE	JAKi IN	Overall
Haemoglobin response†	34% (11/32)	66% (2/3)	41% (5/12)	38.3% (18‡/47)

Arm 1B Non-TD cohort: Mean haemoglobin over time§



*The TD to TI conversion (primary endpoint for TD cohort) defined as absence of RBC transfusions over any 12-week period. Cohort enrolment ongoing. Patients evaluable if non-missing baseline, ongoing and received 12 wks of treatment or discontinued at any time point. TI duration: Longest duration between transfusions for TI pts; Time to TI conversion: Time to last transfusion prior to conversion for TI pts.
†Haemoglobin response (secondary endpoint): Post-baseline mean Hgb increase of at least 1.5g/dL is required for any 12 wks RBC transfusion free period.
‡Median time between prior JAKi therapy and study entry is 17 months; 3 patients (2 JAKi R/R, 1 JAKi IN) received ruxolitinib within 3 months of study entry.
§Mean Hgb over time: Hgb values within 2 wks after transfusion are excluded; 3 patients non-evaluable due to missing baseline.
Hgb, haemoglobin; IE, ineligible; IN, intolerant; JAKi, Janus kinase inhibitor; pts, patients; R/R, refractory/resistant; RBC, red blood cell; SEM, standard error of the mean; TD, transfusion dependence; TI, transfusion independence; wks, weeks.

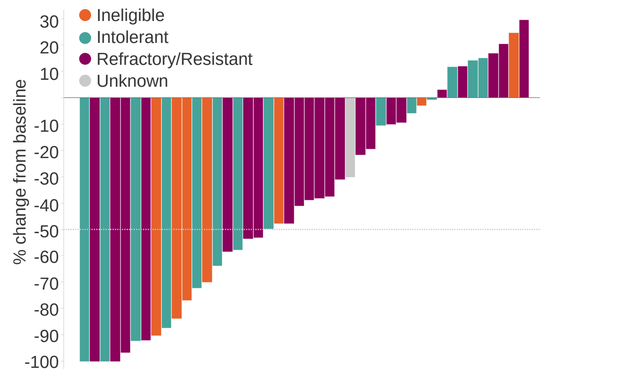
Spleen volume percent change at week 24



	Arm 1 (TD and Non-TD) N=64
SVR35	11% (7/64)
SVR25	31% (20/64)
Median spleen volume % change	-24%
Mean spleen volume % change	-17%

Patients evaluable if non-missing baseline and wk 24 spleen assessment or discontinued at any time without wk 24 spleen assessment. 22 patients non-evaluable: 4 pts due to missing baseline and 18 ongoing pts without wk 24 assessment. 23 pts discontinued without having wk 24 assessment included as non-responders. Patients evaluable for SVR at wk 24: JAKi ineligible (n=10); JAKi intolerant (n=15); JAKi refractory/resistant (n=38); 1 patient with unknown subgroup.
JAKi, Janus kinase inhibitor; Non-TD, nontransfusion dependence; pts, patients; SVR, spleen volume reduction per local review; SVR25, ≥25% spleen volume reduction from baseline; SVR35, ≥35% spleen volume reduction from baseline; TD, transfusion dependence; Wk, Week.

