Safety and Tolerability of Inhaled Molgramostim in Autoimmune Pulmonary Alveolar Proteinosis (aPAP)

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OBJECTIVE

To report the long-term safety of inhaled molgramostim nebulizer solution (MOL) administered intermittently in adults with aPAP

CONCLUSIONS

IMPALA-X was an extension study that was discontinued early as intermittent dosing did not show substantial evidence of benefit vs placebo (PBO) in the IMPALA trial

In the 60 patients who participated in this long-term extension of the IMPALA trial, there were no new safety signals observed. The most common treatment-related adverse events (AEs) after 93.4 patient-years of exposure to MOL were mild-to-moderate cough, nasopharyngitis, and respiratory tract infection

The pivotal Phase 3 IMPALA-2 trial of continuous MOL compared with PBO in patients with aPAP is ongoing

DISCLOSURES

Savara Inc. participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster for submission. All authors had access to the data; participated in the development, review, and approval of this poster; and agreed to submit this poster to the European Respiratory Society (ERS) 2022. Savara Inc. funded the research for this study and provided writing support for this poster. Medical writing assistance, funded by Savara Inc., was provided by Melissa Julyanti, PharmD, of JB Ashtin.

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Background

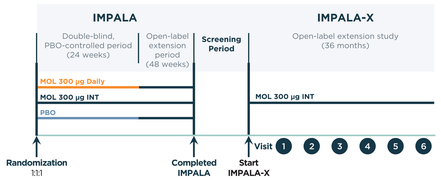
- aPAP is a rare lung disease characterized by the accumulation of lipoproteinaceous surfactant material in the alveoli of the lungs leading to respiratory distress, hypoxemia, and increased infection risk[1,2]
- There is currently no approved pharmacologic treatment for aPAP. The current standard of care is whole-lung lavage, an invasive procedure that has several known complications[2]
- MOL is a recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF) that regulates innate immune functions and surfactant catabolism in alveolar macrophages[3]
- MOL demonstrated greater improvements in pulmonary gas transfer and functional health status compared with PBO in adults with aPAP in the Phase 2/3, 24-week, randomized, double-blind, PBO-controlled multicenter IMPALA trial[4]

Methods

Study Design

- All patients who completed the Phase 2/3, 24-week, randomized, double-blind, PBO-controlled multicenter IMPALA trial[4] were eligible to enroll in IMPALA-X **(Figure 1)**
- IMPALA-X (NCT03482752) was an international, multicenter, open-label, non-controlled extension study in which patients received treatment with inhaled MOL 300 µg/day administered intermittently (1 week on and 1 week off), a regimen used in most published reports for off-label GM-CSF use,[5,6] for up to 36 months
- IMPALA-X was initiated before the evaluation of the IMPALA trial results; results of IMPALA did not support efficacy of intermittent dosing regimen and this dosing regimen was not pursued for further development for marketing authorization. Consequently, IMPALA-X was discontinued early

Figure 1. Study Design



Inclusion Criteria	Exclusion Criteria
• Adults (aged ≥18 years) • History of aPAP • Completed the IMPALA[4] study	• Treatment with GM-CSF products other than MOL within 3 months of baseline • Treatment with any IP other than MOL within 4 weeks of baseline • Connective tissue disease, inflammatory bowel disease, or other autoimmune disorder requiring treatment associated with significant immunosuppression, eg, >10 mg/day systemic prednisolone • History of, or present, myeloproliferative disease or leukemia • Apparent pre-existing concurrent pulmonary fibrosis

aPAP, autoimmune pulmonary alveolar proteinosis; GM-CSF, granulocyte-macrophage colony-stimulating factor; INT, intermittent; IP, investigational product; MOL, molgramostim nebulizer solution; PBO, placebo.

Safety Assessment

- Safety was assessed by monitoring AEs, serious AEs (SAEs), treatment-emergent AEs (TEAEs), adverse drug reactions, and AEs leading to treatment discontinuation

Analysis

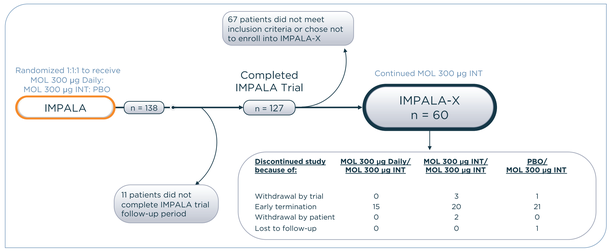
- Descriptive statistics were used to summarize AEs
- Owing to early termination of the trial, data from patients' last visit before study termination were analyzed as visit 7
- The full analysis set included all patients enrolled; the safety analysis set included only patients with exposure to MOL

Results

Patient Disposition

- Among 127 patients who completed the IMPALA trial, 60 entered IMPALA-X and continued to receive MOL until study termination **(Figure 2)**

Figure 2. Patient Disposition



INT, intermittent; MOL, molgramostim nebulizer solution; PBO, placebo.

