OPSYNVI® (macitentan and tadalafil)
OPSYNVI - The A DUE Phase 3 Trial

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A DUE Study[1]

- A DUE was a prospective, multicenter, DB, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive phase 3 study (NCT03904693) that evaluated the efficacy and safety of OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies in patients with PAH.[1]
  - In the 70 patients who were randomized to OPSYNVI vs macitentan 10 mg monotherapy (OPSYNVI _M), the treatment effect was 0.71 (95% CL, 0.61-0.82; *P*<0.0001; 29% reduction) compared with macitentan monotherapy.
  - In the 86 patients who were randomized to OPSYNVI vs tadalafil 40 mg monotherapy (OPSYNVI _T), the treatment effect was 0.72 (95% CL, 0.64-0.80; *P*<0.0001; 28% reduction) compared with tadalafil monotherapy.

Subgroup Analysis[2,3]

- Two subgroup analysis of patients from the A DUE study were conducted:[2,3]
  - Based on background therapy status: A PVR reduction of 30% and 34% was observed among treatment-naïve patients who received OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies, respectively, at week 16. A PVR reduction of 32% and 19% was observed in patients with prior ERA therapy who received OPSYNVI vs macitentan 10 mg monotherapy and in patients with prior PDE-5i therapy who received OPSYNVI vs tadalafil 40 mg monotherapy, respectively, at week 16.[2]
  - Based on age, sex, region, and WHO FC: A prespecified analysis evaluated the efficacy (PVR) and safety of OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies.[3]

OL Interim Analysis[4]

- In an OL interim analysis, which evaluated the effect of OPSYNVI on exercise capacity (6MWD) and NT-proBNP, and its long-term safety and tolerability in patients with PAH, a sustained improvement in 6MWD and NT-proBNP was noted up to 12 months in the OL period.[4]

Post hoc Analysis[5]

- In a post hoc analysis, which evaluated the effect of OPSYNVI vs pooled monotherapy (macitentan or tadalafil) in treatment-naïve patients or those who were on prior monotherapy at randomization, there was an improvement in PVR, 6MWD and NT-proBNP from baseline to week 16 compared to pooled monotherapy in both groups.[5]

Note: 6MWD, 6-minute walk distance; CL, confidence limit; DB, double-blind; ERA, endothelin receptor antagonist; FC, functional class; NT-proBNP, N-terminal pro B-type natriuretic peptide; OL, open-label; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase-5 inhibitor; PVR, pulmonary vascular resistance; WHO, World Health Organization.

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A DUE Study[1,6]

- **A DUE** was a prospective, multicenter, DB, randomized, active-controlled, triple-dummy, parallel-group, group-sequential, adaptive phase 3 study (NCT03904693).
- The study evaluated the efficacy and safety of OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies in patients with PAH (including treatment-naïve patients and patients on ERA or PDE-5i monotherapy at baseline).

Key Eligibility Criteria[7]

- Adult patients (aged ≥18 years) with:
  - Idiopathic, heritable, drug- or toxin-induced PAH or
  - PAH associated with CTD, HIV infection, portal hypertension, or corrected congenital heart disease (simple systemic-to-pulmonary shunts ≥1 year after surgical repair)
- Patients in WHO FC II or III and had 6MWD between 100 m and 450 m.
- PAH-specific treatment naïve or on stable dose (≥3 months) of prior ERA[a] or PDE-5i[b] monotherapy before baseline RHC.

Study Design[1]

Tadalafil Titration Phase (Weeks 1-2)

- Patients received either macitentan 10 mg, tadalafil 20 mg, or both QD as separate tablets along with relevant placebos (to maintain blinding). In week 2, tadalafil was uptitrated to 40 mg QD.[c]

Maintenance Phase (Day 15 to Week 16)

- Patients received macitentan 10 mg, tadalafil 40 mg, or OPSYNVI QD (along with relevant placebos).[d]

OL Treatment Phase (24 Months)

- All patients were enrolled in a 24-month OL treatment phase following completion of 16-week DB treatment, where they received OPSYNVI.

Study Objectives[1]

- **Primary Endpoint:** Change in PVR from baseline to week 16.
- **Secondary Endpoint:** Changes in the following from baseline to week 16:
  - Exercise capacity (6MWD)
  - Cardiopulmonary and cardiovascular symptoms domain scores (PAH-SYMPACT questionnaire)
  - Absence of worsening in WHO FC

Primary Efficacy Results[1]

- OPSYNVI vs macitentan 10 mg monotherapy (OPSYNVI _M, n=70):
  - Treatment effect: 0.71 (95% CL, 0.61-0.82); *P*<0.0001
  - Reduction: 29% compared with macitentan monotherapy
- OPSYNVI vs tadalafil 40 mg monotherapy (OPSYNVI _T, n=86):
  - Treatment effect: 0.72 (95% CL, 0.64-0.80); *P*<0.0001
  - Reduction: 28% compared with tadalafil monotherapy

[a]Bosentan 250 mg total daily dose, macitentan 10 mg total daily dose, and ambrisentan 10 mg total daily dose.
[b]Sildenafil 60-120 mg total daily dose, tadalafil 40 mg total daily dose, and vardenafil 10 mg total daily dose.
[c]Patients on baseline PDE-5i therapy (tadalafil 40 mg, sildenafil 60-120 mg, or vardenafil 10 mg daily) were started on tadalafil 40 mg from day 1.
[d]Down titration of tadalafil to 20 mg was permitted for tolerability issues, while down titration of macitentan was not.
Note: 6MWD, 6-minute walk distance; CL, confidence limit; CTD, connective tissue disease; DB, double-blind; ERA, endothelin receptor antagonist; FC, functional class; HIV, human immunodeficiency virus; OL, open-label; OPSYNVI _M, OPSYNVI group used for comparison vs macitentan; OPSYNVI _T, OPSYNVI group used for comparison vs tadalafil; PAH, pulmonary arterial hypertension; PAH-SYMPACT, PAH-Symptoms and Impact; PDE-5i, Phosphodiesterase-5 inhibitor; PVR, pulmonary vascular resistance; QD, once daily; RHC, right heart catheterization; WHO, World Health Organization.

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Study Design[1,7]

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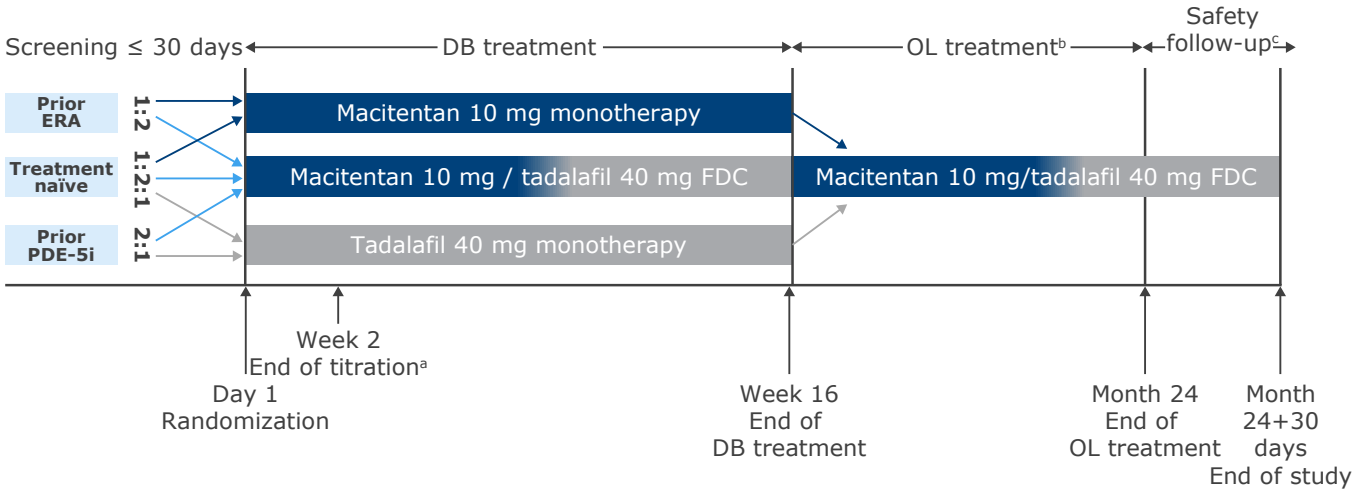

