SSc-PAH: AN INVISIBLE BUT FATAL DISEASE

YOUR EARLY INTERVENTION COULD EXTEND LIVES

For further information regarding Opsumit® (macitentan) or Uptravi® (Selexipag) including indication and adverse effects please refer to the Israeli MOH prescribing information: https://israeldrugs.health.gov.il/#!/byDrug

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PATIENTS WITH SSc ARE AT HIGH RISK OF DEVELOPING PAH[1]

Pulmonary arterial hypertension (PAH) is a severe, progressive and fatal disease characterised by elevated pulmonary arterial pressure, leading to right heart failure and death[2]

APPROXIMATELY 1 IN 10 PATIENTS WITH SYSTEMIC SCLEROSIS (SSc) ARE ESTIMATED TO DEVELOP PAH[3]

PAH IS A SEVERE AND OFTEN FATAL COMPLICATION OF SSc[4]

PAH, pulmonary arterial hypertension; SSc, systemic sclerosis

PAH IS A LEADING CAUSE OF DEATH IN PATIENTS WITH SSc[5]

PAH ACCOUNTS FOR

>50%

OF DEATHS IN SSc-PAH PATIENTS[5]

EARLIER DIAGNOSIS OF SSc-PAH IS ESSENTIAL TO IMPROVING OUTCOMES FOR YOUR PATIENTS[6]

PAH, pulmonary arterial hypertension; SSc, systemic sclerosis

EARLY SCREENING AND REFERRAL IMPROVE SURVIVAL OUTCOMES[6]

AT 8 YEARS, THERE IS A DIFFERENCE OF

47%

IN SURVIVAL RATES BETWEEN PATIENTS DIAGNOSED DURING ROUTINE CLINICAL PRACTICE AND THOSE DIAGNOSED USING SCREENING[6]

GUIDELINES RECOMMEND ANNUAL SCREENING FOR PAH IN SSc

2015 ESC/ERS PH guidelines:
Resting echo is recommended as a screening test in asymptomatic patients with SSc, followed by **annual screening** with echo, DLCO and biomarkers[7]

6th World Symposium on Pulmonary Hypertension:
Supports recommendation for **annual screening** for PAH in patients with scleroderma spectrum diseases[8]

Recommendations for screening and detection of CTD-PAH:
Every patient with SSc should be **screened annually** for PAH due to the high prevalence of PAH in SSc[9]

CTD, connective tissue disease; DLCO, carbon monoxide diffusing capacity; ERS, European Respiratory Society; ESC, European Society of Cardiology; PAH, pulmonary arterial hypetension; PH, pulmonary hypertension; SSc, systemic sclerosis

START AHEAD WITH OPSUMIT – AN ORAL ERA WITH PROVEN BENEFICIAL AND SUSTAINED LONG-TERM OUTCOMES IN PAH[11–14]

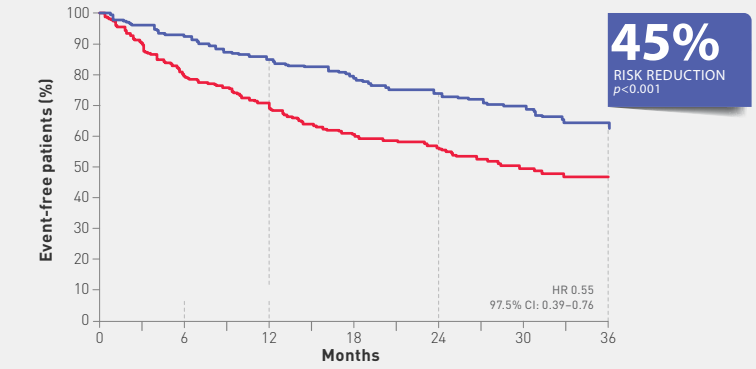
Opsumit® macitentan

The SERAPHIN study is the first and only study to demonstrate a statistically significant long-term benefit with an endothelin receptor antagonist (ERA) vs placebo in PAH based on a composite morbidity-mortality primary endpoint*[11]

31% of patients in SERAPHIN had CTD-PAH[11]

