Entresto®
(sacubitril/valsartan)

Learn about ENTRESTO® (sacubitril/valsartan) clinical trials

ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic heart failure with reduced ejection fraction (HFrEF)[1]

(CaReMe UK Partnership recommends ENTRESTO use in patients with LVEF <35%)[2]

Scan or click the QR code for prescribing information

Adverse Event Reporting:

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Novartis online through the pharmacovigilance intake (PVI) tool at www.novartis.com/report or alternatively email medinfo.uk@novartis.com or call 01276 698370.

* CaReMe UK HF algorithm recommends treatment with ACEi or ARB or sacubitril/valsartan + BB and an MRA as first-line treatment for chronic HFrEF patients.[2]
† ARNi may be used first line as part of cornerstone HFrEF therapy with a BB, MRA and SGLT2i in the 2021 ESC Guidelines for the treatment of chronic HFrEF patients.[3]
‡ The 2022 AHA/ACC/HFSA Update recommends ARNi as a replacement for ACEi/ARB as a first-line treatment for all appropriate HFrEF patients.[4]

The recommended starting dose of ENTRESTO is one tablet of 49 mg/51 mg twice daily, except in the situations described below. The dose should be doubled at 2-4 weeks to the target dose of one tablet of 97 mg/103 mg twice daily, as tolerated by the patient.[1] Please refer to the ENTRESTO SmPC for further guidance.

This promotional material has been developed and funded by Novartis Pharmaceuticals UK Ltd.
Intended for UK healthcare professionals only.

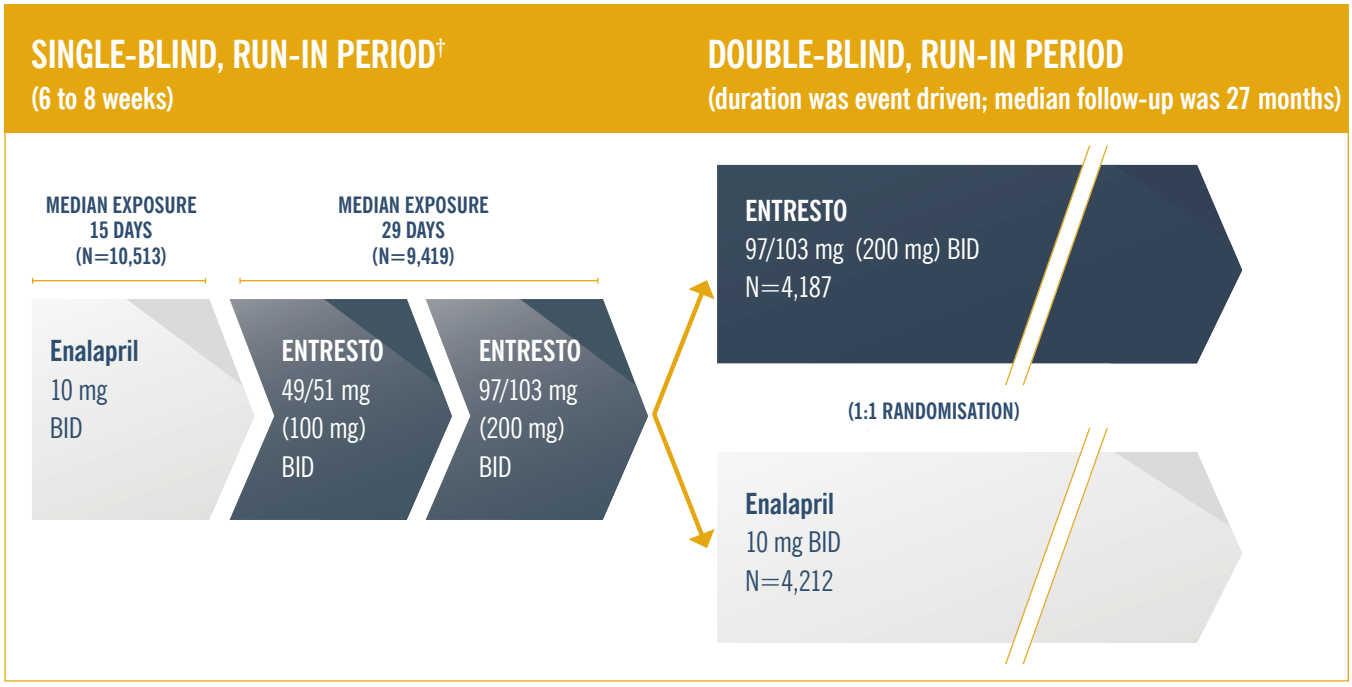
Entresto® (sacubitril/valsartan)

PARADIGM-HF

ENTRESTO demonstrated superior efficacy to ACEi (enalapril) in symptomatic chronic HFrEF patients*[5]

Study design:

PARADIGM-HF was a multinational, randomised, double-blind trial comparing ENTRESTO to enalapril in 8,442 symptomatic (NYHA Class II–IV) chronic HFrEF patients (LVEF ≤40%, amended later to ≤35%).[5]



Adapted from McMurray et al. 2014.[5]

ENTRESTO should not be co-administered with an ACEi or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACEi, it must not be started for at least 36 hours after discontinuing ACEi therapy.[1]

Primary endpoint[5]

The primary outcome was a composite of CV death or first hospitalisation for HF, but the trial was designed to detect a difference in the rates of death from CV causes

Key inclusion criteria‡[5]

Patients (over 18 years) must have NYHA Class II, III or IV symptoms, and an ejection fraction of 40% or less (which was changed to 35% or less by an amendment to the protocol). All patients were required to be treated with a stable dose of ACEi/ARB before enrolment.§ Patients were also required to have a plasma BNP level of ≥150 pg/mL (or an NT-proBNP level of ≥600 pg/mL)

Patient characteristics‡[5]

PARADIGM-HF included patients with NYHA Class II–IV (>95%), and an average LVEF of 29%. At baseline, the average age of patients was 64 years, mean SBP was 121 mmHg and 93% of patients were taking BBs and 55.6% MRAs

* For the primary endpoint, composite of CV death or first HF hospitalisation, ENTRESTO was superior to enalapril (P<0.0001). The median follow-up duration was 27 months.[5]
† All patients were on an ACEi or ARB prior to the run-in period.[5]
‡ The key inclusion criteria and patient characteristics presented here are not exhaustive; to see these in full, please refer to McMurray JJV et al. N Engl J Med 2014;371:993-1004.[5]
§ Equivalent to enalapril 10 mg/day for at least 4 weeks prior to screening.[5]

Prescribing information and adverse event reporting information can be found at the front of this material.

