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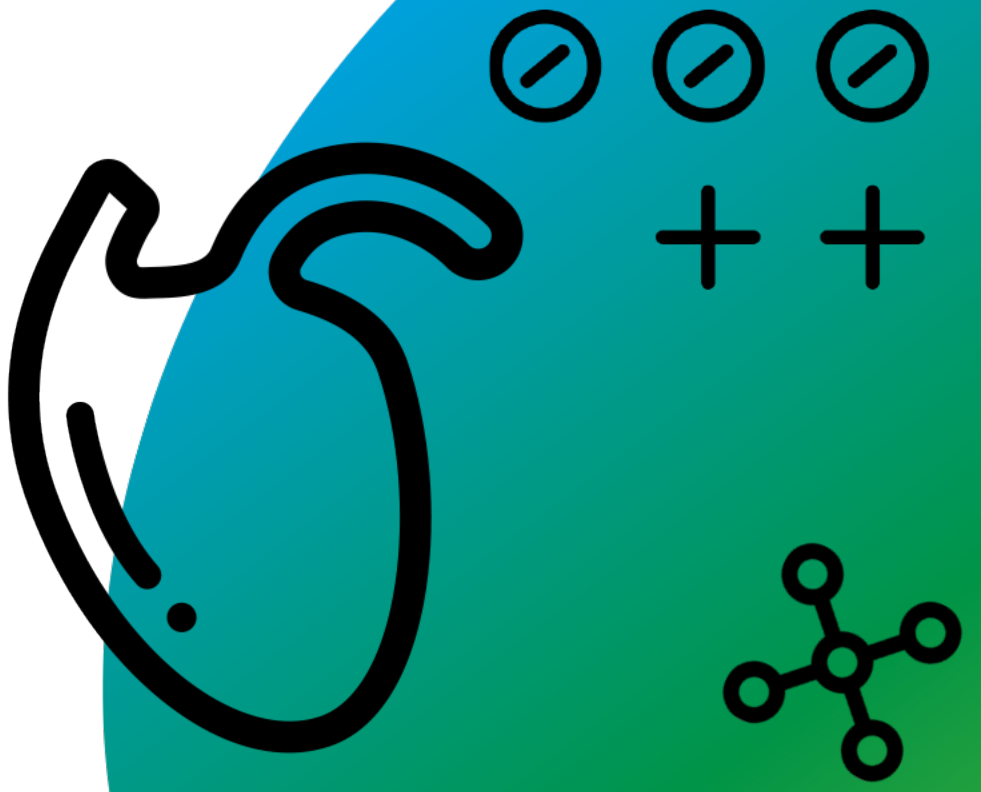
TRYVIO™ (aprocitentan) 12.5mg tablets

JERAYGO™ aprocitentan

The **first and only** hypertension therapy targeting the **endothelin** pathway



TRYVIO in the difficult-to-control treatment landscape | August 2025

TRYVIO (aprocitentan): The only approved therapy for difficult-to-control hypertension

1 Difficult-to-control hypertension

2 The optimal endothelin blocker

3 Compelling efficacy & safety data

4 Differentiated profile in high-risk populations

5 Strong advocacy – ready to launch

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The above information contains certain "forward-looking statements", relating to the company's business, which can be identified by the use of forward-looking terminology such as “intend”, "estimates", "believes", "expects", "may", "are expected to", "will", "will continue", "should", "would be", "seeks", "pending" or "anticipates" or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company's investment and research and development programs, business development activities and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company's existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected. Rounding differences in the numbers presented may occur.

TRYVIO (aprocitentan): The only approved therapy for difficult-to-control hypertension

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1 Difficult-to-control hypertension

Hypertension is the number one modifiable risk factor of cardiovascular morbidity and premature death –
Risk is even greater in patients whose blood pressure is difficult-to-control

The Global Burden of Disease 2021, The Lancet 2024

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Difficult-to-control versus resistant hypertension

Hypertension guidelines recommend less than

130/80 mmHg[2]

as a **blood pressure goal**

Resistant hypertension

Patients whose blood pressure remains high, despite receiving at least three antihypertensives of different pharmacological classes, including a diuretic, at optimal dose.

References: 1. Institute for Health Metrics and Evaluation (IHME). **Global Burden of Disease 2021: Findings from the GBD 2021 Study.** Seattle, WA: IHME, 2024.
2. Whelton PK, e*t al. Hypertension.* 2018;71(6):1269-1324.