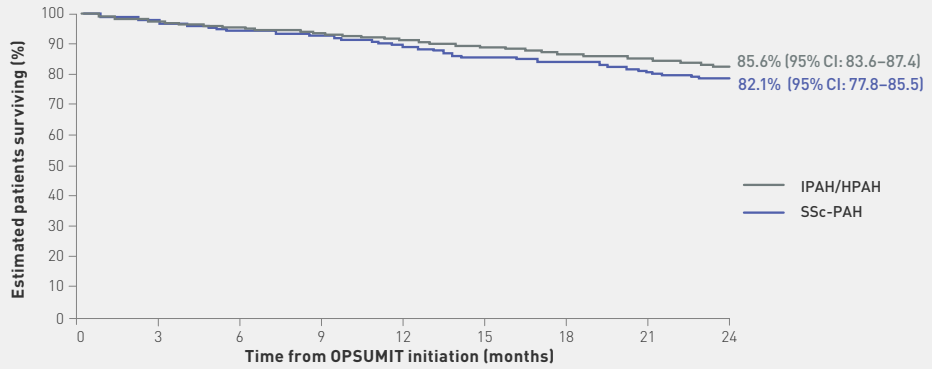
Real-world data from the OPUS and OrPHeUS registries* support the use of OPSUMIT in SSc-PAH, showing similar clinical outcomes in patients with SSc-PAH and patients with idiopathic PAH (IPAH)/heritable PAH (HPAH)[16,17]

OPSUMIT REDUCES THE RISK OF A MORBIDITY OR MORTALITY EVENT* IN PATIENTS WITH PAH VS PLACEBO[11]



Adapted from Pulido *et al.* 2013[11]

REAL-WORLD DATA SUPPORT THE EFFECTIVENESS OF OPSUMIT IN PATIENTS WITH SSc-PAH[17]



Adapted from McLaughlin *et al.* 2019[17]

CONSISTENT WITH THE PRIMARY ENDPOINT, OPSUMIT REDUCED THE RISK OF A MORBIDITY-MORTALITY EVENT* IN **PATIENTS WITH CTD-PAH BY 42% VS PLACEBO****[15]

CI, confidence interval; CTD, connective tissue disease; ERA, endothelin receptor antagonist; HR, hazard ratio; PAH, pulmonary arterial hypertension
*As measured by a composite primary morbidity-mortality endpoint. Results were driven by a decrease in PAH worsening and do not apply to mortality on its own.[11]
**HR 0.58; 95% CI: 0.33–1.02.[15]

OPSUMIT IMPROVES LONG-TERM OUTCOMES IN PAH AND SHOWS **EFFECTIVENESS IN A BROAD PATIENT POPULATION**, INCLUDING PATIENTS WITH **SSc-PAH**[11,12–22]

Adverse events observed in SERAPHIN that were more frequently associated with OPSUMIT included anaemia, bronchitis, headache, oedema and nasopharyngitis.[12] For full safety and tolerability information, please consult the OPSUMIT Prescribing Information.

CI, confidence interval; HPAH, heritable pulmonary arterial hypertension; IPAH, idiopathic pulmonary arterial hypertension; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis
*The OPUS registry included PAH patients with comorbidities including hypertension, oedema, diabetes mellitus, anaemia, signs of right heart failure, autoimmune disease and renal insufficiency.[21,22]

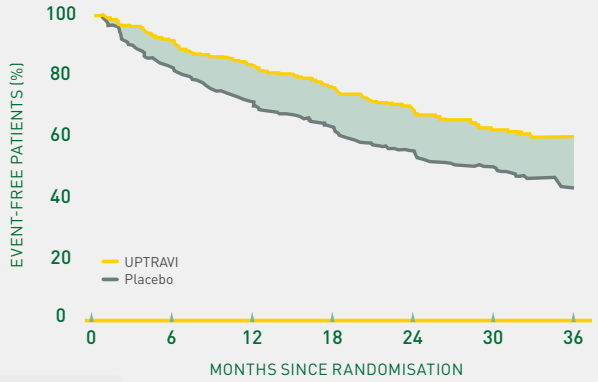
CHANGE THE COURSE OF PAH WITH UPTRAVI – AN ORAL IP RECEPTOR AGONIST SHOWN TO DELAY DISEASE PROGRESSION[23–25]

The GRIPHON trial assessed the effect of UPTRAVI on long-term outcomes in PAH using a robust composite primary endpoint that reflects recommendations from the World Symposium on Pulmonary Hypertension[23,26]

Patients with CTD-PAH comprised **29% of the GRIPHON patient population**[23]

UPTRAVI reduced the risk of morbidity-mortality* in patients with SSc-PAH vs placebo. This response was consistent with that observed in the overall GRIPHON population[28]