Primary Endpoint[1]

- Change in PVR from baseline to week 16

Secondary Endpoints[1]

Changes in the following from baseline to week 16:

- Exercise capacity (6MWD)
- Cardiopulmonary and cardiovascular symptoms domain scores (PAH-SYMPACT questionnaire)
- Absence of worsening in WHO FC

Exploratory Endpoints[1]

Changes in the following from baseline to week 16:

- NT-proBNP levels
- Hemodynamic variables measured by RHC: Systemic blood pressure, mPAP, mRAP, SvO2, systemic vascular resistance, TPR

[a]Titration period: Individual tablets of macitentan 10 mg and tadalafil 20 mg were given during week 1 and macitentan 10 mg and tadalafil 40 mg during week 2; from day 15, M/T FDC was given as a single tablet; tadalafil uptitration was not performed in patients receiving prior PDE-5i monotherapy.
[b]OL titration period: Patients who received macitentan 10 mg monotherapy in the DB treatment will receive individual tablets of macitentan 10 mg and tadalafil 20 mg in week 1 of the OL period, and tadalafil will be uptitrated to 40 mg in week 2. Patients who received tadalafil 40 mg monotherapy during the DB treatment will receive individual tablets of macitentan 10 mg and tadalafil 40 mg in weeks 1 and 2 of the OL period.
[c]Patients who prematurely discontinued the DB study treatment will continue until the end of safety follow-up but will not receive the OL treatment.

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Inclusion Criteria[7,a]

- Adult patients (aged ≥18 years) with:
  - Idiopathic, heritable, or drug- or toxin-induced PAH
  - PAH associated with CTD, HIV infection, portal hypertension, or corrected congenital heart disease (simple systemic-to-pulmonary shunts ≥1 year after surgical repair)
- Patients in WHO FC II or III and had a 6MWD between 100 m and 450 m
- Either PAH-specific treatment naïve or on stable dose (≥3 months) of prior ERA[b] or PDE-5i[c] monotherapy before baseline RHC

Exclusion Criteria[7,a]

- Patients who received treatment with:
  - Soluble guanylate cyclase stimulator, L-arginine, prostanoid, prostacyclin-receptor agonist within 3 months before starting the study treatment
  - Combination therapy with an ERA and a PDE-5i within 3 months before the study treatment or were intolerant to ERA/PDE-5i combination therapy
- Hypersensitivity to the study treatments or excipients of their formulations
- BMI >40 kg/m² at screening
- At least 3 risk factors for heart failure with preserved ejection fraction at screening:
  - BMI >30 kg/m²
  - Diabetes mellitus of any type
  - Essential hypertension
  - CAD; specific risk factors listed in the supplementary appendix
- Other conditions, including:
  - Moderate or severe obstructive/restrictive lung disease before screening
  - Significant aortic or mitral valve disease
  - Pericardial constriction
  - Restrictive or congestive left-sided cardiomyopathy
  - Life-threatening cardiac arrhythmias
  - Significant LV dysfunction or LV outflow obstruction
  - Permanent atrial fibrillation
  - Uncontrolled thyroid disease
  - Pulmonary veno-occlusive disease

[a]Please view the supplementary appendix for a complete list of inclusion/exclusion criteria.
[b]Bosentan 250 mg total daily dose, macitentan 10 mg total daily dose, and ambrisentan 10 mg total daily dose.
[c]Sildenafil 60-120 mg total daily dose, tadalafil 40 mg total daily dose, and vardenafil 10 mg total daily dose.

- Of the 294 patients screened between October 15, 2019, and August 23, 2022, 187 were randomized.[1]
- Overall, 108 patients were assigned to receive OPSYNVI, of whom 70 were randomized to OPSYNVI _M that was compared with the 10 mg macitentan monotherapy group (n=35) and 86 patients were randomized to OPSYNVI _T that was compared with the 40 mg tadalafil monotherapy group (n=44).[1]

Baseline Demographics and Characteristics[1]

Characteristic	OPSYNVI _M (n=70)	Macitentan (n=35)	OPSYNVI _T (n=86)	Tadalafil (n=44)
Female, n (%)	53 (75.7)	29 (82.9)	62 (72.1)	34 (77.3)
Age, mean (SD), years	51.8 (16.1)	51.3 (15.9)	48.7 (16.8)	51.3 (13.7)
Time from diagnosis of PAH, years				
Mean (SD)	1.5 (2.9)	3.2 (6.1)	1.4 (2.3)	0.9 (2.3)
Median (range)	0.14 (0.02-14.84)	0.10 (0.03-27.65)	0.16 (0.02-10.71)	0.33 (0.02-12.83)
PAH etiology, n (%)				
Idiopathic	36 (51.4)	16 (45.7)	47 (54.7)	20 (45.5)
Heritable	3 (4.3)	3 (8.6)	2 (2.3)	2 (4.5)
Drug- or toxin-induced	1 (1.4)	0	1 (1.2)	2 (4.5)
Associated with				
CTD	27 (38.6)	13 (37.1)	29 (33.7)	16 (36.4)
HIV	2 (2.9)	0	3 (3.5)	2 (4.5)
Corrected congenital heart disease	1 (1.4)	2 (5.7)	3 (3.5)	1 (2.3)
Portal hypertension	0	1 (2.9)	1 (1.2)	1 (2.3)
6MWD, mean (SD), m	354.3 (103.5)	347.2 (88.8)	351.0 (98.9)	361.8 (70.4)
WHO FC, n (%)				
II	42 (60.0)	11 (31.4)	51 (59.3)	19 (43.2)
III	28 (40.0)	24 (68.6)	35 (40.7)	25 (56.8)
PVR, dyn·s/cm^5				
Mean (SD)	845.3 (636.6)	827.2 (403.9)	888.7 (639.1)	812.4 (559.0)
Median (range)	632.1 (194-3888)	794.0 (265-1555)	729.6 (194-3888)	690.7 (244-3277)
NT-proBNP, ng/L, median[a] (range)	461.0 (51-23,662)	632.8 (51-5704)	466.1 (51-8420)	428.9 (51-6433)
PAH therapy at baseline, n (%)				
Treatment-naïve	49 (70)	24 (69)	49 (57)	25 (57)
Prior ERA[b]	21 (30)	11 (31)	-	-
Macitentan	10 (14)	5 (14)	-	-
Ambrisentan	7 (10)	3 (9)	-	-
Bosentan	4 (6)	3 (9)	-	-
Prior PDE-5i[b]	-	-	37 (43)	19 (43)[c]
Sildenafil	-	-	28 (33)	11 (25)
Tadalafil	-	-	5 (6)[d]	4 (9)
Sildenafil citrate	-	-	5 (6)	3 (7)