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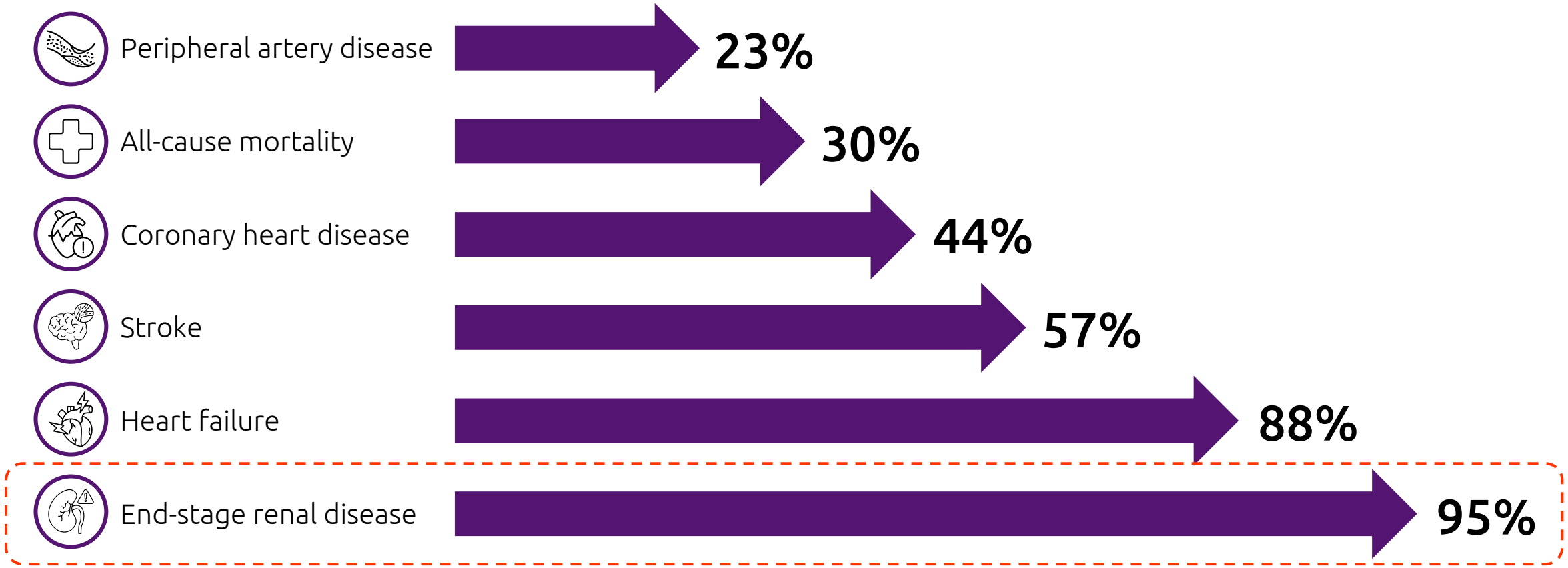
Morbidity and mortality risk is greater in patients whose hypertension is difficult-to-control

Increased risks when comparing individuals with vs. without difficult-to-control hypertension



