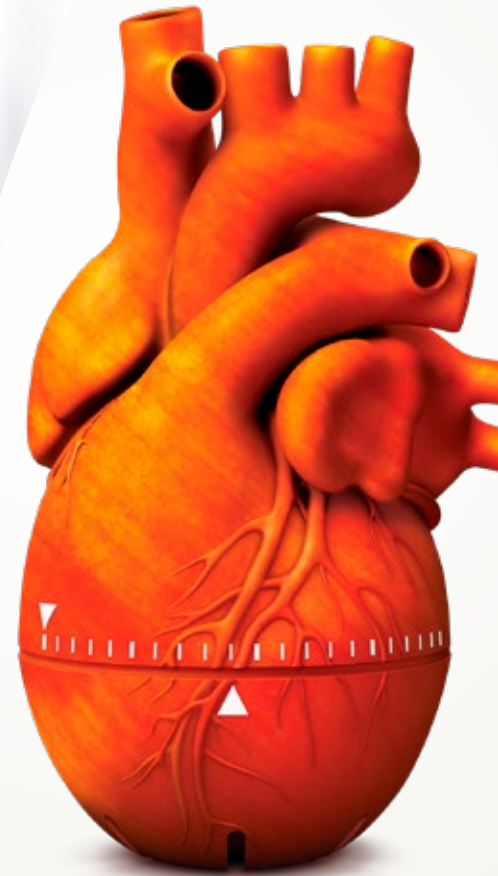


SIMDAX[®] GIVES YOU TIME IN ADVANCED HEART FAILURE

**ORION
PHARMA**
Building well-being



 **SIMDAX[®]**
levosimendan

SIMDAX® IN ADVANCED HEART FAILURE

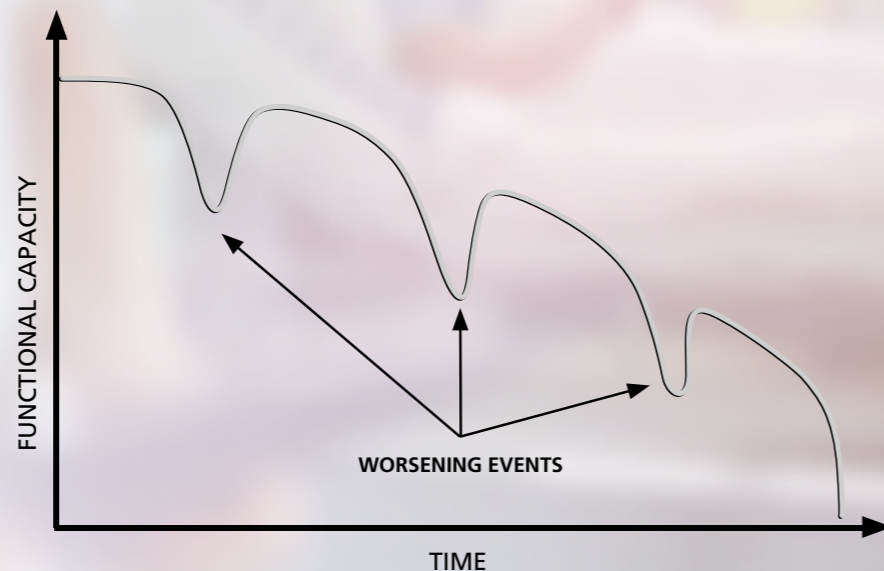
Advanced heart failure (AdHF)¹ is characterized by:

- repeated episodes of cardiac decompensation²
- severely compromised patient quality of life³
- frequent and prolonged hospitalizations⁴
- more pronounced decrease in cardiac function at each successive admission⁴
- increased risk of death³
- increased burden of hospital and social costs³

Repetitive SIMDAX® therapy represents a safe and effective treatment option for stabilizing these patients.⁵

References: 1. Ponikowski P et al. *Eur Heart J.* 2016;37:2129-2200
 2. Roger VL. *Circ Res.* 2013;113:646-659. 3. Braunschweig F. *J Am Coll Cardiol.* 2011;58:738-9 4. Gheorghiade M et al. *Am J Cardiol.* 2005;96[suppl]:11G-17G. 5. Nieminen MS et al. *Int J Cardiol.* 2014;174(2):360-367.