Note: Data presented for the full analysis set.
[a]OPSYNVI _M: (n=67); macitentan monotherapy (n=30); OPSYNVI _T (n=84); tadalafil monotherapy (n=42).
[b]Prior medication is defined as any treatment for which the end date is prior to the first dose of study treatment. Additional prior medications received were the following: OPSYNVI _M group: n=1 iloprost, n=1 riociguat, n=1 sildenafil, n=1 tadalafil; OPSYNVI _T group: n=1 riociguat. Some PAH-specific medications were received on the first day of study treatment: OPSYNVI _M group: n=1 macitentan; macitentan group: n=1 macitentan, n=1 bosentan; OPSYNVI _T group: n=1 sildenafil, n=1 sildenafil citrate; tadalafil group: n=1 sildenafil citrate.
[c]One prior PDE-5i patient had a missing therapy start date and was not included.
[d]One patient who was stratified incorrectly as treatment-naïve received tadalafil until 2 days prior to randomization.

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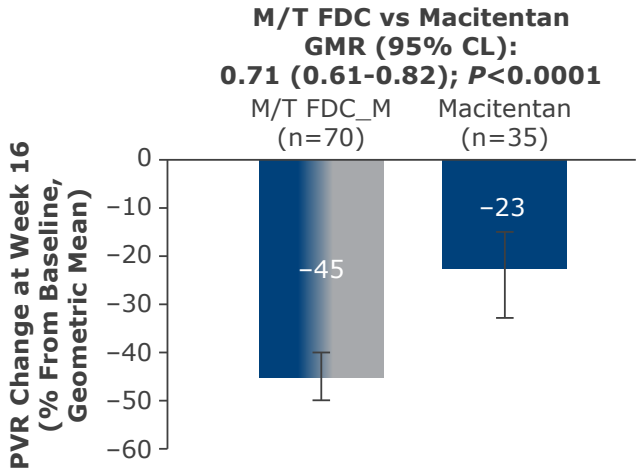
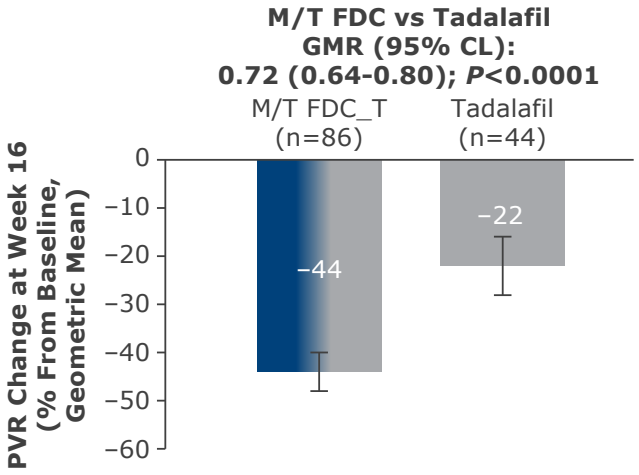
- In the OPSYNVI _M group, the treatment effect was 0.71 (95% CL, 0.61-0.82; *P*<0.0001; 29% reduction) compared to macitentan monotherapy. In the OPSYNVI _T group, the treatment effect was 0.72 (95% CL, 0.64-0.80; *P*<0.0001; 28% reduction) compared with tadalafil monotherapy.[1]

Change in PVR at Week 16[1]





Geometric Mean Change in PVR at Week 16[1]

	OPSYNVI _M (n=70)			Macitentan (n=35)			Treatment Effect, GMR (95% CL); *P* Value
	Baseline[a]	Week 16[a,b]	Change[c]	Baseline[a]	Week 16[a,b]	Change[c]	
PVR, dyn·s/cm^5	834.3 (630.9)	457.3 (329.3)	0.55 (0.50-0.60)	815.9 (401.2)	665.8 (381.9)	0.77 (0.69-0.87)	0.71 (0.61-0.82); <0.0001
	OPSYNVI _T (n=86)			Tadalafil (n=44)			Treatment Effect, GMR (95% CL); *P* Value
	Baseline[a]	Week 16[a,b]	Change[c]	Baseline[a]	Week 16[a,b]	Change[c]	
PVR, dyn·s/cm^5	884.7 (640.3)	513.2 (359.3)	0.56 (0.52-0.60)	802.1 (552.0)	640.3 (378.5)	0.78 (0.72-0.84)	0.72 (0.64-0.80); <0.0001

Data presented for the full analysis set.
[a]Mean (SD).
[b]Number of patients with missing data at week 16: OPSYNVI _M, n=3; macitentan, n=1; OPSYNVI _T, n=2; tadalafil, n=2; data were imputed for these patients.
[c]Geometric mean (95% CL) for the ratio of week 16/baseline PVR.

- In treatment naïve patients, the treatment effect of OPSYNVI (n=49) was 0.70 (95% CL, 0.58-0.84; *P*=0.0002; 30% reduction) and 0.66 (95% CL, 0.56-0.78; *P*<0.0001; 34% reduction) compared with macitentan (n=24) and tadalafil monotherapies (n=25), respectively. In patients receiving prior ERA, the treatment effect of OPSYNVI (n=21) was 0.68 (95% CL, 0.53-0.86; *P*=0.0025; 32% reduction) compared with macitentan monotherapy (n=11) and in patients receiving prior PDE-5i, the treatment effect of OPSYNVI (n=37) was 0.81 (95% CL, 0.70-0.94; *P*=0.0066; 19% reduction) compared with tadalafil monotherapy (n=19).[1]

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- Baseline to week 16 Improvement in 6MWD, mean (SD) 6MWD in all groups:[1]
  - OPSYNVI _M group: 52.9 (10.6) m
  - OPSYNVI _T group: 43.4 (8.4) m
  - Macitentan monotherapy group: 38.5 (11.9) m
  - Tadalafil monotherapy group: 15.9 (6.8) m
- The adjusted treatment effect (compared with monotherapies)[1]
  - OPSYNVI vs macitentan monotherapy: 16.0 m (95% CL, -17.0 to 49.1; *P*=0.380)
  - OPSYNVI vs tadalafil monotherapy: 25.4 m (95% CL, -0.9 to 51.6; *P*=0.059)
- There were improvements in cardiopulmonary and cardiovascular symptoms domain scores of the PAH-SYMPACT questionnaire from baseline to week 16; however, no differences between the groups were noted.[1]
  - Cardiopulmonary symptom score:
    - Treatment effect between OPSYNVI _M (n=66) and macitentan monotherapy (n=33) was -0.03 (95% CL, -0.21 to 0.15)
    - Treatment effect between OPSYNVI _T (n=81) and tadalafil monotherapy (n=42) was -0.04 (95% CL, -0.21 to 0.13)
  - Cardiovascular symptom score:
    - Treatment effect between OPSYNVI _M and macitentan monotherapy was 0.01 (95% CL, -0.17 to 0.19)
    - Treatment effect between OPSYNVI _T and tadalafil monotherapy was 0.02 (95% CL, -0.15 to 0.19)
- Assessment of WHO FC at week 16 was carried out separately in interim analysis and post-interim analysis patients.[1]
  - In the interim analysis group:
    - Absence of worsening was noted in 17 (94.4%) and 20 (90.9%) patients in the macitentan and tadalafil monotherapy groups, respectively, and in 29 (76.3%) and 41 (87.2%) patients in the OPSYNVI _M and OPSYNVI _T groups, respectively; there were no significant differences between the groups
  - In the post-interim analysis group:
    - Absence of worsening was observed in 17 (100%) and 21 (95.5%) patients in the macitentan and tadalafil monotherapy groups, respectively, and in 30 (93.8%) and 35 (89.7%) patients in the OPSYNVI _M and OPSYNVI _T groups, respectively; there were no significant differences between the groups.