1. Muntner P, *et al. Hypertension.* 2014;64(5):1012-1021.

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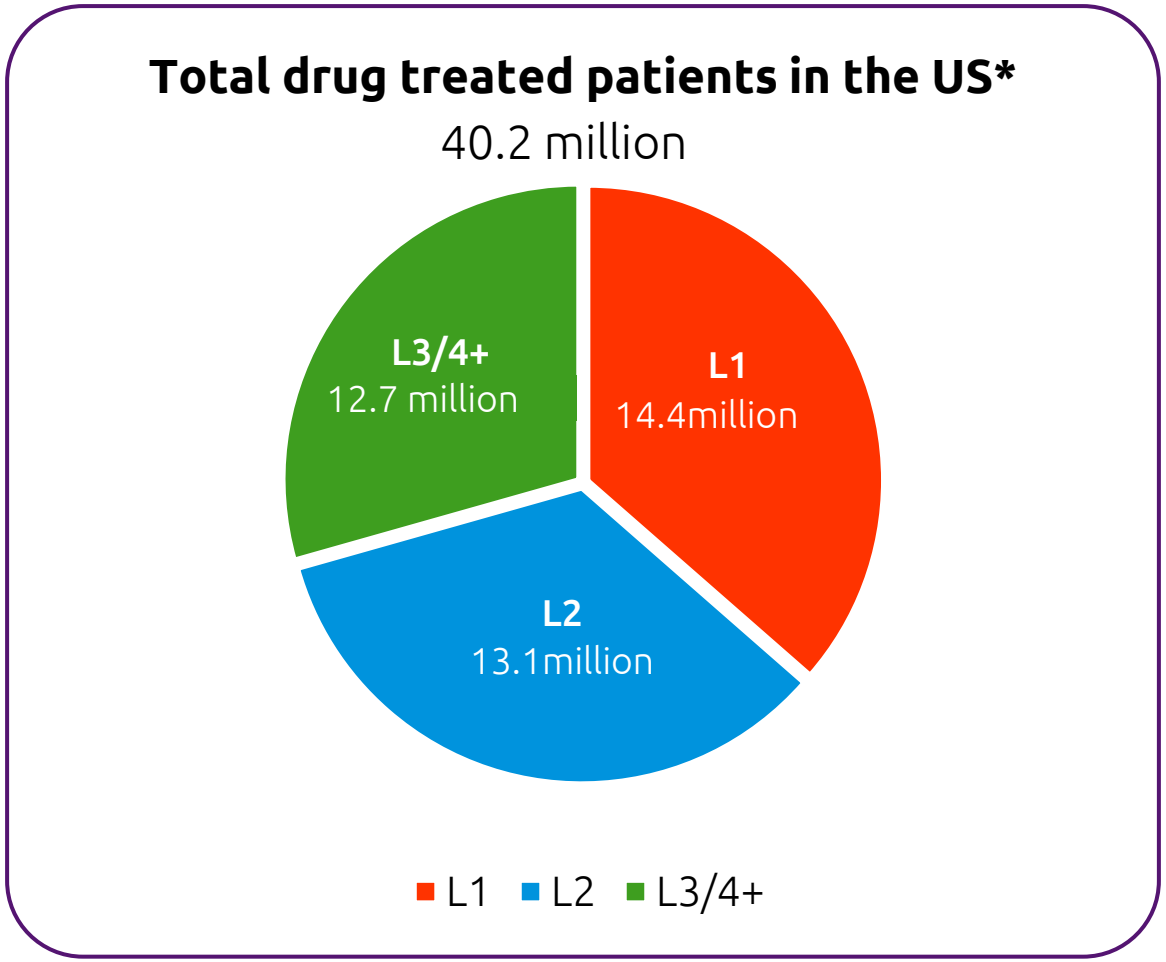
Significant medical need in difficult-to-control hypertension



~26 million US patients are not adequately controlled on other drugs despite treatment and are amenable to TRYVIO according to the US indication

*Source: Komodo claims; 3-Year Dx: Sep'20 - Aug'23; 1-Year Rx: Sep'22 - Aug'23.

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2 The optimal endothelin blocker

Aprocitentan targets the endothelin system and represents the first drug from the established ERA class – optimized for patients with difficult-to-control hypertension

