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Sustained Control of Excessive Erythropoiesis by the TMPRSS6 Antisense Inhibitor Sapablursen in Polycythemia Vera: IMPRSSION Trial Treatment Extension Data

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Background

- Polycythemia vera (PV) is a myeloproliferative neoplasm driven by an acquired Janus kinase 2 gene (*JAK2*) mutation and characterized by erythrocytosis, elevated hematocrit (HCT), and increased risk of thrombosis[1,2]
  - Controlling HCT levels below 45% is a key therapeutic goal to reduce thrombotic events[2]
  - While phlebotomy is the standard of care, it is not successful in maintaining HCT below 45% in many patients and can cause hypovolemia. In addition, phlebotomy does not alleviate symptoms and may worsen symptoms of iron deficiency and fatigue[3,4]
- Sapablursen (ISIS 702843, ONO-0530) is an investigational, liver-directed, ligand-conjugated antisense oligonucleotide medicine that targets transmembrane serine protease 6 (TMPRSS6), a negative regulator of the iron-regulatory hormone hepcidin[5]
- The primary results of the IMPRSSION study (NCT05143957), an ongoing, open-label phase 2 trial of 2 sapablursen dose cohorts in patients with phlebotomy-dependent PV, were previously presented[6]
- Treatment with sapablursen met the primary endpoint in both the low- and high-dose cohorts and significantly reduced phlebotomy rates during the primary endpoint window (Weeks 17–37)[6]

Aims

- To report the long-term safety and efficacy of sapablursen over a total of 73 weeks, including a 36-week treatment extension period during which dose increases above the original assignment were allowed

Methods

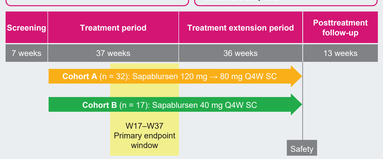
Study design and treatment

- IMPRSSION is a phase 2, multicenter, open-label study of sapablursen in patients with PV (**Figure 1**)
  - Eligible patients met 2016 World Health Organization diagnostic criteria for PV and were required to have had ≥3 phlebotomies within the 6 months prior to screening, including ≥1 phlebotomy in the last 12 weeks
    - Patients were not required to have HCT <45% to be eligible
  - Patients received subcutaneous sapablursen every 4 weeks at a high (Cohort A, 120 mg or 80 mg) or low dose (Cohort B, 40 mg) during a 37-week treatment period, followed by an additional 36-week treatment extension period
    - Guidelines for dose adjustments were provided based on local laboratory results to maintain HCT ≥38% and <45%
    - A dose reduction was allowed if HCT was ≤40% and required if HCT was <38%; a dose increase was allowed after Week 37 if HCT was ≥43% and required if HCT was ≥45%
    - Phlebotomy was required if the local laboratory HCT measurement was ≥45%; confirmation was not required
  - Data are reported through the 36-week treatment extension period (73 weeks total)

Figure 1. Overview of the IMPRSSION Study

Key inclusion criteria[7]
- Clinical diagnosis of PV consistent with the WHO 2016 diagnostic criteria (*JAK2* mutation required)
- Phlebotomy-dependent (≥3 in the prior 6 months and 1 in the last 12 weeks prior to randomization)
- No eligibility restrictions based on hematocrit level
- Current or previous cytoreductive therapy not needed; if current, stable dose for ≥3 months

Key endpoints
- Primary: Reduction in the weekly rate of phlebotomies
- Secondary: Change in mean MPN-SAF-TSS score
- Exploratory: Serum hepcidin and hematocrit control (<45%) without receiving phlebotomy (confirmation of hematocrit ≥45% was not required), and change from baseline in TSAT over time
- Safety: Adverse events, vital signs, ECG, and clinical laboratory tests



Patients in Cohort A were initially assigned to receive 120 mg; all patients were subsequently switched to 80 mg due to reductions in hemoglobin. The initial dose was split into 2 administrations, with half delivered on day 1 and half on day 15.
ECG, electrocardiogram; *JAK2*, Janus kinase 2 gene; MPN-SAF-TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; PV, polycythemia vera; Q4W, every 4 weeks; SC, subcutaneous; TSAT, transferrin saturation; W, week; WHO, World Health Organization.