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- NT-proBNP decreased in all groups from baseline, with greater reduction observed in the OPSYNVI groups.[1]
  - The treatment effect, GMR was 0.57 (95% CL, 0.41-0.80; *P*=0.0015) between OPSYNVI and macitentan monotherapy.
  - The treatment effect, GMR was 0.57 (95% CL, 0.42-0.77; *P*=0.0003) between OPSYNVI and tadalafil monotherapy.
- Changes in other hemodynamic variables favored the OPSYNVI treatment over macitentan and tadalafil monotherapies.[1]

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- Three patients died in the OPSYNVI group due to:[1]
  - Cardiac failure
  - Clostridium difficile gastroenteritis
  - COVID-19 pneumonia
- These deaths were determined to be unrelated to treatment by the investigators.[1]

Safety and Tolerability[1]

Characteristic	OPSYNVI (n=107)	Macitentan 10 mg Monotherapy (n=35)	Tadalafil 40 mg Monotherapy (n=44)
Mean (SD) exposure, weeks	14.9 (4.5)	16.9 (1.3)	16.0 (1.0)
Patients with ≥1 AE[a], n (%)	88 (82.2)	25 (71.4)	35 (79.5)
Patients with ≥1 SAE[a,b], n (%)	15 (14.0)	3 (8.6)	4 (9.1)
Patients with ≥1 AE leading to premature treatment discontinuation[a], n (%)	9 (8.4)	0	2 (4.5)
Patients with AEs[c], n (%)			
Headache	18 (16.8)	6 (17.1)	6 (13.6)
Peripheral edema	14 (13.1)	4 (11.4)	5 (11.4)
Diarrhea	5 (4.7)	0	6 (13.6)
Patients with AESI[a,d], n (%)			
Edema and fluid retention	22 (20.6)	5 (14.3)	7 (15.9)
Anemia[e]	20 (18.7)	1 (2.9)	1 (2.3)
Hypotension	8 (7.5)	0	0
Hepatic disorders	1 (0.9)	1 (2.9)	4 (9.1)

Data presented for the safety set (patients who received ≥1 dose of study drug).
[a]Treatment-emergent period spanned from the first intake of study drug in the DB treatment period until 30 days after the end of DB treatment or start of OL treatment.
[b]The most frequent SAEs reported in ≥1 patient in the OPSYNVI group were cardiac failure (n=2; 1.9%) and dyspnea (n=2; 1.9%).
[c]AEs experienced by ≥10% of patients in any group.
[d]Grouped terms.
[e]One patient with anemia required transfusion for improving hemoglobin levels. Except for 1, all cases of anemia were of mild/moderate severity.

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- **Grünig et al (2023)**[2] conducted a subgroup analysis of patients from the A DUE study based on their background therapy status (treatment-naïve, prior ERA, or prior PDE-5i) to evaluate the efficacy (PVR and 6MWD) and safety of OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies.
- Of the 108 patients randomized to OPSYNVI, 49 were treatment-naïve, 21 had prior ERA therapy and 37 had prior PDE-5i therapy. Of the 35 patients randomized to the macitentan group, 24 were treatment-naïve and 11 had prior ERA therapy. Of the 44 patients randomized to the tadalafil group, 25 were treatment-naïve and 19 had prior PDE-5i therapy.[2]

Baseline Demographics and Characteristics by Subgroup[2]

Characteristic	Treatment-Naïve			Prior ERA		Prior PDE-5i	
	M (n=24)	T (n=25)	OPSYNVI (n=49)	M (n=11)	OPSYNVI (n=21)	T (n=19)	OPSYNVI (n=37)
Female, n (%)	22 (91.7)	20 (80.0)	33 (67.3)	7 (63.6)	20 (95.2)	14 (73.7)	29 (78.4)
Age, mean (SD), years	51.0 (17.6)	52.6 (14.8)	53.1 (17.8)	52.0 (12.0)	48.9 (11.1)	53.8 (12.3)	42.8 (13.5)
6MWD, mean (SD), m	324.1 (96.0)	349.6 (81.6)	352.9 (111.0)	397.6 (39.4)	357.6 (85.7)	377.9 (50.0)	348.6 (81.4)
WHO FC, n (%)							
II	4 (16.7)	8 (32.0)	28 (57.1)	7 (63.6)	14 (66.7)	11 (57.9)	23 (62.2)
III	20 (83.3)	17 (68.0)	21 (42.9)	4 (36.4)	7 (33.3)	8 (42.1)	14 (37.8)
PVR, mean (SD), dyn·s/cm^5	908.9 (350.0)	921.8 (664.9)	842.2 (661.5)	649.0 (471.1)	852.4 (589.7)	668.4 (344.5)	950.3 (611.7)

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Change in 6MWD From Baseline to Week 16 by Subgroup[2]

	Treatment-Naïve[a]		Prior ERA[a]		Prior PDE-5i[a]	
	Change in 6MWD at Week 16	**(95% CL); *P* Value[b]**	**Change in 6MWD at Week 16**	**(95% CL); *P* Value[b]**	**Change in 6MWD at Week 16**	**(95% CL); *P* Value[b]**
OPSYNVI _M[c]	20.38 m	(-20.30 to 61.08); 0.3214	8.49 m	(-41.00 to 57.95); 0.7279	-	-
OPSYNVI _T[c]	33.04 m	(-5.31 to 71.39); 0.0902	-	-	25.89 m	(0.88-50.90); 0.0427

Note: Hyphens indicate blank cells implying values not determined or data not available.
[a]Missing data at Week 16 were imputed for the following: Treatment-naïve: OPSYNVI (n=1), macitentan (n=2), tadalafil (n=1); Prior ERA: OPSYNVI (n=2); Prior PDE-5i: OPSYNVI (n=1), tadalafil (n=2).
[b]p-values are exploratory and are not adjusted for adaptive design or multiplicity.
[c]The adjusted change from baseline differences for OPSYNVI vs macitentan 10mg and tadalafil 40mg (treatment effect), mean change and CLs are presented.