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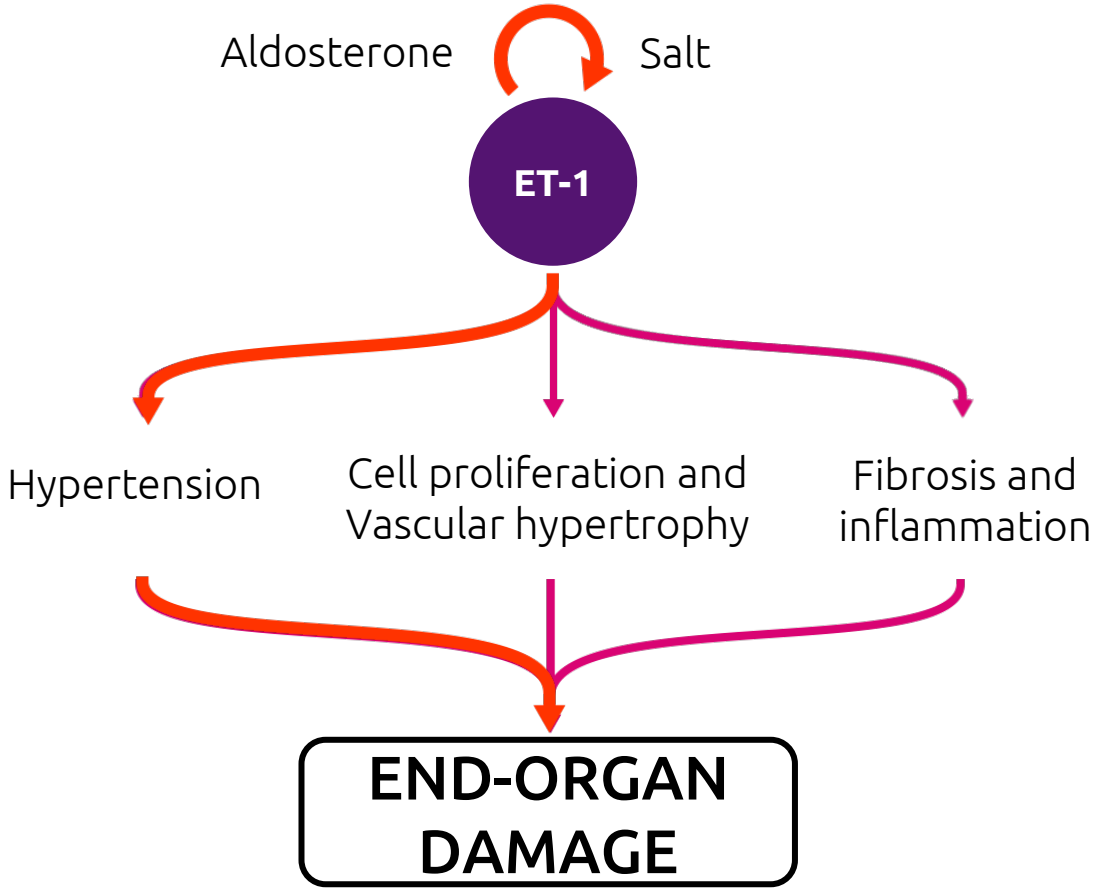
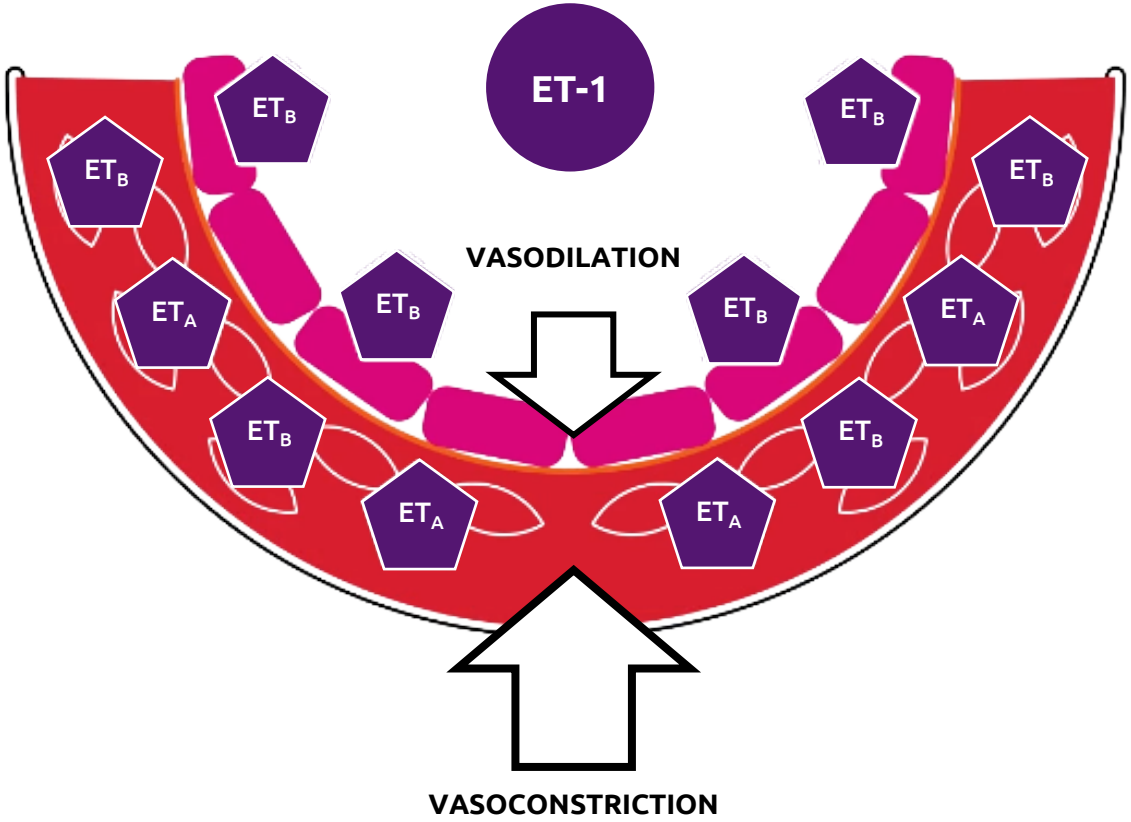
The endothelin system