Efficacy:

20% RR vs ACEi (enalapril) **IN CV DEATH OR FIRST HOSPITALISATION FOR HF** ARR **4.7%**[1]

Composite primary endpoint events:
914 (21.8%) vs 1,117 (26.5%); HR=0.80, 95% CI: 0.73–0.87; P<0.001[1,5]

20% RR vs ACEi (enalapril) **IN CV DEATH** ARR **3.1%**[1]

Co-primary endpoint events:
558 (13.3%) vs 693 (16.5%); HR=0.80, 95% CI: 0.71–0.89; P<0.001[1,5]

21% RR vs ACEi (enalapril) **IN FIRST HOSPITALISATION FOR HF** ARR **2.8%**[1]

Co-primary endpoint events:
537 (12.8%) vs 658 (15.6%); HR=0.79, 95% CI: 0.71–0.89; P<0.001[1,5]

PARADIGM-HF was stopped early due to a clear benefit with ENTRESTO over ACEi (enalapril)[5]

In a *post hoc* analysis of PARADIGM-HF, the following projected life expectancies were estimated:*[6]

- 55-year-old patients: **11.6 additional years** with enalapril vs **12.9 years** with ENTRESTO (mean benefit: 1.4 years; 95% CI: -0.1 to 2.8)
- 65-year-old patients: **10.0 additional years** with enalapril vs of **11.4 years** with ENTRESTO (mean long-term benefit of 1.3 years; 95% CI: 0.3 to 2.4)

* A *post hoc* analysis of PARADIGM-HF estimated the long-term treatment effects of ENTRESTO vs enalapril by deriving actuarial estimates of age-specific event rates and expected survival times, using data regarding the age at randomisation and the age at the time of an outcome event. Survival analysis was modelled using the patients' age as the time scale (rather than the time since randomisation) to estimate the projected effect of ENTRESTO vs enalapril over the duration of patients' lifetimes. The effect of treatment on the average duration of event-free survival was estimated by comparing the area under the survival curves.[6]

Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

Safety profile:

AEs (%)[5]

Event	ENTRESTO (N=4,187)	Enalapril (N=4,212)	P value
	No. (%)		
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with systolic blood pressure <90 mm Hg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10 (NS)
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	0.15 (NS)
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19 (NS)
Use of catecholamines or glucocorticoids without hospitalisation	6 (0.1)	4 (0.1)	0.52 (NS)
Hospitalisation without airway compromise	3 (0.1)	1 (<0.1)	0.31 (NS)
Airway compromise	0	0	—

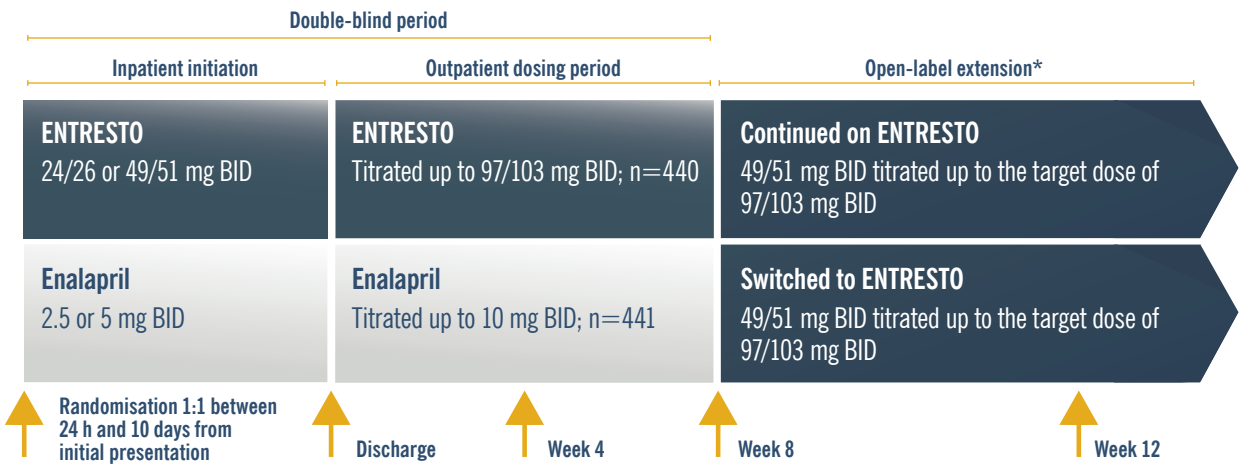
Adapted from McMurray et al. 2014.[5]

Most commonly reported AEs with ENTRESTO were hypotension (17.6%), hyperkalaemia (11.6%) and renal impairment (10.1%)[1,5]

ENTRESTO resulted in faster and significantly greater reduction in NT-proBNP vs ACEi (enalapril) (46.7% vs 25.3% at Week 4, HR: 0.71, 95% CI: 0.63–0.8; P<0.001; primary endpoint)[7]

Study design:

PIONEER-HF was a prospective, multicentre, double-blind, randomised, active-controlled trial designed to assess, over an 8-week period, the safety, tolerability and efficacy of in-hospital initiation of ENTRESTO compared with enalapril in 881 adult patients in the United States with chronic HFrEF (EF ≤40% and NT-proBNP ≥1,600 pg/mL or BNP ≥400 pg/mL) haemodynamically stabilised during hospitalisation for an episode of ADHF.[7]



A 36-hour washout period is required when switching between an ACEi and ENTRESTO.

Adapted from Velazquez et al. 2019[7] and DeVore et al. 2019.[8]

Patients in the PIONEER-HF trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[7]

Endpoints[7]

The primary endpoint was time-averaged proportional change in NT-proBNP concentration from baseline through Weeks 4 and 8. Secondary biomarker outcomes included time-averaged proportional changes in the high sensitivity troponin T concentration, BNP concentration and ratio of BNP to NT-proBNP. Key safety outcomes were incidences of worsening renal function, hyperkalaemia, symptomatic hypotension and angioedema. The exploratory endpoints included the outcome of a composite of serious clinical events including death, rehospitalisation for HF, implantation of a LV device and inclusion on the list of patients eligible for heart transplantation

Key inclusion criteria†[7]

- Patients were ≥18 years
- Hospitalised for an episode of ADHF
- Randomised no earlier than 24 h and up to 10 days after initial presentation while still hospitalised
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1,600 pg/mL or BNP ≥400 pg/mL

Patients must have been haemodynamically stabilised before randomisation, defined as:

- SBP ≥100 mmHg for the prior 6 h; no symptomatic hypotension
- No increase in IV diuretics in prior 6 h
- No IV vasodilators in prior 6 h
- No IV inotropes in prior 24 h

Patient characteristics†[7]

PIONEER-HF included patients with NYHA Class I–IV (25% patients NYHA Class II and 63% patients NYHA Class III); 48% of patients had prior treatment with ACEi or ARB and had an average LVEF of 25%.
At baseline, the average age of patients was 62 years, 65% had been previously diagnosed with HF, the mean SBP was 118 mmHg and the median NT-proBNP concentration was 4,812 pg/mL.
Approximately 60% of patients were taking BBs and about 10% MRAs

ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1]
ENTRESTO is not indicated for the treatment of acute HF.[1]

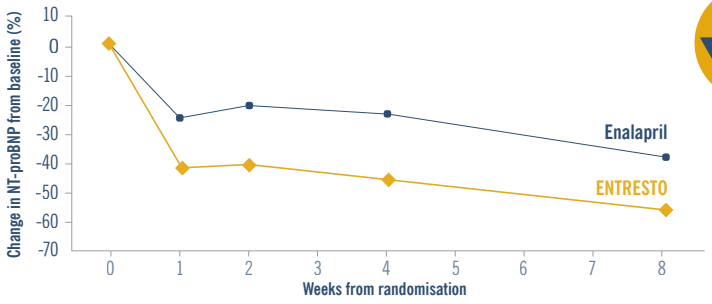
* Entering the open-label phase, regardless of prior drug or dose, all patients were administered ENTRESTO 49/51 mg BID and were titrated as early as Week 1 to the target dose 97/103 mg BID. Follow labelled dosing recommendations.[7]
† The key inclusion criteria and patient characteristics presented here are not exhaustive; to see these in full, please refer to Velazquez EJ et al. N Engl J Med 2019;380(6):539-548.[7]

Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

Efficacy:

Primary endpoint



↓29% Greater reduction in NT-proBNP with ENTRESTO vs ACEi (enalapril) from baseline through Weeks 4 and 8*[7]