Functional capacity during the progression of heart failure



SIMDAX® MAINTAINS PATIENT STABILITY IN ADVANCED HEART FAILURE

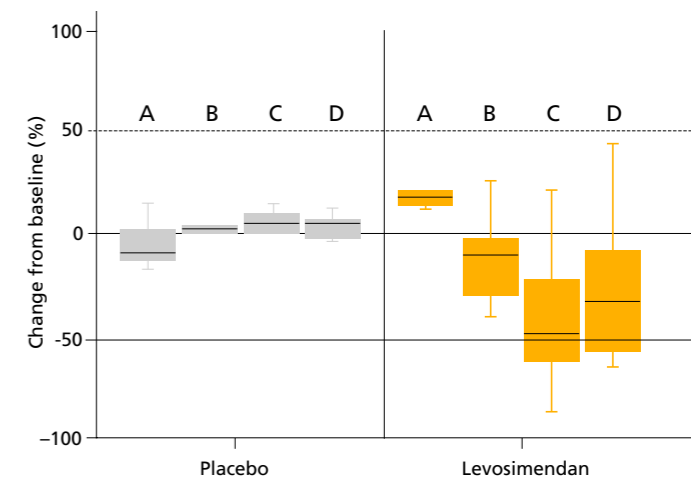
The benefits of the repetitive use of SIMDAX® in advanced heart failure have been assessed in several independent randomized trials including, in total, more than 500 patients.¹

The use of SIMDAX® is associated with improvements in hemodynamics, symptoms, rehospitalization rates, and biomarkers (see chart).^{1,2}

The current data and clinical experience suggest that in selected patients, intermittent/repetitive SIMDAX® can be used in advanced heart failure to maintain patient stability.¹

References: 1. Nieminen MS et al. *Int J Cardiol.* 2014;174(2):360-367.
 2. Parissis JT et al. *Heart.* 2006;92:1768-1772.

Effects of levosimendan in advanced heart failure



Levosimendan improved left ventricle performance and had favorable effects on markers of neurohormonal and immune activation, without exacerbating myocardial injury. Patients with decompensated chronic heart failure were treated with levosimendan every 3 weeks for 5 times.²

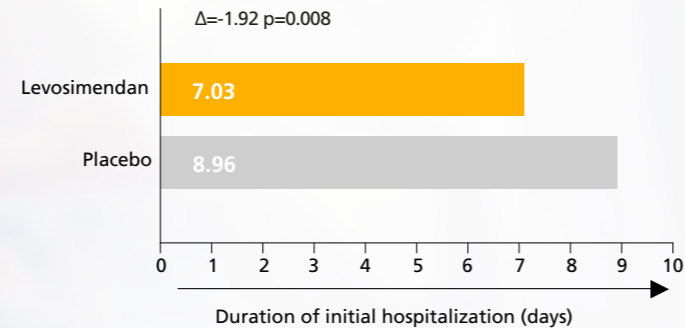
A = Ejection fraction
 B = End systolic stress
 C = NT-proBNP
 D = Interleukin 6

IN HOSPITALIZATION FOR AHF, THE EFFECTS OF SIMDAX® ALLOW A SHORTER HOSPITAL STAY

SIMDAX®, on top of standard of care, shortens hospital stay in acute heart failure. These data have been shown in a phase III study (vs placebo).^{1,2}

Hospital stay is reduced by
1.92 DAYS

Hospitalization length of acute heart failure patients



Data from an economic analysis of the REVIVE II study of 600 patients hospitalized for treatment of acute decompensated heart failure.¹

References:

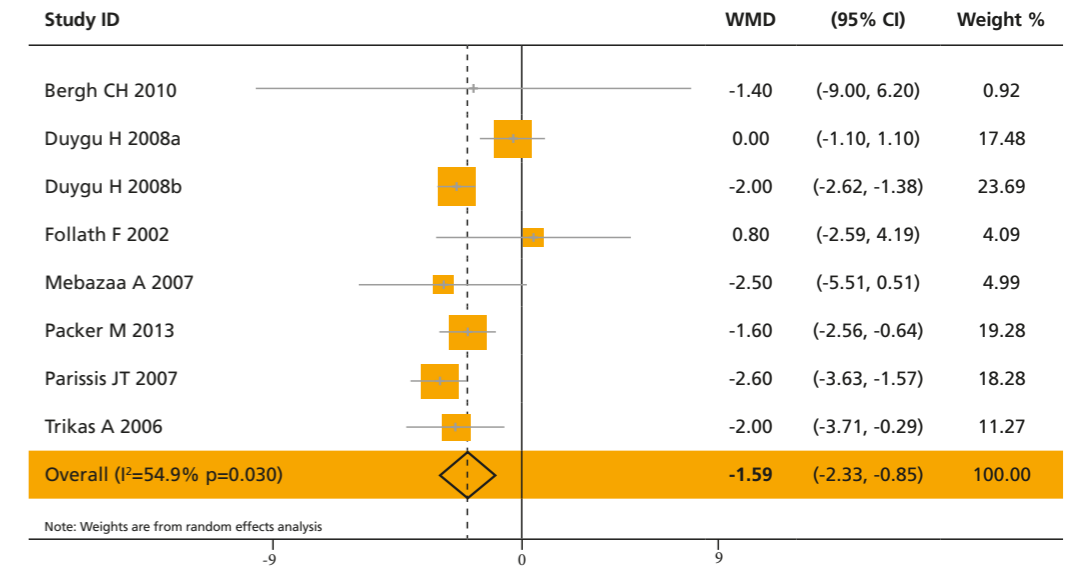
1. De Lissovoy G et al. *Eur J Health Econ.* 2010;11:185–193.
2. Packer M et al. *JACC Heart Fail.* 2013;1(2):103-11.

SHORTER HOSPITAL STAYS ARE CONFIRMED BY META-ANALYSIS

These results are corroborated by a meta-analysis of 8 studies in which SIMDAX® was used in cardiology settings:

Length of stay in hospital was decreased by 1.59 days in SIMDAX® treated patients in addition to a significant reduction in mortality.¹

Meta-analysis of the levosimendan effects on length of stay in hospital¹

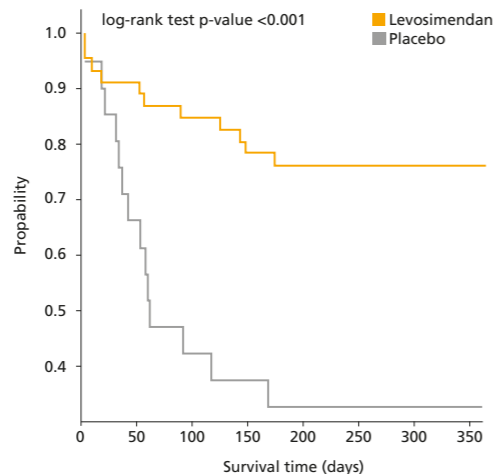


Reference: 1. Landoni G et al. *Crit Care Med.* 2012;40:634–646 (electronic supplementary material).

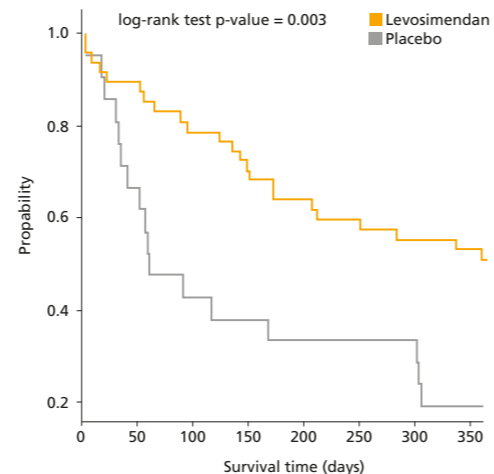
REPEATED TREATMENT WITH SIMDAX® REDUCES RE-HOSPITALIZATION...

In the LION-HEART Study,¹ the treatment with 6 cycles of intermittent infusions of levosimendan every 2 weeks at a dose of 0.2 µg/kg/min in outpatients with advanced heart failure significantly reduced the risk of heart failure hospitalization and the risk of the combined end-point of all-cause death or heart failure hospitalization, showing a lesser decline in their health-related QoL over time.