Results

Patient demographics and baseline clinical characteristics

- Overall, 73 patients were screened, and 49 received at least 1 dose of sapablursen in either Cohort A (n = 32) or Cohort B (n = 17)
  - The median age was 61 (range, 39–82) years, 40 (82%) patients were male, and 30 (61%) were high risk (aged >60 years and/or with a history of a prior thrombotic event; **Table 1**)
  - Of the 49 patients enrolled, 23 (72%) patients in Cohort A and 14 (77%) patients in Cohort B completed the 73-week treatment period

Table 1. Patient Demographics and Baseline Clinical Characteristics

	Cohort A (n = 32)	Cohort B (n = 17)	All patients (N = 49)
Age, years, median (P25, P75)	62 (55, 67)	61 (51, 69)	61 (54, 68)
Sex, n (%)			
Female	4 (13)	5 (29)	9 (18)
Male	28 (88)	12 (71)	40 (82)
Ethnicity, not Hispanic or Latino, n (%)	29 (91)	17 (100)	46 (94)
Race, n (%)			
Black	0	1 (6)	1 (2)
White	29 (91)	16 (94)	45 (92)
Other[a]	3 (9)	0	3 (6)
Disease duration, years, mean ± SD	4.2 ± 3.9	3.9 ± 3.8	4.1 ± 3.8
***JAK2* mutational status, n (%)**			
JAK2 V617F	29 (91)	16 (94)	45 (92)
JAK2 exon 12	3 (9)	1 (6)	4 (8)
Risk category, n (%)			
Low	12 (38)	7 (41)	19 (39)
High[b]	20 (63)	10 (59)	30 (61)
Baseline laboratory values, mean ± SD			
Hematocrit, %	46.4 ± 3.6	45.5 ± 3.4	46.1 ± 3.5
Hemoglobin, g/dL	14.0 ± 1.3	13.9 ± 1.3	14.0 ± 1.3
Number of phlebotomies (6 months prior to the study), median	5.0	5.0	5.0
Baseline phlebotomy plus any cytoreductive therapy, n (%)			
Baseline hydroxyurea use	11 (34)	8 (47)	19 (39)
Baseline interferon use	2 (6)	1 (6)	3 (6)
Baseline ruxolitinib use	0	1 (6)	1 (2)

[a]Included Arab, declined to specify, and unknown. [b]Aged >60 years and/or with a prior thrombotic history.
JAK2, Janus kinase 2 gene; P25/75, 25th/75th percentile; SD, standard deviation.

Phlebotomy

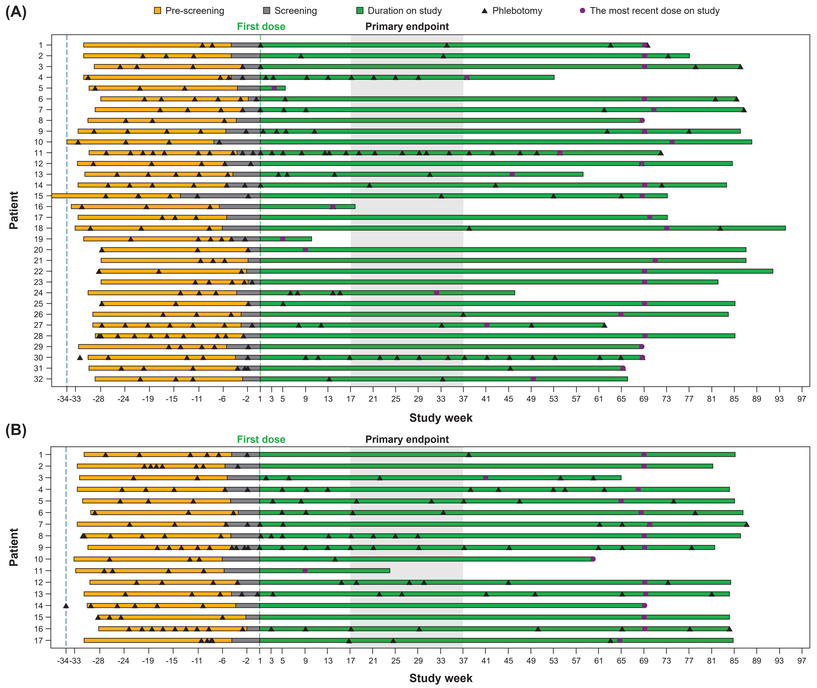
- In both cohorts, the weekly phlebotomy rate decreased significantly during the primary endpoint window (Weeks 17–37) and was maintained at a low level during the 36-week extension period (Weeks 37–73; **Table 2** and **Figure 2**)