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Safety

- AEs, SAEs, and AEs leading to treatment discontinuation were reported more by treatment-naïve patients than those who had prior ERA or PDE-5i therapies.[2]

Safety and Tolerability by Subgroup[2]

Characteristic	Treatment-Naïve			Prior ERA		Prior PDE-5i	
	M (n=24)	T (n=25)	OPSYNVI (n=49)	M (n=11)	OPSYNVI (n=21)	T (n=19)	OPSYNVI (n=37)
Exposure, mean (SD), weeks	16.8 (1.3)	15.9 (1.1)	14.3 (5.3)	17.1 (1.5)	14.6 (5.2)	16.1 (0.7)	15.7 (2.8)
Patients with ≥1 AE, n (%)	17 (70.8)	20 (80.0)	43 (87.8)	8 (72.7)	16 (76.2)	15 (78.9)	29 (78.4)
Patients with ≥1 SAE, n (%)	2 (8.3)	3 (12.0)	8 (16.3)	1 (9.1)	3 (14.3)	1 (5.3)	4 (10.8)
Patients with ≥1 AE leading to premature discontinuation, n (%)	0	2 (8.0)	6 (12.2)	0	1 (4.8)	0	2 (5.4)
Patients with treatment-emergent AE leading to death[a], n (%)	0	0	0	0	1 (4.8)	0	1 (2.7)
Patients with AEs[b], n (%)							
Headache	3 (12.5)	3 (12.0)	8 (16.3)	3 (27.3)	4 (19.0)	3 (15.8)	6 (16.2)
Peripheral edema	4 (16.7)	4 (16.0)	7 (14.3)	0	2 (9.5)	1 (5.3)	5 (13.5)
Peripheral swelling	1 (4.2)	0	7 (14.3)	0	0	0	0
Cough	0	0	5 (10.2)	1 (9.1)	0	2 (10.5)	1 (2.7)
Anemia	0	0	5 (10.2)	0	1 (4.8)	0	2 (5.4)
Diarrhea	0	4 (16.0)	4 (8.2)	0	0	2 (10.5)	1 (2.7)
Dyspepsia	0	3 (12.0)	4 (8.2)	0	0	0	0
Back pain	1 (4.2)	2 (8.0)	3 (6.1)	0	2 (9.5)	2 (10.5)	0
Hemoglobin decreased	0	0	3 (6.1)	0	0	0	5 (13.5)
Hypotension	0	0	3 (6.1)	0	3 (14.3)	0	2 (5.4)
Myalgia	0	0	3 (6.1)	0	2 (9.5)	2 (10.5)	1 (2.7)
Arthralgia	2 (8.3)	4 (16.0)	2 (4.1)	0	0	0	2 (5.4)
COVID-19	2 (8.3)	0	2 (4.1)	0	0	2 (10.5)	1 (2.7)
Pain in extremity	0	3 (12.0)	1 (2.0)	0	1 (4.8)	0	1 (2.7)
Noncardiac chest pain	0	1 (4.0)	1 (2.0)	0	1 (4.8)	2 (10.5)	1 (2.7)
Patients with AESIs, n (%)							
Edema and fluid retention	5 (20.8)	4 (16.0)	15 (30.6)	0	2 (9.5)	3 (15.8)	5 (13.5)
Anemia	1 (4.2)	1 (4.0)	11 (22.4)	0	1 (4.8)	0	8 (21.6)
Hypotension	0	0	3 (6.1)	0	3 (14.3)	0	2 (5.4)
Hepatic disorders	1 (4.2)	3 (12.0)	0	0	0	1 (5.3)	1 (2.7)
Hemoglobin[c], n (%)							
<8 g/dL	0	0	2 (4.4)	0	0	0	0
<10 g/dL	1 (4.2)	0	5 (11.1)	0	1 (5.6)	0	5 (13.5)
Decrease from baseline ≥5 g/dL	0	0	3 (6.7)	0	0	0	0
ALT/AST ≥3×ULN, n (%)	0	2 (8.0)	0	0	0	0	1 (2.7)

Note: Analyses were performed in the safety set which included all patients who received at least 1 dose of the study treatment.
[a]Treatment-emergent period was defined as the first intake of the study treatment in the DB period up to and including minimum of end-of-treatment of the DB plus 30 days or the start date of OL treatment. In total, 3 deaths were reported in the study and were judged by the investigators as unrelated to treatment: n=1 cardiac failure, prior ERA/OPSYNVI group; n=1 clostridium difficile gastroenteritis, prior PDE-5i/OPSYNVI group; n=1 COVID-19 pneumonia (off-treatment), treatment-naïve/OPSYNVI group.
[b]AEs by preferred term experienced by ≥10% of patients in any group.
[c]n=45 in the treatment-naïve OPSYNVI group and n=18 in the prior ERA OPSYNVI group.

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- **Jansa et al (2023)**[3] conducted a prespecified subgroup analysis of patients from the A DUE study based on age, sex, region, and WHO FC to evaluate the efficacy (PVR) and safety of OPSYNVI vs macitentan 10 mg and tadalafil 40 mg monotherapies.

Patient Characteristics by Age[3]

Characteristic	18-64 Years				≥65 Years			
	OPSYNVI_M (n=53)	M (n=27)	OPSYNVI_T (n=67)	T (n=34)	OPSYNVI_M (n=53)	M (n=27)	OPSYNVI_T (n=67)	T (n=34)
Female, n (%)	41 (77.4)	23 (85.2)	49 (73.1)	26 (76.5)	12 (70.6)	6 (75.0)	13 (68.4)	8 (80.0)
Age, mean (SD), years	45.8 (13.6)	45.2 (12.4)	42.3 (13.0)	48.0 (10.8)	70.6 (5.1)	72.0 (4.0)	71.1 (5.1)	70.6 (4.7)
PVR, mean (SD), dyn.s/cm^5	935.4 (683.6)	904.0 (414.1)	982.1 (676.4)	859.6 (596.7)	564.4 (343.8)	568.3 (236.8)	559.5 (323.3)	652.1 (387.9)

Patient Characteristics by Sex[3]

Characteristic	Male				≥65 Years			
	OPSYNVI_M (n=17)	M (n=27)	OPSYNVI_T (n=67)	T (n=34)	OPSYNVI_M (n=53)	M (n=29)	OPSYNVI_T (n=62)	T (n=34)
Age, mean (SD), years	49.4 (19.2)	53.8 (15.8)	49.5 (17.4)	56.0 (16.0)	52.6 (15.1)	50.8 (16.1)	48.3 (16.7)	52.3 (13.0)
PVR, mean (SD), dyn.s/cm^5	857.7 (648.6)	841.1 (415.3)	831.0 (575.0)	918.9 (493.2)	841.3 (638.9)	824.4 (408.9)	911.0 (665.4)	781.1 (580.0)

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Patient Characteristics by Region[3]

Characteristic	US				Non-US			
	OPSYNVI_M (n=10)	M (n=4)	OPSYNVI_T (n=13)	T (n=13)	OPSYNVI_M (n=60)	M (n=31)	OPSYNVI_T (n=73)	T (n=31)
Female, n (%)	9 (90.0)	3 (75.0)	11 (84.6)	9 (69.2)	44 (73.3)	26 (83.9)	51 (69.9)	25 (80.6)
Age, mean (SD), years	55.4 (14.7)	51.3 (19.7)	55.3 (14.4)	56.8 (11.9)	51.2 (16.4)	51.4 (15.7)	47.5 (17.0)	51.6 (14.2)
PVR, mean (SD), dyn.s/cm^5	1001.4 (433.1)	709.4 (456.2)	953.2 (409.9)	677.8 (227.8)	819.2 (663.7)	842.4 (402.4)	877.2 (673.3)	868.9 (645.0)

Patient Characteristics by WHO FC[3]