Patients

- Baseline demographics were generally comparable among patients in each treatment arm except a higher population of males than females in the MOL 300 µg INT/MOL 300 µg INT group **(Table 1)**

Table 1. Baseline Demographics[a]

Parameter	MOL 300 µg Daily/ MOL 300 µg INT N = 15	MOL 300 µg INT/ MOL 300 µg INT N = 23	PBO/ MOL 300 µg INT N = 22
Male, n (%)	7 (46.7)	18 (78.3)	11 (50.0)
White, n (%)	12 (80.0)	21 (91.3)	21 (95.5)
Age, years			
Mean (SD)	48.7 (14.0)	46.7 (12.8)	45.6 (14.4)
Median (IQR)	55.0 (24.0, 71.0)	47.0 (20.0, 76.0)	47.5 (22.0, 71.0)
BMI, kg/m^2			
Mean (SD)	27.3 (5.1)	27.0 (3.9)	25.5 (5.6)
Median (IQR)	27.5 (17.8, 38.5)	27.5 (19.3, 34.3)	26.2 (15.1, 38.5)

BMI, body mass index; IQR, interquartile range; INT, intermittent; MOL, molgramostim nebulizer solution; PBO, placebo.
[a]Based on the full analysis set.

Safety

- The study was terminated early; therefore, no patients completed the planned 36 months of the study
- Overall, no new or unexpected safety concerns were identified in the study; rates of AEs, SAEs, TEAEs, and adverse drug reactions were low **(Table 2)**
- The most frequently reported TEAEs were cough, nasopharyngitis, and respiratory tract infection **(Table 3)**
- Most TEAEs were mild or moderate in severity; the rate of severe TEAEs was <1 per patient-year
- No TEAEs led to study drug discontinuation
- Eight patients experienced treatment-emergent SAEs: alveolar proteinosis (n = 3), respiratory failure (n = 1), HIV infection (n = 1), laryngitis (n = 1), back pain (n = 1), and cellulitis (n = 1); none of these events were related to the study drug
- One death was reported due to COVID-19 infection 24 days after the last MOL dose

Table 2. Overview of TEAEs[a]

Parameter	MOL 300 µg Daily/ MOL 300 µg INT N = 15 PY = 26.6	MOL 300 µg INT/ MOL 300 µg INT N = 22 PY = 33.7	PBO/ MOL 300 µg INT N = 22 PY = 33.1
	Events (Events/PY)		
AE	74 (2.79)	50 (1.48)	41 (1.24)
SAE	2 (0.08)	2 (0.06)	3 (0.09)
TEAEs	60 (2.26)	43 (1.27)	35 (1.06)
Serious TEAEs	2 (0.08)	3 (0.09)	3 (0.09)
Severe TEAEs	2 (0.08)	2 (0.06)	3 (0.09)
Moderate TEAEs	12 (0.45)	12 (0.36)	16 (0.48)
Mild TEAEs	46 (1.73)	29 (0.86)	16 (0.48)
TE ADRs	2 (0.08)	1 (0.03)	0
TEAEs leading to treatment discontinuation	0	0	0
TEAEs leading to trial withdrawal	0	0	0
Fatal AEs	0	0	0

AE, adverse event; INT, intermittent; MOL, molgramostim nebulizer solution; PBO, placebo; PY, patient-years; SAE, serious adverse event; TE ADR, treatment-emergent adverse drug reaction; TEAE, treatment-emergent adverse event.
[a]Based on the safety analysis set, N = 59.

Table 3. TEAEs Reported By ≥5% of Patients[a]

	MOL 300 µg Daily/ MOL 300 µg INT N = 15	MOL 300 µg INT/ MOL 300 µg INT N = 22	PBO/ MOL 300 µg INT N = 22
	n (%)		
Any TEAEs ≥5% of patients	13 (86.7)	8 (36.4)	11 (50.0)
Cough	4 (26.7)	3 (13.6)	0
Respiratory tract infection	3 (20.0)	1 (4.5)	0
Arthralgia	3 (20.0)	1 (4.5)	0
Nasopharyngitis	2 (13.3)	1 (4.5)	4 (18.2)
Dyspnea	2 (13.3)	1 (4.5)	0
Fatigue	2 (13.3)	0	1 (4.5)
Bronchitis	1 (6.7)	2 (9.1)	0
Alveolar proteinosis	1 (6.7)	1 (4.5)	2 (9.1)
Pneumonia	1 (6.7)	1 (4.5)	1 (4.5)
COVID-19	1 (6.7)	1 (4.5)	2 (9.1)

INT, intermittent; MOL, molgramostim nebulizer solution; PBO, placebo; TEAE, treatment-emergent adverse event.
[a]Based on the safety analysis set, N = 59.