HF Hospitalization



All-Cause death or HF Hospitalization



Reference:

1. Comin-Colet J et al *Eur J Heart Fail* 2017 [ePub Dec 30]

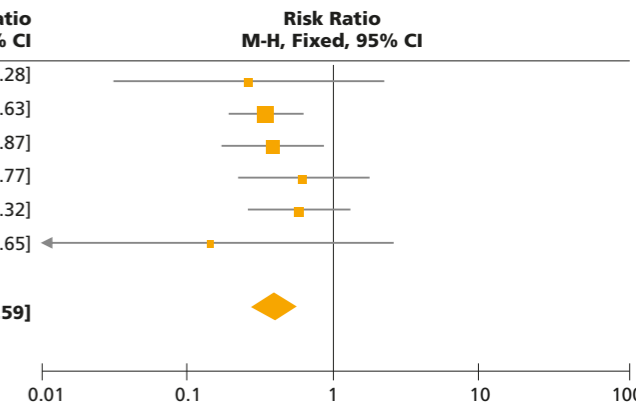
...AS CONFIRMED BY A META-ANALYSIS

Repetitive or intermittent administration of SIMDAX® for patients with advanced heart failure is associated with a reduction in the re-hospitalization rate at 3 months¹

Meta-analysis of repetitive use of levosimendan in advanced heart failure

Study or Subgroup	Levosimendan Events	Levosimendan Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bonios 2012	1	19	3	15	6.45%	0.26 [0.03, 2.28]
Comin-Colet 2015	11	48	14	21	37%	0.34 [0.19, 0.63]
Garcia-Gonzalez 2016	9	70	9	27	24.7%	0.39 [0.17, 0.87]
Kleber 2009	5	18	4	9	10.1%	0.63 [0.22, 1.77]
Malfatto 2012	7	22	6	11	15.2%	0.58 [0.26, 1.32]
Mavrogeni 2007	0	30	3	30	6.6%	0.14 [0.01, 2.65]
Total (95% CI)		207		113	100%	0.40 [0.27, 0.59]
Total events	33		39			

Heterogeneity: Chi² = 2.40, df = 5 (p=0.79); I² = 0%
 Test for overall effect: Z = 4.69 (p<0.00001)



References: 1. Silvetti S et al. *ESC Heart Failure* 2017;4:595-604

SIMDAX® AND QUALITY OF LIFE

Advanced heart failure is **characterized by poor quality of life (QoL) and frequent hospitalizations.**¹

The efficacy of SIMDAX® in advanced heart failure was not only assessed by parameters such as clinical status, hemodynamics, neurohormonal status, and echo indices, but also by QoL-related parameters, such as **functional capacity, exercise performance, psychological status, and frequency of re-hospitalizations**, which are more relevant from the patient perspective.²

References: 1. Jaarsma T *et al.* *Eur. J Heart Fail.* 2009;11:433–443.
2. Nieminen MS *et al.* *Int J Cardiol.* 2015;191:256–264.



SIMDAX® AND QUALITY OF LIFE IN ADVANCED HEART FAILURE

Levosimendan appears more favourable in quality of life related variables than other vasoactive agents

	Hemodynamics		Neurohormones	QoL-related parameters				Survival
	Cardiac index	Congestion/PCWP		Dyspnoea	Rehospitalization rate	Depression	MLHFQ/KCCQ	
Dobutamine	↑↑	↓	↓	↓	↑ ^B	n.d.	n.d.	↓ ^G
Milrinone	↑↑	↓↓	↔	↓	↔ ^C	n.d.	n.d.	↓ ^H
Levosimendan	↑↑	↓↓	↓	↓	↓ ^B	↓ ^F	↓ ^F	↑ ^{B,I}
Nitroprusside	↑ ^A	↓↓	↓	↓	↔ ^D	n.d.	n.d.	↑ ^C
Nesiritide	↑ ^A	↓↓	↓	↓	↔ ^E	n.d.	n.d.	↔ ^J

Effects of inotropic and vasoactive therapies currently used in clinical practice on outcomes in AdHF patients.¹ ^Aindirect effect; ^Baccording to Fedele F *et al.* 2011; ^Caccording to Lewis DA *et al.* 2003; ^Daccording to Mullens W *et al.* 2008; ^Eaccording to O'Connor CM *et al.* 2011; ^Faccording to Parissis JT *et al.* 2007; ^Gaccording to Capomolla S *et al.* 2001 (vs nitroprusside); ^Haccording to Packer M *et al.* 1991; ^Iaccording to meta-analyses by Nieminen MS *et al.* 2014 and Silvetti S *et al.* 2014; ^Jaccording to Reed SD *et al.* 2013; n.d. = no relevant data obtained by cross-searching PubMed for ("parameter" AND "active compound"[ti]).