Characteristic	FC II				FC III			
	OPSYNVI_M (n=42)	M (n=11)	OPSYNVI_T (n=51)	T (n=19)	OPSYNVI_M (n=28)	M (n=24)	OPSYNVI_T (n=35)	T (n=25)
Female, n (%)	31 (73.8)	10 (90.9)	35 (68.6)	16 (84.2)	22 (78.6)	19 (79.2)	27 (77.1)	18 (72.0)
Age, mean (SD), years	51.1 (15.9)	52.7 (10.0)	48.6 (15.6)	53.5 (12.4)	52.9 (16.6)	50.7 (18.1)	48.7 (18.6)	52.8 (14.8)
PVR, mean (SD), dyn.s/cm^5	689.2 (465.3)	550.6 (368.9)	750.2 (507.6)	763.6 (687.7)	1079.4 (782.3)	954 (358.6)	1090.6 (756)	849.5 (449.4)

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Change in PVR at Week 16 by Prespecified Subgroups[3]

Characteristic	OPSYNVI_M (n/n)	GMR LS (95% CL)	$P_{interaction}$ Value	OPSYNVI_T (n/n)	GMR LS (95% CL)	$P_{interaction}$ Value
All patients	70/35	0.71 (0.61-0.82)	-	86/44	0.73 (0.65-0.81)	-
Age						
18-64 years	53/27	0.67 (0.57-0.79)	0.1695	67/34	0.69 (0.61-0.78)	0.0724
65 years	17/8	0.82 (0.57-1.17)		19/10	0.89 (0.66-1.19)	
Sex						
Female	53/29	0.72 (0.62-0.84)	0.4833	62/34	0.71 (0.63-0.80)	0.3935
Male	17/6	0.58 (0.33-1.00)		24/10	0.80 (0.60-1.07)	
Race						
White	48/20	0.75 (0.62-0.90)		52/29	0.76 (0.65-0.88)	
Black or African American	2/1	-	0.1677	2/2	0.81 (0.24-2.71)	0.8477
Asian	17/12	0.59 (0.46-0.76)		30/11	0.71 (0.60-0.84)	
Other	1/0	-		1/0	-	
Region						
US	10/4	0.81 (0.45-1.43)	0.4246	13/13	0.79 (0.59-1.07)	0.3526
Non-US	60/31	0.69 (0.59-0.81)		73/31	0.70 (0.62-0.80)	
WHO FC						
II	42/11	0.73 (0.58-0.92)	0.6219	51/19	0.74 (0.64-0.86)	0.7053
III	28/24	0.68 (0.55-0.84)		35/25	0.70 (0.59-0.84)	

Note: GMRs could not be calculated for some groups due to small patient numbers.

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AEs by Age[3]

Characteristic	18-64 Years				≥65 Years			
	OPSYNVI_M (n=53)	M (n=27)	OPSYNVI_T (n=67)	T (n=34)	OPSYNVI_M (n=17)	M (n=8)	OPSYNVI_T (n=19)	T (n=10)
Exposure, mean (SD), weeks	14.8 (5.1)	16.9 (1.3)	15.3 (4.1)	16.1 (1.1)	13.2 (5.5)	16.7 (1.4)	13.5 (5.3)	15.8 (0.3)
Patients with ≥1 AE, n (%)	44 (83.0)	20 (74.1)	55 (82.1)	28 (82.4)	15 (88.2)	5 (62.5)	17 (89.5)	7 (70.0)
Patients with ≥1 SAE, n (%)	5 (9.4)	3 (11.1)	5 (7.5)	2 (5.9)	6 (35.3)	0	7 (36.8)	2 (20.0)
Patients with ≥1 AE leading to treatment discontinuation, n (%)	4 (7.5)	0	5 (7.5)	2 (5.9)	3 (17.6)	0	3 (15.8)	0

AEs by Sex[3]

Characteristic	Male				Female			
	OPSYNVI_M (n=17)	M (n=6)	OPSYNVI_T (n=24)	T (n=10)	OPSYNVI_M (n=53)	M (n=29)	OPSYNVI_T (n=62)	T (n=34)
Exposure, mean (SD), weeks	16.2 (2.8)	17.5 (1.5)	16.1 (2.3)	16.2 (0.7)	13.8 (5.7)	16.7 (1.3)	14.5 (4.9)	15.9 (1.0)
Patients with ≥1 AE, n (%)	14 (82.4)	5 (83.3)	20 (83.3)	9 (90.0)	45 (84.9)	20 (69.0)	52 (83.9)	26 (76.5)
Patients with ≥1 SAE, n (%)	4 (23.5)	2 (33.3)	5 (20.8)	2 (20.0)	7 (13.2)	1 (3.4)	7 (11.3)	2 (5.9)
Patients with ≥1 AE leading to treatment discontinuation, n (%)	1 (5.9)	0	1 (4.2)	0	6 (11.3)	0	7 (11.3)	2 (5.9)

AEs by Region[3]

Characteristic	US				≥65 Years			
	OPSYNVI_M (n=10)	M (n=4)	OPSYNVI_T (n=13)	T (n=13)	OPSYNVI_M (n=60)	M (n=31)	OPSYNVI_T (n=73)	T (n=31)
Exposure, mean (SD), weeks	16.6 (0.9)	16.3 (1.2)	16.3 (1.0)	16.0 (0.7)	14.0 (5.5)	16.9 (1.3)	14.7 (4.7)	16.0 (1.1)
Patients with ≥1 AE, n (%)	10 (100.0)	4 (100.0)	13 (100.0)	11 (84.6)	49 (81.7)	21 (67.7)	59 (80.8)	24 (77.4)
Patients with ≥1 SAE, n (%)	0	0	0	1 (7.7)	11 (18.3)	3 (9.7)	12 (16.4)	3 (9.7)
Patients with ≥1 AE leading to treatment discontinuation, n (%)	1 (10.0)	0	1 (7.7)	0	6 (10.0)	0	7 (9.6)	2 (6.5)

AEs by WHO FC[3]

Characteristic	FC II				FC III			
	OPSYNVI_M (n=42)	M (n=11)	OPSYNVI_T (n=51)	T (n=19)	OPSYNVI_M (n=28)	M (n=24)	OPSYNVI_T (n=35)	T (n=25)
Exposure, mean (SD), weeks	14.5 (5.4)	16.7 (1.3)	14.8 (4.9)	16.2 (0.6)	14.2 (5.0)	16.9 (1.3)	15.2 (3.7)	15.8 (1.1)
Patients with ≥1 AE, n (%)	36 (85.7)	9 (81.8)	44 (86.3)	14 (73.7)	23 (82.1)	16 (66.7)	28 (80.0)	21 (84.0)
Patients with ≥1 SAE, n (%)	8 (19.0)	1 (9.1)	8 (15.7)	1 (5.3)	3 (10.7)	2 (8.3)	4 (11.4)	3 (12.0)
Patients with ≥1 AE leading to treatment discontinuation, n (%)	4 (9.5)	0	6 (11.8)	0	3 (10.7)	0	2 (5.7)	2 (8.0)

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- **Chin et al (2024)**[4] conducted an interim analysis of the ongoing 24-month OL period (data cutoff, April 28, 2023) of the phase 3 A DUE study evaluating the effect of OPSYNVI on exercise capacity (6MWD), NT-proBNP, and its long-term safety and tolerability in patients with PAH.
- A total of 185 patients received OPSYNVI in the DB and/or OL period, of whom 113 continued to the OL period.[4]