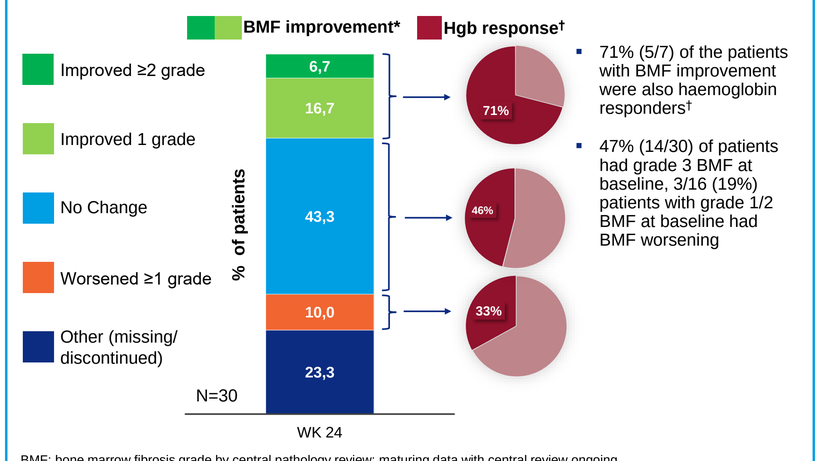
TSS percent change at week 24



	Arm 1 (TD and Non-TD) N=64
TSS50	28% (18/64)
Median TSS % change	-40%
Mean TSS % change	-40%

Patients evaluable if non-missing baseline and week 24 TSS assessment or discontinued at any time without wk 24 TSS assessment. 22 patients non-evaluable: 7 pts due to missing baseline and 15 ongoing pts did not reach wk 24 as of data cut-off. 20 patients discontinued without wk 24 assessment are included as non-responders. Patients evaluable for TSS at wk 24: JAKi ineligible (n=8); JAKi intolerant (n=18); JAKi refractory/resistant (n=37); 1 patient with unknown subgroup.
JAKi, Janus kinase inhibitor; Non-TD, nontransfusion dependence; pts, patients; TD, transfusion dependence; TSS, Total Symptom Score; TSS50, ≥50% reduction in total symptom score from baseline; Wk, Week.

Bone marrow fibrosis improvement* per central read and haemoglobin response†

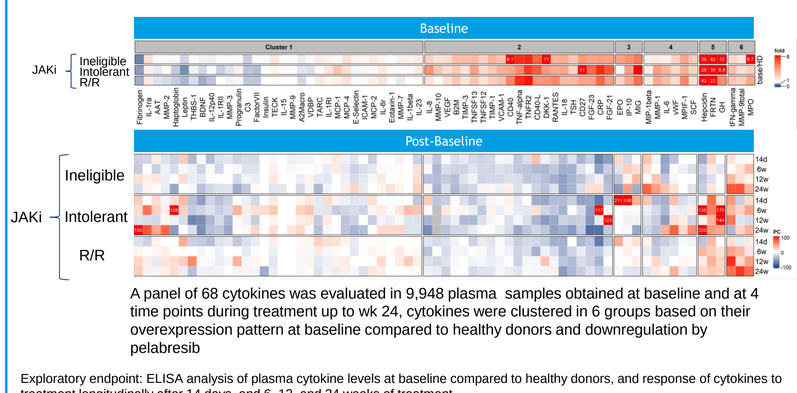


- 71% (5/7) of the patients with BMF improvement were also haemoglobin responders†
- 47% (14/30) of patients had grade 3 BMF at baseline, 3/16 (19%) patients with grade 1/2 BMF at baseline had BMF worsening

BMF: bone marrow fibrosis grade by central pathology review; maturing data with central review ongoing.
*Exploratory endpoint: Patients evaluable if non-missing baseline bone marrow assessment.
†Secondary endpoint: Post-baseline mean Hgb increase of at least 1.5g/dL for any 12 wks RBC transfusion free period.
BMF, bone marrow fibrosis; Hgb, haemoglobin; RBC, red blood cell; Wk, Week.

Changes in plasma levels of myelofibrosis-associated / inflammation-related cytokines

- 21 cytokines, involved in TNFR2 non-canonical NF-kB pathway, IL-10, IL-4, IL-13, IL-18 signaling and associated with myelofibrosis pathogenesis were the most strongly downregulated by pelabresib
- Downregulation was rapid (14 days) and durable (through 24 weeks)



A panel of 68 cytokines was evaluated in 9,948 plasma samples obtained at baseline and at 4 time points during treatment up to wk 24, cytokines were clustered in 6 groups based on their overexpression pattern at baseline compared to healthy donors and downregulation by pelabresib

Exploratory endpoint: ELISA analysis of plasma cytokine levels at baseline compared to healthy donors, and response of cytokines to treatment longitudinally after 14 days, and 6, 12, and 24 weeks of treatment.
IL, interleukin; JAKi, Janus kinase inhibitor; NF-kB; nuclear factor kappa b; R/R, refractory/resistant; TNFR2, tumour necrosis factor receptor 2; Wk, week.