Reference: 1. Nieminen MS *et al.* *Int J Cardiol.* 2014;174(2):360–367.

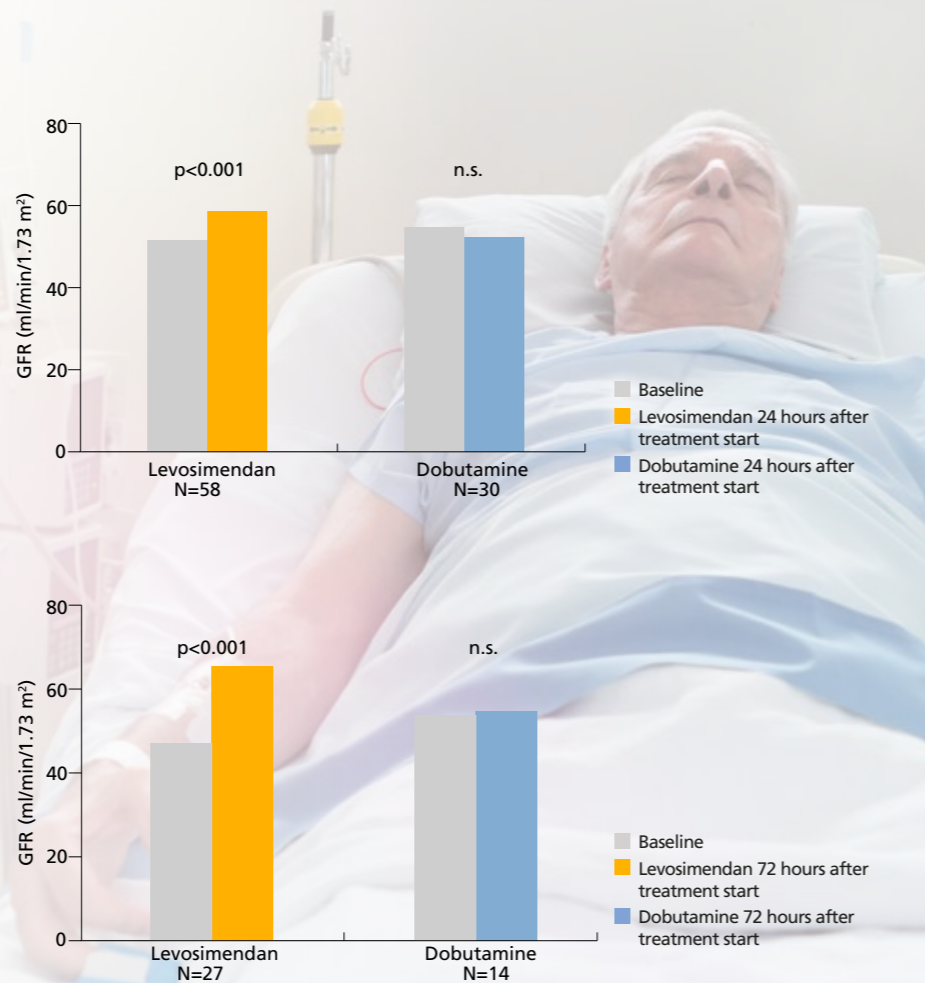
THE BENEFITS OF SIMDAX® FOR RENAL FUNCTION

GFR improved in SIMDAX® compared to dobutamine-treated patients with heart failure who required inotropic therapy.¹

A placebo-controlled study in patients hospitalized for decompensated heart failure and renal dysfunction, showed a statistically significant **improvement of GFR in SIMDAX®-treated patients.**²

The peak effect was seen at three days after a 24 hour infusion and the effects persisted up to 14 days.²