Percent change with ENTRESTO vs ACEi (enalapril): -46.7% vs −25.3%; ratio of change: 0.71 (95% CI: 0.63–0.81); P<0.001[7]

Exploratory endpoints

↓42% **RR of serious clinical outcomes† with ENTRESTO vs ACEi (enalapril)**

Effect through Week 8 ARR: enalapril, 16.3%; ENTRESTO, 9.8%; HR=0.58, 95% CI: 0.40–0.85; P=0.005[9]

↓39% **RR of HF rehospitalisations with ENTRESTO vs ACEi (enalapril)**

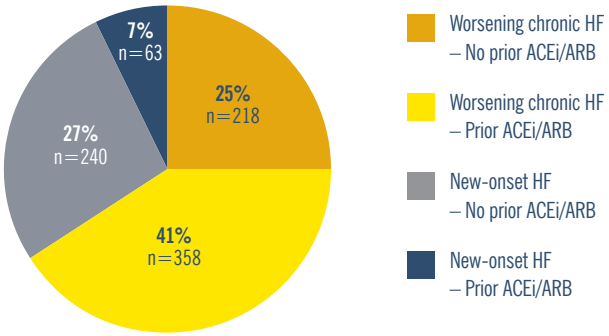
Effect through Week 8 ARR: enalapril, 13.6%; ENTRESTO, 8.5%; HR=0.61, 95% CI: 0.40–0.93; P=0.021[9]

Adapted from Velazquez et al. 2019.[7]

It was observed in an exploratory endpoint that the rate of HF rehospitalisation was lower in the ENTRESTO group vs ACEi (enalapril)[7-9]

Patient baseline characteristics

Objective: to determine how prior HF history and treatment with ACEi/ARB affected the results in four different patient subgroups[10]



Efficacy and safety outcomes

- NT-proBNP declined significantly with ENTRESTO vs ACEi (enalapril) at 8 weeks in all subgroups (P<0.001)[10]
- Patients on ENTRESTO had a lower incidence of the composite of CV death or re-hospitalisation, however this reduction was not significant in the subgroup for no prior ACEi/ARB‡[10]
- The incidence of AEs was comparable between ENTRESTO and ACEi (enalapril) across all four subgroups[10]

Adapted from Ambrosy et al. 2020.[10]

ENTRESTO should not be co-administered with an ACEi or an ARB. Due to the potential risk of angioedema when used concomitantly with an ACEi, it must not be started for at least 36 hours after discontinuing ACEi therapy.[1]

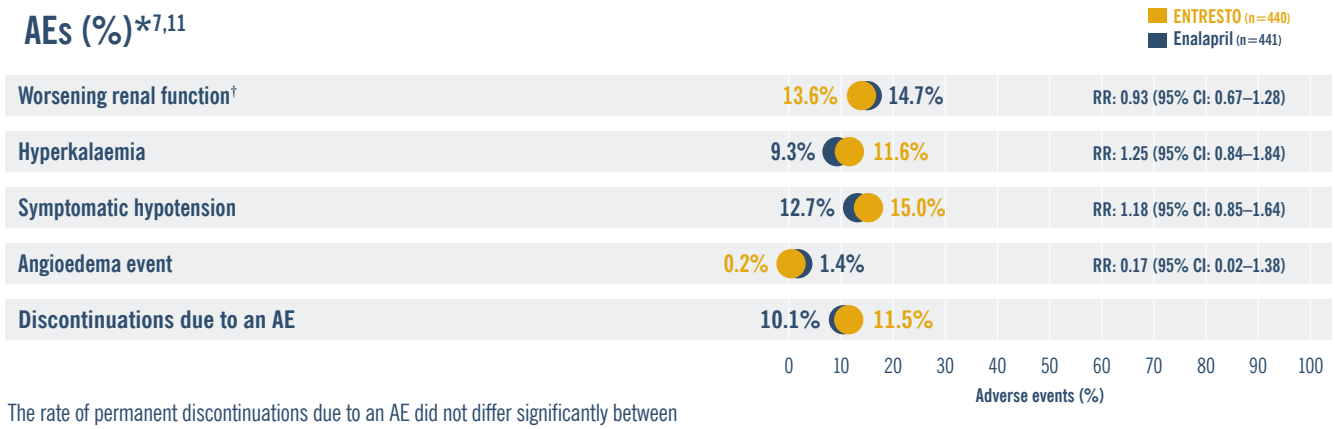
ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1] ENTRESTO is not indicated for the treatment of acute HF.[1] Patients in the PIONEER-HF trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[7]

* Ratio of geometric mean of values obtained at Weeks 4 and 8 to the baseline value: 0.53 in the ENTRESTO group vs 0.75 in the enalapril group.[7]
† Serious clinical outcomes include HF hospitalisation or CV death.[9]
‡ The reduction in incidence of the composite of CV death or HF rehospitalisation in the ENTRESTO vs ACEi (enalapril) group was not significant in the subgroup with no prior ACEi/ARB (P=0.197).[10]

Prescribing information and adverse event reporting information can be found at the front of this material.

Safety profile:

AEs (%)*[7,11]



The rate of permanent discontinuations due to an AE did not differ significantly between the two treatment groups[7]

Adapted from Velazquez et al. 2019. (incl. supplementary appendix).[7,11]

ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1] ENTRESTO is not indicated for the treatment of acute HF.[1] Patients in the PIONEER-HF trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[7]

* The rates of worsening renal function, hyperkalaemia, symptomatic hypotension and angioedema were the key safety outcomes evaluated in this study, and did not differ significantly between the two groups. AEs that take longer to transpire may not have appeared in this study.[7]

† Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg/dL or more (≥44 μmol/L) and a decrease in the estimated glomerular filtration rate of 25% or more.[7]

Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

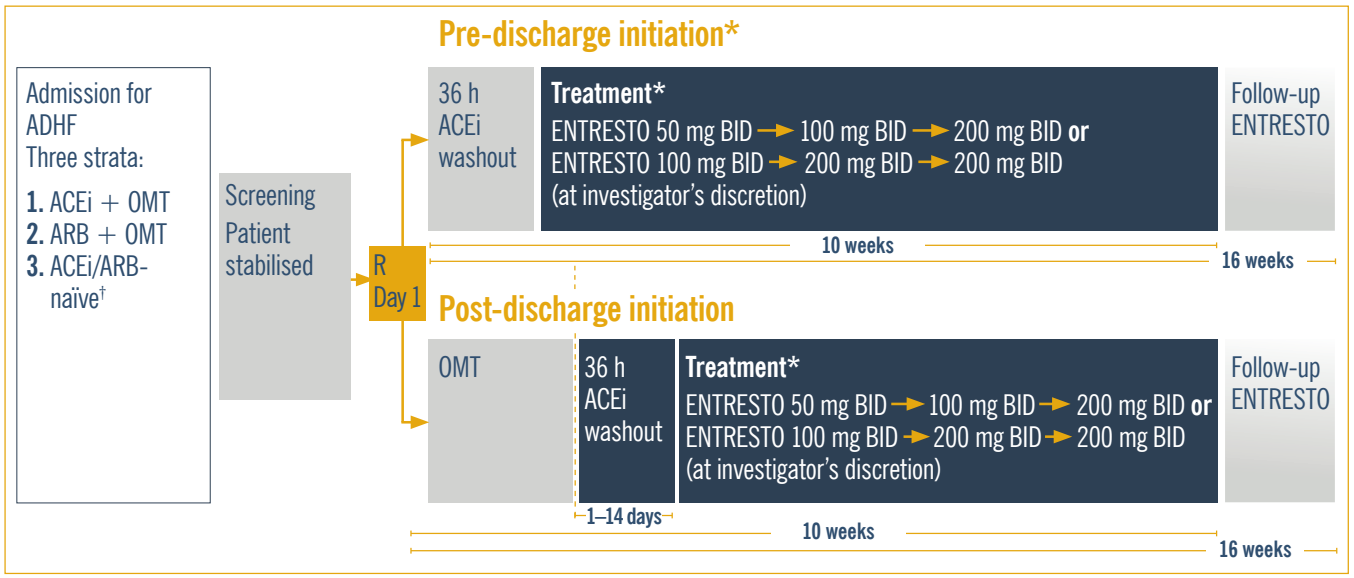
Entresto® (sacubitril/valsartan)