Table 2. Reduction in Phlebotomy Rate

	Cohort A	Cohort B
Primary endpoint window, n	32	17
Phlebotomy weekly rate, mean ± SD		
Baseline	0.15 ± 0.07	0.17 ± 0.07
Weeks 17–37	0.05 ± 0.09	0.07 ± 0.07
Mean change	−0.10	−0.10
P-value	<0.0001	0.0001
Extension treatment period, n[a]	29	16
Phlebotomy weekly rate, mean ± SD		
Weeks 37–73	0.03 ± 0.05	0.04 ± 0.04
Mean change	−0.12	−0.13
P-value	<0.0001	<0.0001
Number of phlebotomies, median (P25, P75)		
n[a]	29	16
Baseline (6 months prior to study)	5.0 (3.0, 6.0)	5.0 (3.5, 6.5)
Weeks 17–37 (20 weeks)	0.0 (0.0, 1.0)	1.5 (0.0, 2.5)
Weeks 1–37 (37 weeks)	1.0 (0.0, 2.0)	2.5 (1.0, 4.0)
Weeks 37–73 (36 weeks)	0.0 (0.0, 2.0)	1.0 (0.0, 2.5)

[a]Includes patients who completed the 37-week treatment period (those with at least 1 observation on or after the Week 37 visit during the 73-week treatment period).
The baseline rate of phlebotomy was defined as the number of phlebotomies in the 6 months prior to screening and was normalized to a weekly event rate.
P25/75, 25th/75th percentile; SD, standard deviation.

Figure 2. Reduction in Phlebotomy Rate Over Time by Patient in (A) Cohort A and (B) Cohort B



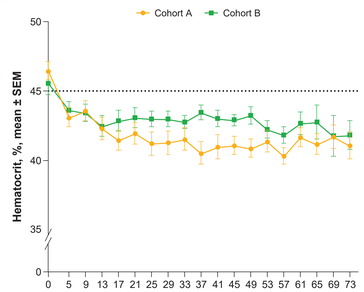
HCT and dose adjustment based on HCT

- Administration of sapablursen resulted in a dose- and time-dependent reduction (mean ± standard deviation) in HCT from baseline to Week 37 of 46.4% ± 3.6% to 40.5% ± 4.4% in Cohort A, and from 45.5% ± 3.4% to 43.5% ± 2.2% in Cohort B
- The reduction in HCT was maintained during the extension period (Week 73) in both Cohorts A (41.1% ± 4.0%) and B (41.8% ± 3.7%; **Figure 3**)
  - Three patients in Cohort A increased the dose to 120 mg and 2 subsequently increased the dose to 160 mg; 12 patients reduced the dose during the treatment extension period based on the HCT dose adjustment criteria and 1 paused dosing based on hemoglobin criteria
  - Dose increases to 80 mg in 11 patients in Cohort B resulted in better HCT control during the treatment extension period; the dose was not reduced in any patients in Cohort B during the treatment extension period

Other parameters

- Sapablursen treatment also led to a dose- and time-dependent increase from baseline in serum ferritin (**Figure 4**), with corresponding reductions in transferrin saturation levels (**Figure 5**) during the 73-week treatment period

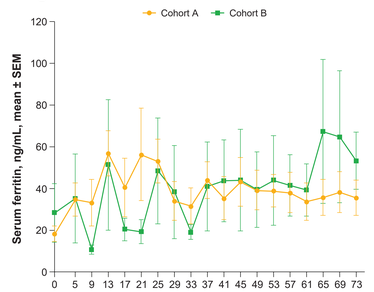
Figure 3. Decrease in Hematocrit Levels Over Time



Cohort A, n = 32 32 31 30 30 29 29 27 29 29 28 26 25 25 24 24 24 22 18
Cohort B, n = 17 17 17 17 17 15 16 16 15 16 16 15 15 15 15 15 14 14 13

SEM, standard error of the mean.