Increased expression of ET_B in smooth muscle cells amplifies vasoconstriction effects of endothelin



Abbreviations: ET_A and ET_B, endothelin receptor A and B; ET, endothelin

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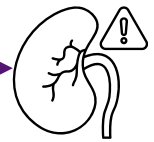
Endothelin is upregulated and it is the key driver of difficult-to-control hypertension in these patients

Comorbidities that are at high risk for difficult to control hypertension

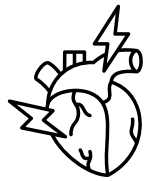
- High body weight
- Black
- Post-menopausal women
- Obstructive sleep apnea
- Type 2 diabetes
- Heart failure
- Chronic kidney disease

Difficult-to-control hypertension

Consequently, patients are at significant risk of several life-threatening diseases



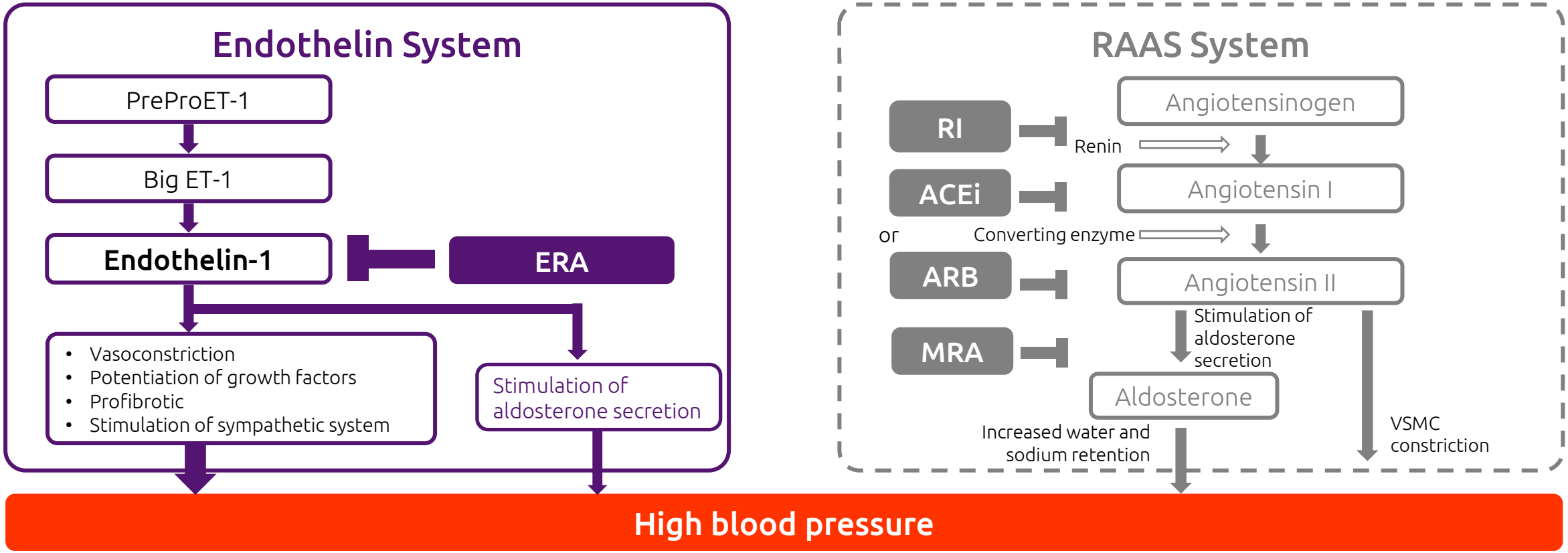
Chronic kidney disease



Heart failure

Stroke

Blockade of the RAAS pathway is the focus of current marketed and developmental therapies