TRANSITION

In-hospital ENTRESTO initiation: efficacy, feasibility and safety profile[12]

Study design:

TRANSITION was a randomised, parallel, open-label study comparing pre-(≥12 h) vs post-discharge (within 1–14 days) initiation of ENTRESTO in patients with chronic HFrEF (NYHA Class II–IV HF, LVEF ≤40%) following haemodynamic stabilisation after an episode of ADHF. It was a 10-week, randomised, parallel, multicentre, open-label study conducted in 1,002 patients.[12]



Adapted from Wachter et al. 2019.[12]

Patients in the TRANSITION trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[12]

Primary endpoint[12]

To evaluate the proportion of patients in the pre- vs post-discharge treatment initiation groups who achieved the target ENTRESTO dose of 200 mg (97 mg/103 mg) BID at the end of Week 10 after randomisation

Key inclusion criteria[12]

- Hospitalised due to an episode of ADHF
- Diagnosis of HFrEF NYHA Class II–IV and LVEF ≤40% at screening
- Patients haemodynamically stabilised (while in the hospital) for at least 24 h leading to randomisation defined as:
  - No need for IV diuretics 24 h prior to signing ICF
  - Did not receive any IV vasodilators (except nitrates) and/or any IV inotropic therapy from the time of presentation with ADHF to randomisation
  - SBP ≥110 mmHg for at least 6 h prior to randomisation

Patient characteristics[12]

TRANSITION included patients mostly with NYHA Class II and III (98%) and included both newly diagnosed patients (29%) and patients who were ACEi/ARB-naïve prior to the ADHF event (24%).
At baseline, the average age of patients was 67 years, with mean LVEF of 29%, mean SBP of 124 mmHg and median NT-proBNP of 1,744 pg/mL

ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1] ENTRESTO is not indicated for the treatment of acute HF.[1]

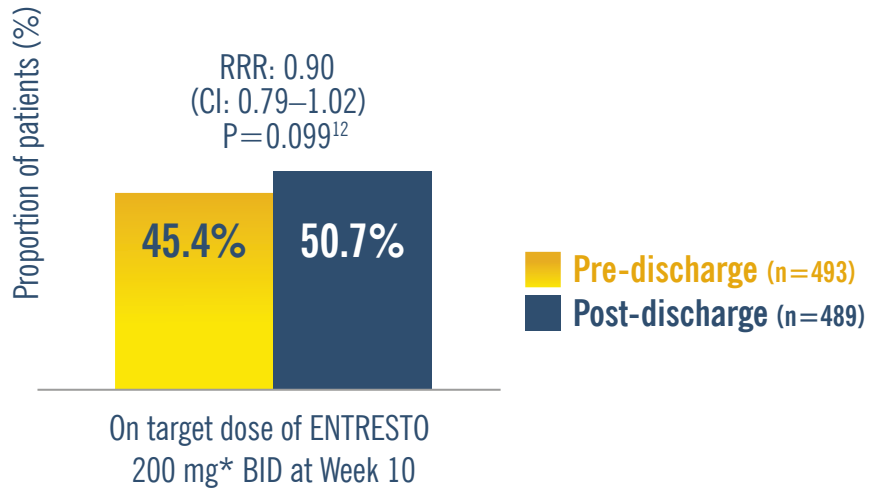
* Initiated ≥12 hours before discharge and ≤7 days post-randomisation.[12]
† No previous ACEi/ARB treatment or no ACE/ARB treatment in the 4 weeks prior to hospitalisation for an episode of ADHF.[12]

Prescribing information and adverse event reporting information can be found at the front of this material.

Efficacy:

There was no significant difference in the primary endpoint: the proportion of pre- and post-discharge stabilised chronic HFrEF patients achieving the target dose of ENTRESTO 200 mg BID (97 mg/103 mg) at Week 10.[12] ARR was not calculated during this study.

Primary endpoint



Adapted from Wachter et al. 2019.[12]

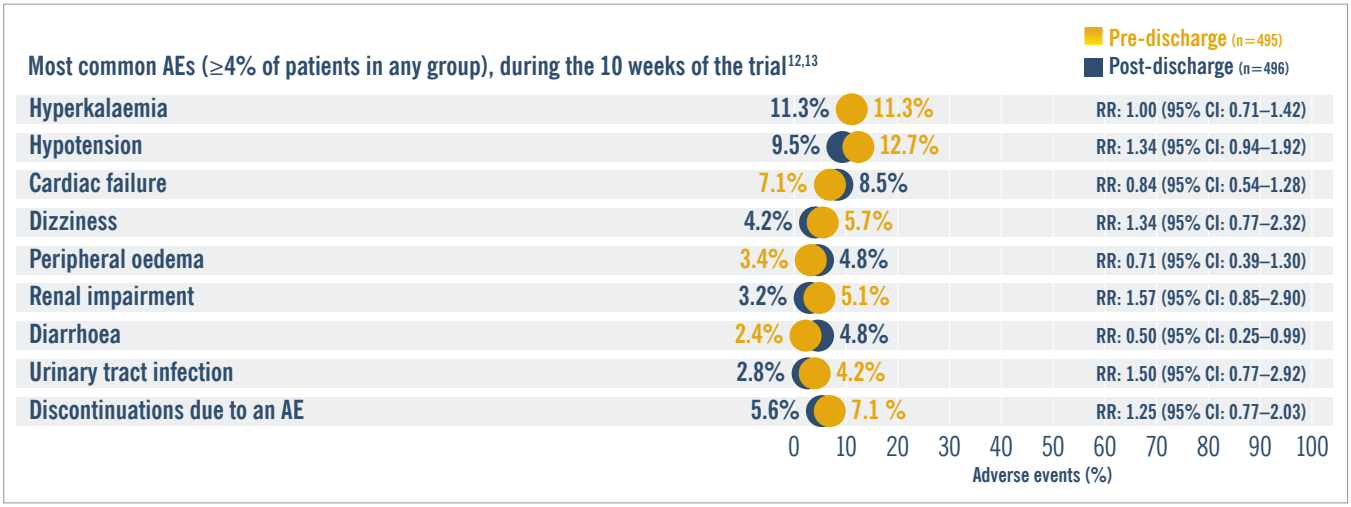
ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1] ENTRESTO is not indicated for the treatment of acute HF.[1] Patients in the TRANSITION trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[12]

* The licensed doses of ENTRESTO are listed as constituents of the salt complex, e.g. 200 mg is available as 97 mg/103 mg tablets, 100 mg is available as 49 mg/51 mg tablets.[1]

Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

Safety profile:



Adapted from Wachter et al. 2019. (incl. supplementary information).[12,13]