Summary of adverse events

Treatment-Emergent Adverse Events*	All Grade N=86[2] n (%)	Grade 3 N=86[2] n (%)	Grade 4 N=86† n (%)
Haematological Events			
Thrombocytopenia‡	33 (38%)	16 (19%)	3 (4%)
Anaemia	21 (24%)	13 (15%)	0
Non-haematological Events			
Gastrointestinal Events			
Diarrhoea	29 (34%)	5 (6%)	0
Nausea	28 (33%)	0	0
Constipation	18 (21%)	1 (1%)	0
Other Non-haematological Events			
Asthenic conditions§	28 (33%)	2 (2%)	0
Dysgeusia	20 (23%)	0	0
Respiratory tract infection¶	20 (23%)	4 (5%)	0
Pruritus	19 (22%)	2 (2%)	0

- 78 patients (91%) reported at least one TEAE, 21 patients (24%) reported at least one SAE, and 51 patients (59%) reported at least one ≥ grade 3 TEAE
- The most common (≥20%) haematologic TEAEs were thrombocytopenia and anaemia
- The most common (≥20%) non-haematologic TEAEs were diarrhoea, nausea, asthenic conditions, taste changes, RTIs, pruritus and constipation
- SAEs reported in ≥2 pts were dyspnoea (4 pts), anaemia, RTIs, hyperkalaemia and hyponatraemia (3 pts each), and pyrexia, syncope, acute kidney injury and pulmonary edema (2 pts each)
- 16 pts (19%) reported TEAEs that led to pelabresib discontinuation
- There were no on-treatment deaths

*TEAEs of all grade that occurred in ≥20% of patients; †Safety evaluable population: Received at least one dose of study drug as of the data cut; ‡Includes TEAE platelet count decrease; §Include TEAEs of fatigue, malaise, lethargy; ¶Includes TEAEs of upper respiratory tract infection (RTI), lower RTI, viral upper RTI, influenza, laryngitis, bronchitis, sinusitis, nasopharyngitis, pneumonia, COVID-19.
pts, patients; RTI, respiratory tract infection; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

Pelabresib monotherapy in advanced myelofibrosis patients evaluated to date that are refractory/resistant, ineligible or intolerant to JAKi treatment:

- Clinical activity observed based on preliminary results of spleen volume reduction, symptom reduction, haemoglobin benefit and warrants further investigation
- Exploratory analysis showed bone marrow fibrosis improvement in a subset of patients and plasma cytokines involved in myelofibrosis pathogenesis were reduced during treatment with pelabresib
- Majority of the most common treatment-emergent adverse events were low grade
- Additional clinical and translational updates from MANIFEST Arm 3 (JAKi naïve 1st line MF pts) and Arm 2 (2nd line MF pts with suboptimal response to ruxolitinib) will be presented during the BSH22-OR18 oral
- MANIFEST-2, a Phase 3 randomized double-blind trial of pelabresib + ruxolitinib vs placebo + ruxolitinib in JAKi naïve MF patient population, has been initiated and is open for enrolment (NCT04603495; https://www.manifestclinicaltrials.com)

JAKi, Janus kinase inhibitor; MF, myelofibrosis.