Baseline Demographics and Characteristics of Patients in the Interim Analysis[4]

Characteristic	OPSYNVI (DB and/or OL)[a] n=185	OPSYNVI (in DB)[b] n=107
Female, n (%)	144 (77.8)	82 (76.6)
Age, mean (SD), years	50.2 (15.4)	48.7 (15.8)
Time from diagnosis of PAH, years		
Mean (SD)	2.0 (3.6)	1.8 (2.8)
Median (range)	0.46 (0.02-28.0)	0.41 (0.02-14.84)
PAH etiology, n (%)		
Idiopathic	93 (50.3)	58 (54.2)
Heritable	9 (4.9)	4 (3.7)
Drug- or toxin-induced	3 (1.6)	1 (0.9)
Associated with		
CTD	65 (35.1)	36 (33.6)
HIV	6 (3.2)	4 (3.7)
Corrected congenital heart disease	6 (3.2)	3 (2.8)
Portal hypertension	3 (1.6)	1 (0.9)
6MWD, mean (SD), m	366 (91.4)	352 (96.1)
WHO FC, n (%)[c]		
I	6 (3.2)[c]	0
II	109 (58.9)	65 (60.7)
III	70 (37.8)	42 (39.3)
PVR, mean (SD), dyn·s/cm^5	777 (548.0)	882 (627.2)
NT-proBNP, median (range), ng/L[d]	435 (51-23,662)	426 (51-23,662)

[a]Data are presented for the combined safety set of patients who received OPSYNVI at any time in the DB and/or ongoing OL period (April 2023 data cutoff); baseline was defined as the last assessment prior to the first intake of OPSYNVI (or titration dose) in either the DB or OL period.
[b]Data are presented for patients who received at least 1 dose of OPSYNVI in the DB period6; baseline was defined as the last nonmissing assessment performed on or before the DB study treatment start date.
[c]A DUE included patients in FC II and III only; FC I patients here reflect patients who improved while in the study.
[d]OPSYNVI (DB and/or OL), n=179; OPSYNVI (in DB), n=104.

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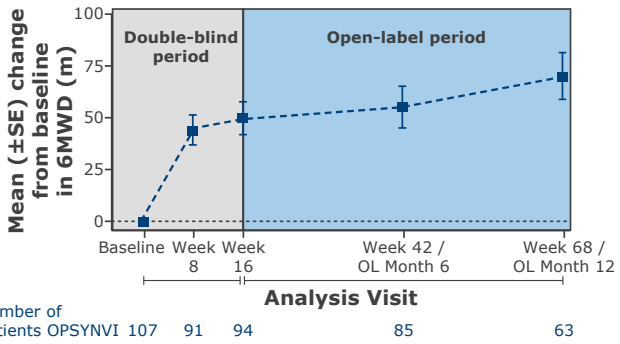
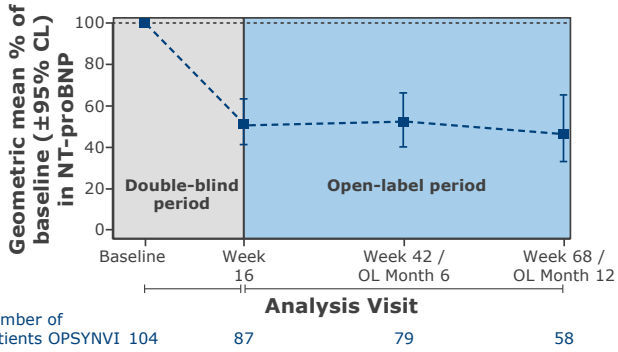
- At 12 months, a sustained improvement was reported in 6MWD (OL period).[4]
- Reduction in NT-proBNP was reported during DB period and in OL period it remained stable up to 12 months.[4]

Mean Change From Baseline in 6MWD[4]



Data are presented for patients with nonmissing values at both baseline and postbaseline who started treatment with OPSYNVI in the DB period (N=107).

Geometric Mean Percentage of Baseline in NT-proBNP[4]



Data are presented for patients with nonmissing values at both baseline and postbaseline who were randomized to receive OPSYNVI for the DB period (N=104).

All-Cause and PAH-Related Hospitalizations in the DB and OL Periods[4]

Characteristic	OPSYNVI (in DB)[a] n=107
Patient-years in study	154.3
Exposure, median (range), weeks	74.4 (0.6-151.6)
All-cause hospitalizations	
Hospitalizations per person-year	0.3
Inpatient hospital days per person-year	2.8
PAH-related hospitalizations	
Hospitalizations per person-year	0.1
Inpatient hospital days per person-year	0.9

Medical encounters considered hospitalizations were intensive care unit, hospice/palliative care unit, hospital inpatient department, long-term care facility, and rehabilitation center. Hospitalization events were not clinical event committee adjudicated.
[a]Data are presented for patients who received at least 1 dose of OPSYNVI in the DB period (April 2023 data cutoff).

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- A total of 6 deaths occurred, which were considered unrelated to treatment, and 2 were non-treatment emergent.[4]

Safety and Tolerability in the Interim Analysis[4]

Characteristic	OPSYNVI (DB and/or OL)[a] n=185
Exposure, median (range), weeks	75.4 (0.6-151.6)
Patients with ≥1 AE, n (%)	173 (93.5)
Patients with ≥1 SAE, n (%)	49 (26.5)
Patients with ≥1 AE leading to premature discontinuation, n (%)	17 (9.2)
AEs (preferred term), n (%)[b]	
COVID-19	43 (23.2)
Headache	27 (14.6)
Peripheral edema	21 (11.4)
Anemia	20 (10.8)
Patients with AESIs (grouped terms), n (%)	
Anemia	43 (23.2)
Edema and fluid retention	34 (18.4)
Hypotension	12 (6.5)
Hepatic disorders	10 (5.4)
Patients with low hemoglobin, n (%)[c]	
<8 g/dL	4 (2.3)
<10 g/dL	26 (14.7)
Decrease from baseline ≥5 g/dL	5 (2.8)
Patients with liver abnormalities, n (%)[d]	
ALT/AST ≥3×ULN	7 (3.9)
Deaths (preferred term), n (%)[e]	4 (2.2)
Gastroenteritis clostridial (DB)	1 (0.5)
Cardiac failure (DB)	1 (0.5)
Right ventricular failure (OL)	1 (0.5)
Respiratory failure (OL)	1 (0.5)

[a]Data are presented for the combined safety set of patients who received OPSYNVI at any time in the DB and/or ongoing OL period. Treatment emergent safety events with OPSYNVI are described; treatment-emergent defined as from first intake of study treatment up to end of treatment, + 30 days post treatment.
[b]Occurring in >10% patients.
[c]n=177.
[d]n=178.
[e]Not including 2 deaths (COVID-19 pneumonia and cerebrovascular accident) that occurred >30 days after end of treatment (97 and 398 days, respectively).

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- **Grünig et al (2024)[5]** conducted a post hoc analysis of patients who were treatment-naïve or on prior monotherapy at randomization, to evaluate the effect of OPSYNVI vs pooled monotherapy (macitentan or tadalafil) at treatment initiation and at escalation.
- Please refer to the baseline characteristics of Grünig et al (2023) subgroup analysis for detailed information on patient disposition.