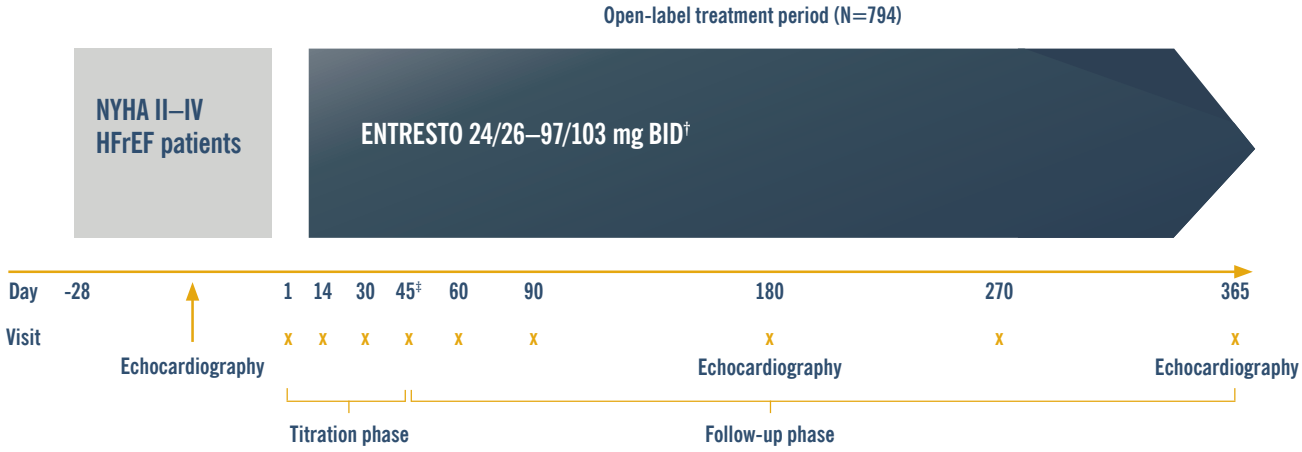
ENTRESTO is a first-in-class ARNi indicated in adult patients for the treatment of symptomatic chronic HFrEF.[1] ENTRESTO is not indicated for the treatment of acute HF.[1] Patients in the TRANSITION trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[12]

Prescribing information and adverse event reporting information can be found at the front of this material.

PROVE-HF was a prospective exploratory analysis where reverse cardiac remodelling and improvements in markers of cardiac function vs baseline were observed[14]

Study design:

PROVE-HF was a Phase IV, single-arm, multicentre, open-label trial in the United States conducted in 794 patients, of which 654 (82.4%) patients completed the 52-week study. This study evaluated the effects of ENTRESTO on biomarkers, cardiac remodelling and patient-reported outcomes in HFrEF. The correlation between the change in concentration of NT-proBNP and E/e' was added to the statistical analysis plan prior to the database lock.*[14]



X = Vital status/events (CV death, HF hospitalisation, worsening HF), physical examination, blood samples for safety chemistry and biomarkers, urine sampling, HF symptom assessment, KCCQ-23.

Adapted from Januzzi et al. 2019 (incl. supplementary information).[14,15]

Primary endpoint[14]

The primary outcome was the correlation between changes in NT-proBNP concentration and cardiac remodelling measure, assessed by changes in left ventricular ejection fraction, left ventricular end-diastolic volume index, left ventricular end-systolic volume index and left atrial volume from baseline to 12 months. Correlation between the change in concentration of NT-proBNP and E/e'§ was added to the statistical analysis plan prior to database lock

Key inclusion criteria[15]

- Patients were ≥18 years
- Patients with HFrEF who are candidates for on-label ENTRESTO treatment per the standard of care
- NYHA Class II, III or IV
- LVEF ≤40% within the preceding 6 months
- Stable dose of loop diuretic for the 2 weeks preceding study start

Patient characteristics[14]

Nearly all patients in PROVE-HF (98%) were NYHA Class II or III. At baseline, 76%, 35% and 95% of patients were taking guideline-directed ACEi/ARB, MRA and BB treatments, respectively. The average age of patients was 65 years, with an average LVEF of 28% and median NT-proBNP of 816 pg/mL

* PROVE-HF was a prospective, Phase IV, 52-week, open-label, single-group exploratory analysis (n=794). The primary endpoint was the correlation between changes in NT-proBNP concentration and cardiac remodelling, assessed by change in LVEDVI, LVESVI, LVEF, and LAVI from baseline to 12 months. Correlation between the change in concentration of NT-proBNP and E/e' was added to the statistical analysis plan prior to database lock. At 12 months, the change in $\log_2$–NT-proBNP concentration was correlated with changes in LVEF ($r = -0.381$ [IQR: −0.448 to −0.310]; P<0.001), LVEDVI ($r = 0.320$ [IQR: 0.246–0.391]; P<0.001), LVESVI ($r = 0.405$ [IQR: 0.335–0.470]; P<0.001), LAVI ($r = 0.263$ [IQR: 0.186–0.338]; P<0.001), and E/e' ($r = 0.269$ [IQR: 0.182–0.353]; P<0.001). Median NT-proBNP concentration at baseline was 816 pg/mL (IQR: 332–1822) and 455 pg/mL (IQR: 153–1090) at 12 months (difference, P<0.001). This study was an exploratory analysis and no confirmatory clinical conclusions can be drawn from such analysis.[14] † Standard HF therapy was continued throughout the study with the exception of ACEi/ARB.[15] ‡ At Day 45, KCCQ-23 was not administered.[15] § E/e' was added to the statistical analysis plan prior to database lock.[14]

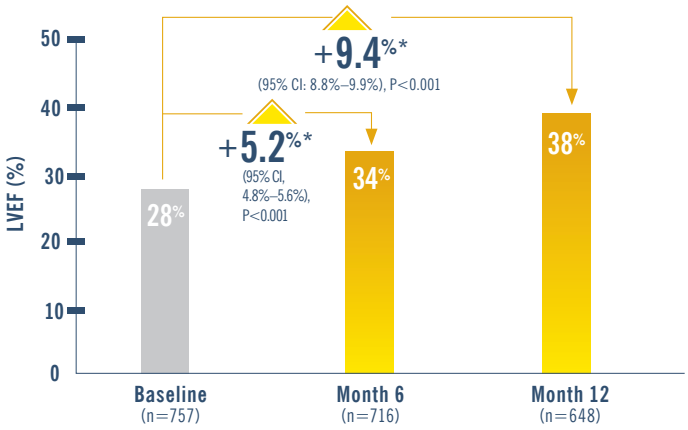
Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

Efficacy:

Primary endpoint: there was a statistically significant correlation between the reduction in NT-proBNP and echocardiographic measures between baseline, 6 months and 12 months (all correlations/r values were $< \pm 0.4$ and $P < 0.001$).[14]

ENTRESTO showed improvements in LVEF from baseline to 6 and 12 months (P<0.001)[14]



ENTRESTO was observed to be associated with an increase in markers of cardiac remodelling from baseline to 6 and 12 months (P<0.001)[14]

Remodelling parameter	Mean change from baseline at 6 months (95% CI)	Mean change from baseline at 12 months (95% CI)
LVESVi (mL/m^2)	-8.7 (-9.18 to -8.15)	-15.3 (-16.03 to -14.55)
LVEDVi (mL/m^2)	-6.7 (-7.11 to -6.19)	-12.3 (-12.92 to -11.58)
LAVi (mL/m^2)	-4.4 (-4.73 to -3.99)	-7.6 (-7.98 to -7.15)
E/e'	-1.2 (-1.63 to -0.83)	-1.3 (-1.74 to -0.86)