TIME TO FIRST MORBIDITY-MORTALITY EVENT* IN GRIPHON (OVERALL POPULATION)[23]

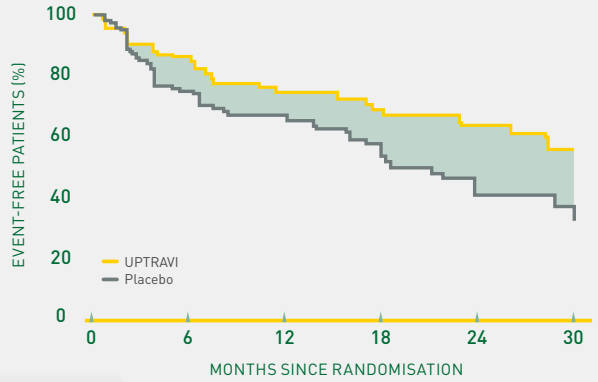


PATIENTS AT RISK							
UPTRAVI	574	455	361	246	171	101	40
Placebo	582	433	347	220	149	88	28

40%
RISK REDUCTION
HR 0.60; 99% CI: 0.46–0.78; $p<0.001$

Adapted from Sitbon *et al.* 2015[23]

TIME TO FIRST MORBIDITY-MORTALITY EVENT* IN GRIPHON (SSc-PAH POPULATION)[28]



PATIENTS AT RISK						
UPTRAVI	77	56	42	34	20	9
Placebo	93	60	47	30	19	9

44%
RISK REDUCTION
HR 0.56; 95% CI: 0.34–0.91

Adapted from Gaine *et al.* 2017[28]

EARLY USE OF UPTRAVI PROVIDES A **LASTING BENEFIT FOR PAH PATIENTS**[23,27]

CI, confidence interval; CTD, connective tissue disease; HR, hazard ratio; IP, prostacyclin; PAH, pulmonary arterial hypertension
*As measured by a composite primary endpoint. Results were driven by a decrease in hospitalisation and other disease progression events and not by mortality on its own.[23]

UPTRAVI DELAYS **DISEASE PROGRESSION AND IMPROVES LONG-TERM OUTCOMES IN SSc-PAH**, A POPULATION PREVIOUSLY CONSIDERED DIFFICULT TO TREAT[28]

In GRIPHON, the most common adverse events were headache, flushing, nasopharyngitis, diarrhoea, vomiting, nausea, jaw pain, myalgia, arthralgia and pain in extremity.[24] For full safety and tolerability information, please consult the UPTRAVI Prescribing Information.

CI, confidence interval; HR, hazard ratio; PAH, pulmonary arterial hypertension; SSc, systemic sclerosis
*As measured by a composite primary endpoint. Results were driven by a decrease in hospitalisation and other disease progression events and not by mortality on its own.[28]

HELP FACILITATE EARLIER TREATMENT AND IMPROVED OUTCOMES FOR YOUR PATIENTS WITH SSc-PAH

- PAH is a silently progressive disease and a leading cause of death in SSc-PAH patients[5]
- Early identification of PAH is critical to improving patient outcomes[6]
  - Guidelines recommend annually screening SSc patients for PAH[7–9]
  - The DETECT algorithm can be used to screen for PAH in SSc[7,10]
  - Refer patients to PH centres early to confirm PAH diagnosis
- Early PAH treatment with OPSUMIT and UPTRAVI makes a difference
  - Proven to delay disease progression and improve long-term outcomes in a broad range of patients, including those with SSc-PAH[11–13,15–25,28,29]
  - Both OPSUMIT and UPTRAVI are recommended in combination therapy[7] and have been shown to reduce morbidity-mortality* vs placebo when used as combination therapy**[20,25]

ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension; PDE-5i, phosphodiesterase type-5 inhibitor; PH, pulmonary hypertension; SSc, systemic sclerosis; WHO, World Health Organization

*As measured by a composite primary endpoint. Results were driven by a decrease in hospitalisation and other disease progression events and not by mortality on its own.[11,23]

**OPSUMIT in combination with PDE-5i or oral/inhaled prostanoid in the SERAPHIN trial.[11] UPTRAVI in combination with ERA and PDE-5i in GRIPHON.[23]

OPSUMIT® is an endothelin receptor antagonist (ERA) indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). OPSUMIT also reduced hospitalization for PAH.[12]

UPTRAVI is indicated for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients with WHO functional class (FC) II–III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type-5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.[24]

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