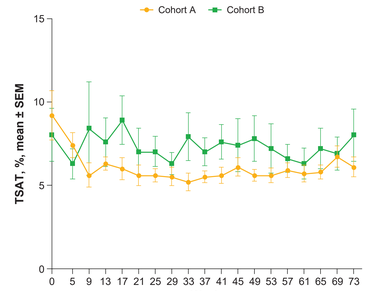
Figure 4. Serum Ferritin Levels Over Time



Cohort A, n = 32 29 8 28 8 9 29 11 12 28 20 20 18 24 17 19 21 18 18
Cohort B, n = 17 17 6 15 13 11 14 14 15 16 15 14 15 14 15 15 14 13 14

SEM, standard error of the mean.

Figure 5. TSAT Levels Over Time



Cohort A, n = 32 30 8 29 10 9 27 11 13 29 18 16 20 24 20 18 21 19 18
Cohort B, n = 17 17 7 17 12 11 15 15 15 16 16 14 15 15 15 15 13 14 14

SEM, standard error of the mean; TSAT, transferrin saturation.

Safety

- Sapablursen was generally safe and well tolerated (**Table 3**)
- During the 73-week treatment period, anemia was reported in 15 (46.9%) patients in Cohort A and 7 (41.2%) patients in Cohort B
  - Two patients in Cohort A (6.3%) developed a Grade 2 hemoglobin decrease, one of which was in the context of coronary artery bypass grafting surgery
  - One patient in Cohort A (3.1%) developed a Grade 3 hemoglobin decrease in the context of an unrelated bleeding gastric ulcer during the initial 37-week treatment period
- Injection-site reactions occurred in 6 of 49 (12.2%) patients with sapablursen administered once every 4 weeks
  - Injection-site reactions did not recur following multiple injections, were not progressive, and resolved spontaneously
- During the study, 1 death occurred due to transformation to acute myeloid leukemia, which was deemed not related to the study drug

Table 3. Summary of TEAEs Occurring During the 73-Week Treatment Period

	Cohort A (n = 32)	Cohort B (n = 17)	All patients (N = 49)
TEAEs	31 (97)	17 (100)	48 (98)
Mild	8 (25)	5 (29)	13 (27)
Moderate	14 (44)	8 (47)	22 (45)
Severe	9 (28)	4 (24)	13 (27)
TEAEs related to study drug	24 (75)	9 (53)	33 (67)
Serious TEAEs	6 (19)	4 (24)	10 (20)
TEAEs leading to study drug discontinuation	2 (6)	3 (18)	5 (10)
TEAEs leading to death	1 (3)	0	1 (2)
TEAEs occurring in >10% of all patients			
Anemia	15 (47)	7 (41)	22 (45)
Fatigue	13 (41)	3 (18)	16 (33)
Diarrhea	9 (28)	4 (24)	13 (27)
Pruritus	8 (25)	3 (18)	11 (22)
Headache	10 (31)	2 (12)	12 (24)
Nausea	7 (22)	2 (12)	9 (18)
Dizziness	8 (25)	0	8 (16)
Arthralgia	7 (22)	2 (12)	9 (18)
Dyspnea	7 (22)	0	7 (14)
Constipation	5 (16)	3 (18)	8 (16)
Muscle spasms	4 (13)	2 (12)	6 (12)
COVID-19	5 (16)	2 (12)	7 (14)
AST increased	4 (13)	2 (12)	6 (12)
ALT increased	3 (9)	2 (12)	5 (10)
Lymphocyte count decreased	3 (9)	2 (12)	5 (10)
Cough	4 (13)	1 (6)	5 (10)
Fall	3 (9)	2 (12)	5 (10)
Patients with ≥1 injection-site reaction	5 (16)	1 (6)	6 (12)
Injection-site pain	3 (9)	0	3 (6)
Injection-site bruising	1 (3)	1 (6)	2 (4)
Injection-site discomfort	1 (3)	0	1 (2)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

Conclusions

- The investigational drug sapablursen administered subcutaneously once every 4 weeks led to durable hematocrit control through 73 weeks of treatment in patients with PV in the phase 2 IMPRSSION study
- Sapablursen was generally safe and well tolerated in the 73-week treatment period, with a low rate of injection-site reactions
- These findings highlight the sustained control of excessive erythropoiesis with sapablursen and establish 80 mg once every 4 weeks as an optimal starting dose for future studies. A phase 3 study evaluating the safety and efficacy of sapablursen in patients with PV is underway (NCT07429266)

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Disclosures

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