Adapted from Januzzi et al. 2019.[14]

In a prospective exploratory analysis, ENTRESTO was observed to be associated with reverse cardiac remodelling measures and an increase in cardiac volume and function from baseline[14]

* LSM change from baseline.[14]

Safety profile:

AEs[14,15]	N=794 n (%)
Hypotension (systolic blood pressure <90 mmHg)	140 (17.6)
Dizziness	133 (16.8)
Hyperkalaemia (Potassium >5.3 mEq/L)	105 (13.2)
Worsening kidney function*	98 (12.3)
Angioedema No treatment or antihistamines only without hospitalisation Use of catecholamines or glucocorticoids without hospitalisation Hospitalisation without airway compromise Airway compromise	 2 (0.3) 0 0 0

Adapted from Januzzi et al. 2019 (incl. supplementary information).[14,15]

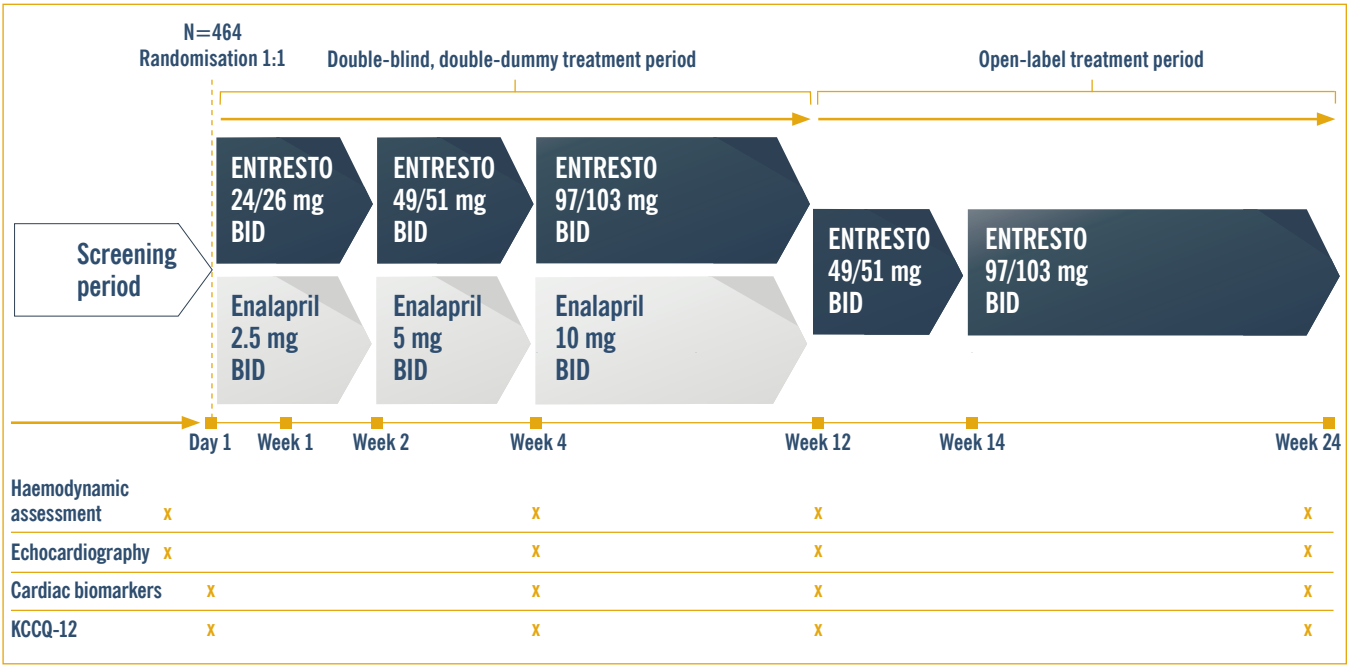
The most frequent AEs in PROVE-HF, a prospective exploratory analysis, were hypotension (17.6%), dizziness (16.8%), hyperkalaemia (13.2%) and worsening kidney function (12.3%)[14]

* Decrease in estimated glomerular filtration rate of ≥35% from baseline or an increase in creatinine of ≥0.5 mg/dL from baseline and a decrease in estimated glomerular filtration rate of ≥25% from baseline at a given visit.[15]

EVALUATE-HF: a multicentre, double-blind, forced-titration trial investigating haemodynamics and cardiac remodelling outcomes with ENTRESTO vs enalapril (primary endpoint not met)*[16]

Study design:

EVALUATE-HF was a multicentre, randomised, double-blind, double-dummy, parallel group, active-controlled, forced-titration trial comparing ENTRESTO vs enalapril on changes in central aortic stiffness in patients with HFrEF over 12 weeks. It was conducted in 464 patients.[16]



Adapted from Desai et al. 2019 (incl. supplementary information).[16,17]

Primary and secondary endpoints[16]

The primary outcome was the between-group difference in change in aortic characteristic Zc from baseline to Week 12.† The secondary outcomes included: change from baseline to Week 12 in NT-proBNP and predefined cardiac remodelling measures‡

Key inclusion criteria[16]

- Patients were ≥50 years
- LVEF ≤40%
- NYHA Class I, II or III
- Systolic blood pressure >105 mmHg at screening and randomisation
- History of hypertension
- Treatment with stable doses of guideline-directed medical therapy other than ACEi or ARBs

Patient characteristics[16]

Two thirds of patients randomised in EVALUATE-HF (67%) were NYHA Class II. At baseline, the average age of patients was 67 years, with a mean LVEF of 34%, mean SBP of 130 mmHg and mean NT-proBNP of 575 pg/mL. 84%, 25% and 86% of patients were taking guideline-directed ACEi/ARB, MRA and BB treatments, respectively

* EVALUATE-HF was a multicentre, randomised, double-blind, double-dummy, parallel group, active-controlled, forced-titration trial (n=464) which investigated haemodynamics and cardiac remodelling outcomes in ENTRESTO-treated patients vs enalapril-treated patients, where the primary endpoint (change from baseline to Week 12 in aortic characteristic Zc, a measure of central aortic stiffness) was not met, however selected secondary cardiographic endpoints, including left ventricular end-diastolic and end-systolic volumes, left atrial volume and mitral E/e' ratio, were met, suggesting improvement in cardiac remodeling.[16]

† Primary endpoint not met. The primary endpoint was the change from baseline to Week 12 in aortic characteristic Zc, a measure of central aortic stiffness.[16]