Baseline Demographics and Characteristics by Background Treatment Status[5]

Characteristic	Treatment-Naïve		Prior Treated	
	OPSYNVI (n=49)	Pooled Monotherapy (n=49)	OPSYNVI (n=58)	Pooled Monotherapy (n=30)
Female, n (%)	33 (67.3)	42 (85.7)	49 (84.5)	21 (70.0)
Age, mean (SD), years	53.1 (17.8)	51.8 (16.1)	45.0 (12.9)	53.1 (12.0)
Time from diagnosis of PAH, mean (SD), years	0.5 (1.5)	1.4 (4.5)	2.9 (3.2)	2.8 (4.5)
6MWD, mean (SD), m	353 (111.0)	337 (88.9)	352 (82.4)	385 (46.7)
WHO FC, n (%)				
II	27 (14.6)	12 (24.5)	37 (63.8)	18 (60.0)
III	21 (11.4)	37 (75.5)	21 (36.2)	12 (40.0)
PVR, mean (SD), dyn·s/cm^5	20 (10.8)	916 (528.9)	915 (600.5)	661 (387.6)
NT-proBNP, median (range)[a], ng/L	20 (10.8)	684 (51-6433)	234 (51-23,662)	338 (51-4604)

[a]Treatment-naïve: OPSYNVI (n=47), pooled monotherapy (n=44); prior treated: OPSYNVI (n=57), pooled monotherapy (n=28).

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- There was an improvement in PVR, 6MWD and NT-proBNP from baseline to week 16 with OPSYNVI compared to pooled monotherapy in both groups, which are summarized in the table below.[5]

Change From Baseline to Week 16 in Efficacy Variables With OPSYNVI[5]

Characteristic	Treatment-Naïve			Prior Treated		
	OPSYNVI (n=49)	Pooled Monotherapy (n=49)	*P* value[a]	OPSYNVI (n=58)	Pooled Monotherapy (n=30)	*P* value[a]
Change in PVR[b]	-49	-28	<0.0001	-35	-13	<0.0001
Reduction, %	32			24		
GMR (95% CL)[c]	0.68 (0.60-0.78)			0.76 (0.67-0.86)		
Mean change in 6MWD[d]	54.8	28.5	0.0791	39.4	18.3	0.0940
Mean (SE)[e] , m	26.2 (-3.1 to 55.5)			21.1 (-3.7 to 45.9)		
Characteristic	**OPSYNVI (n=49)**	**Pooled Monotherapy (n=49)**	***P* value[a]**	**OPSYNVI (n=58)**	**Pooled Monotherapy (n=30)**	***P* value[a]**
Change in NT-proBNP[f]	-62	-38	0.0020	-24	6	0.0353
Reduction, %	41			27		
GMR (95% CL)[c]	0.59 (0.43-0.82)			0.73 (0.55-0.98)		

[a]P values are exploratory and not adjusted for adaptive design or multiplicity.
[b]Missing data at Week 16 were imputed for the following: treatment-naïve: OPSYNVI (n=1), pooled monotherapy (n=2); prior treated: OPSYNVI (n=3), pooled monotherapy (n=1).
[c]Adjusted geometric mean ratio of end of double-blind treatment to baseline for OPSYNVI vs pooled monotherapy.
[d]Missing data at week 16 were imputed for the following: treatment-naïve: OPSYNVI (n=1), pooled monotherapy (n=3); prior treated: OPSYNVI (n=3), pooled monotherapy (n=2).
[e]Adjusted change (least squares mean) from baseline difference for OPSYNVI vs pooled monotherapy.
[f]Missing data at week 16 were imputed for the following: treatment-naïve: OPSYNVI (n=6), pooled monotherapy (n=2); prior treated: OPSYNVI (n=6), pooled monotherapy (n=2).

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6MWD	6-minute walk distance	**M/T FDC**	Macitentan/tadalafil fixed-dose combination
AE	Adverse event	**NT-proBNP**	N-terminal pro B-type natriuretic peptide
AESI	Adverse event of special interest	**OL**	Open-label
ALT	Alanine aminotransferase	**OPSYNVI_M**	OPSYNVI group used for comparison vs macitentan
AST	Aspartate aminotransferase	**OPSYNVI_T**	OPSYNVI group used for comparison vs tadalafil
BMI	Body mass index	**PAH**	Pulmonary arterial hypertension
CL	Confidence limit	**PAH-SYMPACT**	Pulmonary Arterial Hypertension-Symptoms and Impact
COVID-19	Coronavirus disease 2019	**PDE-5i**	Phosphodiesterase type-5 inhibitor
CTD	Connective tissue disease	**PVR**	Pulmonary vascular resistance
DB	Double-blind	**QD**	Once daily
ERA	Endothelin receptor antagonist	**RHC**	Right heart catheterization
FC	Functional class	**SAE**	Serious adverse event
FDC	Fixed-dose combination	**SD**	Standard deviation
GMR	Geometric mean ratio	**SE**	Standard error
HIV	Human immunodeficiency virus	**SvO2**	Mixed venous oxygen saturation
LS	Least squares	**TPR**	Total pulmonary resistance
LV	Left ventricular	**ULN**	Upper limit of normal
mPAP	Mean pulmonary arterial pressure	**US**	United States
mRAP	Mean right atrial pressure	**WHO**	World Health Organization

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A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT® (and/or other resources, including internal/external databases) was conducted on 03 March 2025.

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1. Grünig E, Jansa P, Fan F, et al. Randomized trial of macitentan/tadalafil single-tablet combination therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2024;83(4):473-484.

2. Grünig E, Jansa P, Fan F, et al. Macitentan tadalafil fixed dose combination (FDC) in treatment-naïve and prior monotherapy patients with pulmonary arterial hypertension (PAH): insights from A DUE. Poster presented at: European Society of Cardiology (ESC) Congress; August 25-28, 2023; Amsterdam, Netherlands.

3. Jansa P, Chin K, Grünig E, et al. Macitentan tadalafil fixed dose combination (FDC) in patients with pulmonary arterial hypertension (PAH): a subgroup analysis from A DUE. Poster presented at: European Respiratory Society (ERS) 2023 Congress; September 9-13, 2023; Milan, Italy.

4. Chin KM, Jansa P, Grünig E, et al. Effect on exercise capacity and long-term safety and tolerability of macitentan and tadalafil as a single-tablet combination in patients with pulmonary arterial hypertension from the A DUE open-label interim analysis. Oral Presentation presented at: American Thoracic Society (ATS) Conference; May 17-22, 2024; San Diego, CA.

5. Grünig E, Fan F, Chin KM, et al. Efficacy of macitentan/tadalafil single-tablet combination therapy vs pooled monotherapy in pulmonary arterial hypertension (PAH): A DUE post hoc analysis. Poster presented at: European Respiratory Society (ERS) 2024 Congress; September 7–11, 2024; Vienna, Austria.

6. Chin K, Jansa P, Fan F, et al. Efficacy and safety of macitentan tadalafil fixed dose combination in pulmonary arterial hypertension: results from the randomized controlled phase III A DUE study. Oral Presentation presented at: American College of Cardiology 2023 Annual Scientific Session & Expo Together With World Congress of Cardiology (ACC.23/WCC); March 4-6, 2023; New Orleans, LA.

7. Grünig E, Jansa P, Fan F, et al. Supplement to: Randomized trial of macitentan/tadalafil single-tablet combination therapy for pulmonary arterial hypertension. *J Am Coll Cardiol*. 2024;83(4):473-484.