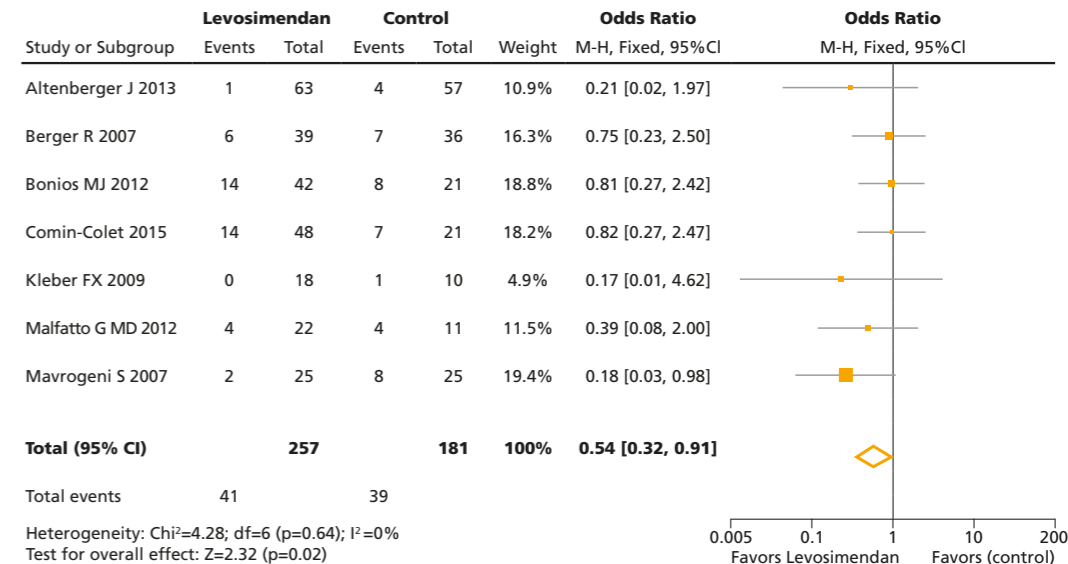
Reference: 1. Yilmaz et al. *Cardiovasc Drugs Ther.* 2007;21:431–435. **2.** Hou Z-Q et al. *Cardiovasc Ther.* 2013;31:108–114.



NO COMPROMISE ON SURVIVAL IN ADVANCED HEART FAILURE

Moreover, recent meta-analysis on the mortality of repetitive use of SIMDAX® shows encouraging results.^{1,2}

Meta-analysis of mortality in advanced heart failure studies of repetitive levosimendan therapy¹



References: 1. Nieminen MS et al. *Int J Cardiol.* 2014;174(2):360–367. **2.** Silvetti S & Nieminen MS *Int J Cardiol.* 2016;202:138–143.

RECOMMENDED PATIENT PROFILE AND DOSING IN ADVANCED HEART FAILURE

A panel of experts from 15 European countries convened to review and discuss the existing data on the repetitive use of SIMDAX®.¹

The panel reached a consensus in potential indications for SIMDAX® in advanced heart failure¹ (see Table I).

The panel also gave recommendations for the optimal dosing (see Table II) which should be considered when administering SIMDAX® to such patients.¹

Reference: 1. Nieminen MS et al. *Int J Cardiol.* 2014;174(2):360–367.

Expert consensus on indication and dosing of levosimendan in advanced heart failure

TABLE I: High-risk setting defining the potential indications for repetitive use of levosimendan in chronic advanced heart failure

Patient characteristics or levosimendan use in advanced heart failure.
• Severe systolic dysfunction (LVEF <35%)
• and/or NYHA IIIb-IV and/or INTERMACS levels 4, 5, 6
• and/or repeated hospitalization or emergency department visits (≥2 in the past year)
• All of the above despite optimal treatment for heart failure

TABLE II: Recommended dosing

As patient characteristics and needs vary considerably, flexible dosing is recommended:
• Infusion rate: 0.05 µg/kg/min to 0.2 µg/kg/min; starting with low dose and increasing stepwise during the remaining time when tolerated
• Bolus dose: not recommended
• Duration: 6 to 24 hours
• Interval: every 2 to 4 weeks