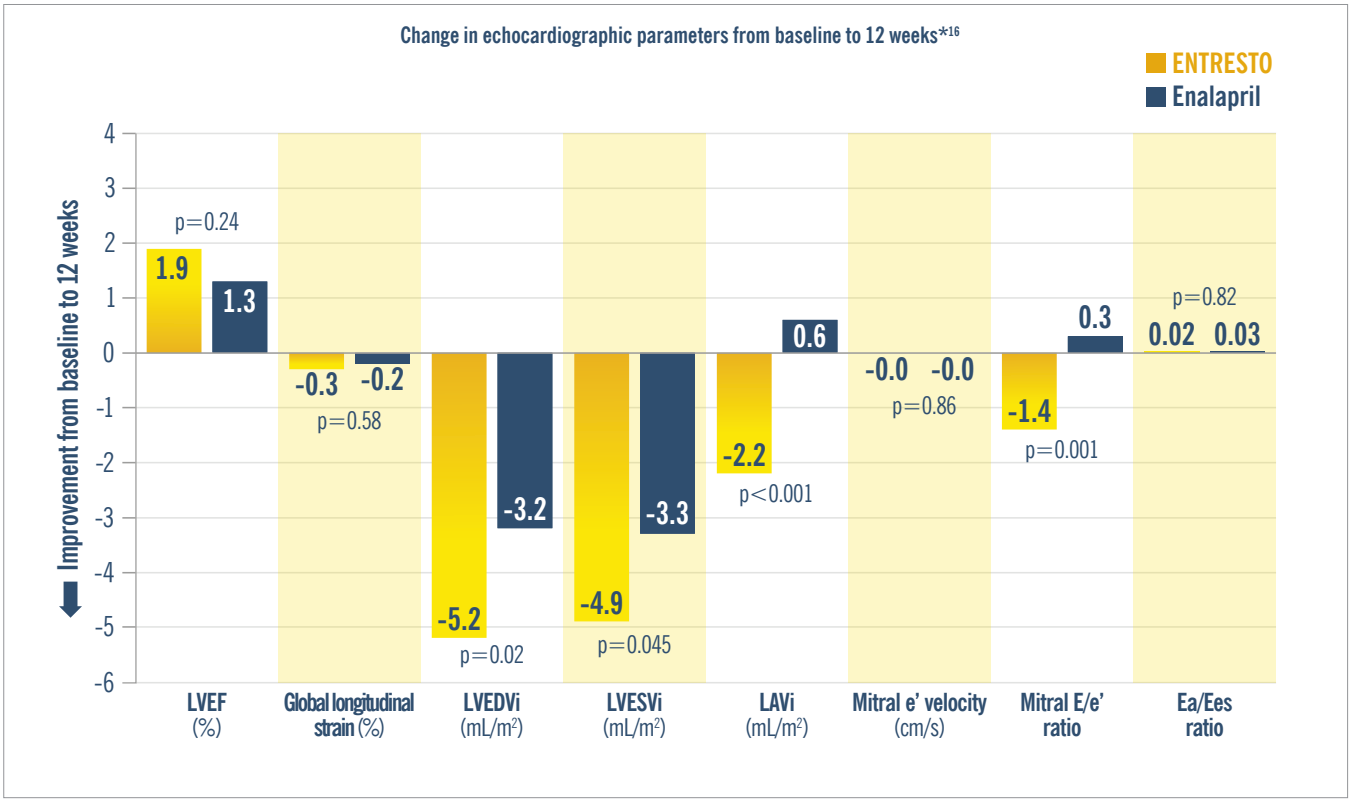
‡ These included LVEF, global longitudinal strain, LAVi, e' velocity, mitral E/e' ratio, LVESVi, LVEDVi and Ea/Ees ratio.[16]

Prescribing information and adverse event reporting information can be found at the front of this material.

Efficacy:

Primary endpoint: ENTRESTO did not meet the primary endpoint. Treatment with ENTRESTO did not significantly reduce central aortic stiffness compared with ACEi (enalapril).[16]

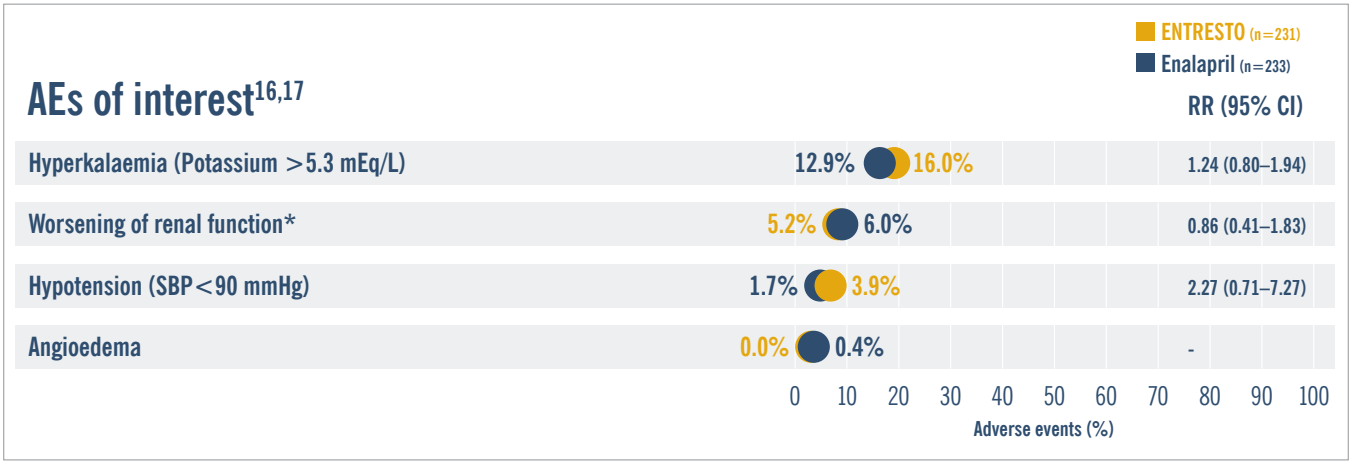
Secondary endpoints: secondary echocardiographic endpoints with ENTRESTO vs ACEi (enalapril).[16]



Adapted from Desai et al. 2019.[16]

* The graph only presents data that showed a significant improvement with ENTRESTO vs enalapril and does not present all the parameters tested. The following parameters were not significant for a between-group difference in change from baseline to 12 weeks for ENTRESTO vs enalapril: LVEF; global longitude strain; mitral e' velocity; Ea/Ees ratio.[16]

Safety profile:



Adapted from Desai et al. 2019 (incl. supplementary statement).[16,17]

The most frequent AEs were hyperkalaemia (16.0% vs 12.9%), worsening of renal function (5.2% vs 6.0%), hypotension (3.9% vs 1.7%) and angioedema (0.0% vs 0.4%) with ENTRESTO vs enalapril, respectively[16,17]

* Defined as decrease in estimated glomerular filtration rate of ≥35% from baseline, or an increase in creatinine of ≥0.5 mg/dL from baseline and a decrease in estimated glomerular filtration rate of ≥25% from baseline at a given visit.[17]

Prescribing information and adverse event reporting information can be found at the front of this material.

ENTRESTO clinical data

Clinical data that support the use of ENTRESTO in your patients with symptomatic chronic HFrEF[5-7,12,14,16,18-20]

PARADIGM-HF

PARADIGM-HF (N=8,442)

ENTRESTO showed **superior efficacy in reducing HF hospitalisations, CV death and improving QoL**, with comparable safety and tolerability vs ACEi (enalapril)[1,5,18,19]

PIONEER-HF

PIONEER-HF (N=881)

ENTRESTO showed significantly **greater reductions in NT-proBNP**, with a comparable safety profile vs ACEi (enalapril), when initiated in hospital following haemodynamic stabilisation after an ADHF episode*[7]

TRANSITION

TRANSITION (N=1,002)

TRANSITION was a randomised, parallel, open-label study comparing pre-(≥12 h) vs post-discharge (within 1–14 days) initiation of ENTRESTO in patients with chronic HFrEF (NYHA Class II–IV HF, LVEF ≤40%) following haemodynamic stabilisation after an episode of ADHF[12]

PROVE-HF

PROVE-HF (N=794)

In a prospective exploratory analysis, ENTRESTO was observed to be associated with **reverse cardiac remodelling and increases in markers of cardiac function** from baseline. Safety events were consistent with those reported in previous trials[14]

EVALUATE-HF

EVALUATE-HF (N=464)