NCG, NG, WP: No disclosures. **MK**: Consultancy and Research Funding from Protagonist Therapeutics; Research Funding from Astellas, Astex, Bristol Myers Squibb, Chimerix, Constellation Pharmaceuticals a MorphoSys Company and Incyte. **JM**: Consultancy from Galecto, Geron and Prelude; Consultancy, Membership on an entity's Board of Directors or Advisory Committees and Research Funding: AbbVie, Celgene/BMS, Constellation Pharmaceuticals a MorphoSys Company, CTI Biopharm, Genentech/Roche, Gilead, Incyte, Kartos, Merck, Novartis, PharmaEssentia, Promedior, Roche and Sierra Oncology; Consultancy and Research Funding from Geron; Research Funding from Forbius and Merus. **FP**: Consultancy from CTI; Membership on an entity's Board of Directors or Advisory Committees: AOP, Celgene, Novartis and Sierra Oncology. **AV**: Honoraria and Membership on an entity's Board of Directors or Advisory Committees: Bristol Myers Squibb, Incyte and Novartis; Membership on an entity's Board of Directors or Advisory Committees: AbbVie. **SV**: Consultancy from Constellation Pharmaceuticals a MorphoSys Company; 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Research Funding from Astellas, Constellation Pharmaceuticals a MorphoSys Company, NS Pharma, Pfizer and Promedior. **GJS**: Consultancy: AstraZeneca, Evidera, Incyte, Kaiser Permanente, NCI, Ono and Pharma; Consultancy, Current equity holder in publicly-traded company, Honoraria, Research Funding and Speakers Bureau: Amgen; Consultancy, Current equity holder in publicly-traded company, Research Funding and Speakers Bureau: BMS/Celgene; Consultancy, Membership on an entity's Board of Directors or Advisory Committees, Research Funding and Speakers Bureau: Incyte; Consultancy, Honoraria, Research Funding and Speakers Bureau: Jazz; Consultancy and Research Funding: Ono-UK and Novartis; Consultancy, Research Funding and Speakers Bureau: Agios; Current equity holder in publicly-traded company: Johnson & Johnson; Current equity holder in publicly-traded company and Research Funding: Pfizer; Honoraria, Research Funding and Speakers Bureau: Astellas, Kite/Gilead, Sanofi and Stemline Therapeutics, Inc.; Honoraria and Speakers Bureau: Pharmacyclics; Other: Chair-unpaid for ASH Foundation; Research Funding: AbbVie, Actinium Pharmaceuticals, Inc., Actuate, Ambit, Ariad, Arog, Bio, Biomed Valley Discoveries, Bluebird Bio, Boehringer-Ingelheim, Celator, Cellerant, Constellation Pharmaceuticals a MorphoSys Company, CTI Biopharma, Cyclacel, Daiichi-Sankyo, Deciphera, Delta-Fly, Elevate, Eli Lilly, Forma, FujiFilm, Gamida Cell Ltd., Genentech-Roche, Geron, Janssen, Kura Oncology, Karyopharm, Leukemia & Lymphoma Society, Malteon, MedImmune, Millennium, National Marrow Donor Program, NIH, Onconova, Onyx, Pharmamar, PrECOG, Regimmune, Samus, Sangamo, Sellas, Takeda, Tolero, Trovagene, UC Davis and UCSD. **RKR**: Consultancy: AbbVie, Blueprint, BMS/Celgene, CTI, Disc Medicine, Jazz Pharmaceuticals, Kartos, Novartis, PharmaEssentia and Sierra Oncology; Consultancy and Research Funding from Incyte and Stemline; Current Employment: Memorial Sloan Kettering; Research Funding from Constellation Pharmaceuticals a MorphoSys Company. **MWD**: Membership on an entity's Board of Directors or Advisory Committees: CTI; 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Presented at the British Society of Haematology Annual Scientific Meeting; 3–5 April 2022.
Pelabresib (CPI-0610) is an investigational new drug and has not been approved by any regulatory authority.

Data cut-off 10 Sep 21

BSH2022 PO-027

General Haematology including ITP & Myeloproliferative Disorders

Natalia Curto-Garcia

Poster presented at: British Society for Haematology Listening • Learning • Leading

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