EVALUATE-HF was a multicentre, double-blind, forced-titration trial investigating haemodynamics and cardiac remodelling outcomes with ENTRESTO vs enalapril (primary endpoint not met)[16]

Make ENTRESTO your first-choice treatment option, wherever your eligible patients are in their chronic HFrEF journey[1-4,6,7,12,14,16,18-20]

ENTRESTO is not indicated for the treatment of acute HF.[1] Patients in the PIONEER-HF/TRANSITION trial were required to be haemodynamically stabilised from an episode of ADHF while in hospital.[7,12]

* The time-averaged reduction in the NT-proBNP concentration was significantly greater in the ENTRESTO group vs the enalapril group; the ratio of the geometric mean of values obtained at Weeks 4 and 8 to the baseline value was 0.53 in the sacubitril–valsartan group as compared with 0.75 in the enalapril group (% change, −46.7% vs. −25.3%; ratio of change with ENTRESTO vs. enalapril, 0.71; 95% CI, 0.63–0.81; P<0.001) The greater reduction in the NT-proBNP concentration with sacubitril–valsartan than with enalapril was evident as early as Week 1 (ratio of change, 0.76; 95% CI, 0.69–0.85). The results remained robust in a multiple imputation analysis that was performed to account for missing data (ratio of change, 0.73; 95% CI, 0.64–0.82). The rates of worsening renal function, hyperkalaemia, symptomatic hypotension and angioedema were the key safety outcomes evaluated in this study, and did not differ significantly between the two groups.[7]

Prescribing information and adverse event reporting information can be found at the front of this material.

NOVARTIS

Entresto®
(sacubitril/valsartan)

REFERENCES

ACC – American College of Cardiology; **ACE** – angiotensin converting enzyme; **ACEi** – angiotensin converting enzyme inhibitor; **ADHF** – acute decompensated heart failure; **AE** – adverse event; **AHA** – American Heart Association; **ARB** – angiotensin receptor blocker; **ARNi** – angiotensin receptor neprilysin inhibitor; **ARR** – absolute risk reduction; **BB** – beta-blocker; **BID** – twice a day; **BNP** – brain natriuretic peptide; **CaReMeUK** – Cardio-Renal-Metabolic Partnership UK; **CI** – confidence interval; **CV** – cardiovascular; **e'** – lateral mitral annular relaxation velocity; **Ea/Ees** – ventricular-vascular coupling ratio; **E/e'** – ratio of early mitral inflow velocity to mitral annular early diastolic velocity; **EF** – ejection fraction; **eGFR** – estimated glomerular filtration rate; **ESC** – European Society of Cardiology; **HF** – heart failure; **HFrEF** – heart failure with reduced ejection fraction; **HFSA** – Heart Failure Society of America; **HR** – hazard ratio; **ICF** – informed consent form; **IV** – intravenous; **KCCQ** – Kansas City Cardiomyopathy Questionnaire; **LAVi** – left atrial volume index; **LSM** – least squares mean; **LV** – left ventricle; **LVEDVi** – left ventricular end-diastolic volume index; **LVEF** – left ventricular ejection fraction; **LVESVi** – left ventricular end-systolic volume index; **MRA** – mineralocorticoid receptor antagonist; **NS** –not significant; **NT-proBNP** – N-terminal-pro-brain natriuretic peptide; **NYHA** – New York Heart Association; **OMT** – optimised medical treatment; **QoL** – quality of life; **R** – randomised; **RR**– relative risk; **RRR** – relative risk reduction; **SBP** – systolic blood pressure; **SGLT2i** – sodium-glucose cotransporter-2 inhibitor; **Zc** – impedance.

References:

1. ENTRESTO Summary of Product Characteristics.

2. CaReMeUK HF algorithm. Available at: https://www.medscape.co.uk/viewarticle/heart-failure-management-algorithm-2022a1001d1y [Accessed March 2025].

3. McDonagh TA, Metra M, Adamo M et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J 2021;42(36):3599-3726.

4. Heidenreich PA, Bozkurt B, Aguilar D et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/ American Heart Association Joint Committee on clinical practice guidelines. Circulation 2022;145(18):e895-e1032.

5. McMurray JJV, Packer M, Desai AS et al. PARADIGM HF Investigators and Committees. Angiotensin neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

6. Claggett B, Packer M, McMurray JJV et al. Estimating the long term treatment benefits of sacubitril valsartan. N Engl J Med 2015;373(23):2289-2290.

7. Velazquez EJ, Morrow DA, DeVore AD et al; for the PIONEER HF Investigators. Angiotensin neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380(6):539-548.

8. DeVore AD, Braunwald E, Morrow DA et al; for the PIONEER-HF Investigators. Initiation of angiotensin-neprilysin inhibition after acute decompensated heart failure: results of the open-label extension of the PIONEER-HF trial. Presented at: American College of Cardiology; March 2019.

9. Morrow DA, Velazquez EJ, DeVore AD et al. Clinical outcomes in patients with acute decompensated heart failure randomly assigned to sacubitril/valsartan or enalapril in the PIONEER-HF trial. Circulation 2019;139(19):2285-2288.

10. Ambrosy AP, Braunwald E, Morrow DA et al; for the PIONEER-HF Investigators. Angiotensin receptor-neprilysin inhibition based on history of heart failure and use of renin-angiotensin system antagonists. J Am Coll Cardiol 2020;76(9):1034-1048.

11. Velazquez EJ, Morrow DA, DeVore AD et al; for the PIONEER HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019;380(6):539-548 (supplementary appendix).

12. Wachter R, Senni M, Belohlavek J et al; on behalf of the TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail 2019;21(8):998-1007.

13. Wachter R, Senni M, Belohlavek J et al; on behalf of the TRANSITION Investigators. Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study. Eur J Heart Fail 2019;21(8):998-1007 (supplementary info).

14. Januzzi JL Jr, Prescott MF, Butler J et al; for the PROVE HF Investigators. Association of change in N terminal pro B type natriuretic peptide following initiation of sacubitril valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 2019;322(11):1085-1095.

15. Januzzi JL Jr, Prescott MF, Butler J et al; for the PROVE HF Investigators. Association of change in N terminal pro B type natriuretic peptide following initiation of sacubitril valsartan treatment with cardiac structure and function in patients with heart failure with reduced ejection fraction. JAMA 2019;322(11):1085-1095 (supplementary info).

16. Desai AS, Solomon SD, Shah AM et al; for the EVALUATE HF Investigators. Effect of sacubitril valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: A randomized clinical trial. JAMA 2019;322(11):1077-1084.

17. Desai AS, Solomon SD, Shah AM et al; for the EVALUATE HF Investigators. Effect of sacubitril valsartan vs enalapril on aortic stiffness in patients with heart failure and reduced ejection fraction: A randomized clinical trial. JAMA 2019;322(11):1077-1084 (supplementary info).

18. Solomon SD, Claggett B, Packer M et al. Efficacy of sacubitril/valsartan relative to a prior decompensation: The PARADIGM HF Trial. JACC Heart Fail 2016;4(10):816-822.

19. Chandra A, Lewis EF, Claggett BL et al. Effects of sacubitril/valsartan on physical and social activity limitations in patients with heart failure: A secondary analysis of the PARADIGM-HF Trial. JAMA Cardiol 2018;3(6):498-505.

20. Lewis EF, Claggett BL, McMurray JJV et al. Health-related quality of life outcomes in PARADIGM HF. Circ Heart Fail 2017;10(8):e003430

NOVARTIS

Entresto®
(sacubitril/valsartan)

NOVARTIS