L. Naseralallah, Blood Pressure 2024; ESH Guidelines 2023

Abbreviations: ACEi , angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ERA, endothelin receptor antagonist; ET, endothelin; MRA, mineralocorticoid receptor antagonist; RAAS, renin-angiotensin-aldosterone system; RI, renin inhibitor; VSMC, vascular smooth muscle cells.

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3 Compelling efficacy & safety data

Aprocitentan demonstrated compelling efficacy, safety and tolerability in difficult-to-control / resistant hypertension

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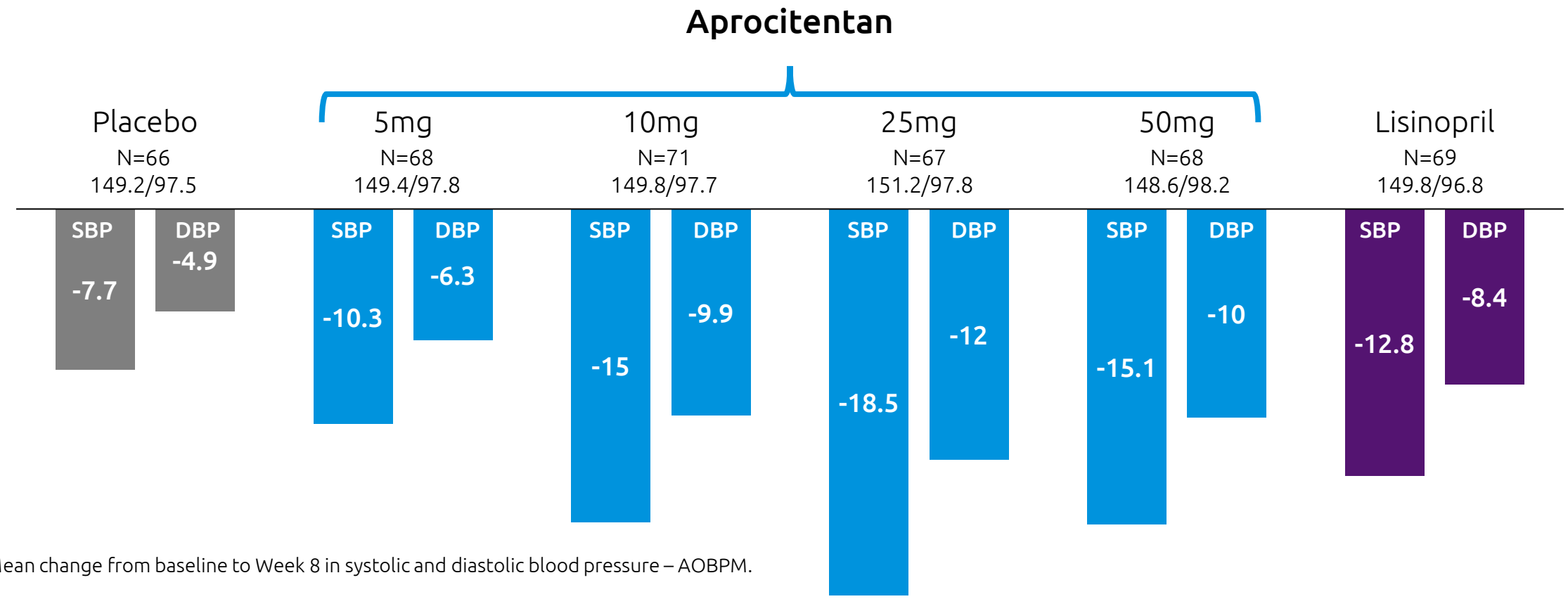
Aprocitentan as monotherapy in systemic hypertension

Phase 2 trial in patients with essential hypertension



Mean change from baseline to Week 8 in systolic and diastolic blood pressure – AOBPM.

Verweij P, et al. *Hypertension*. 2020

Abbreviations: SBP, Systolic blood pressure; DBP, Diastolic blood pressure

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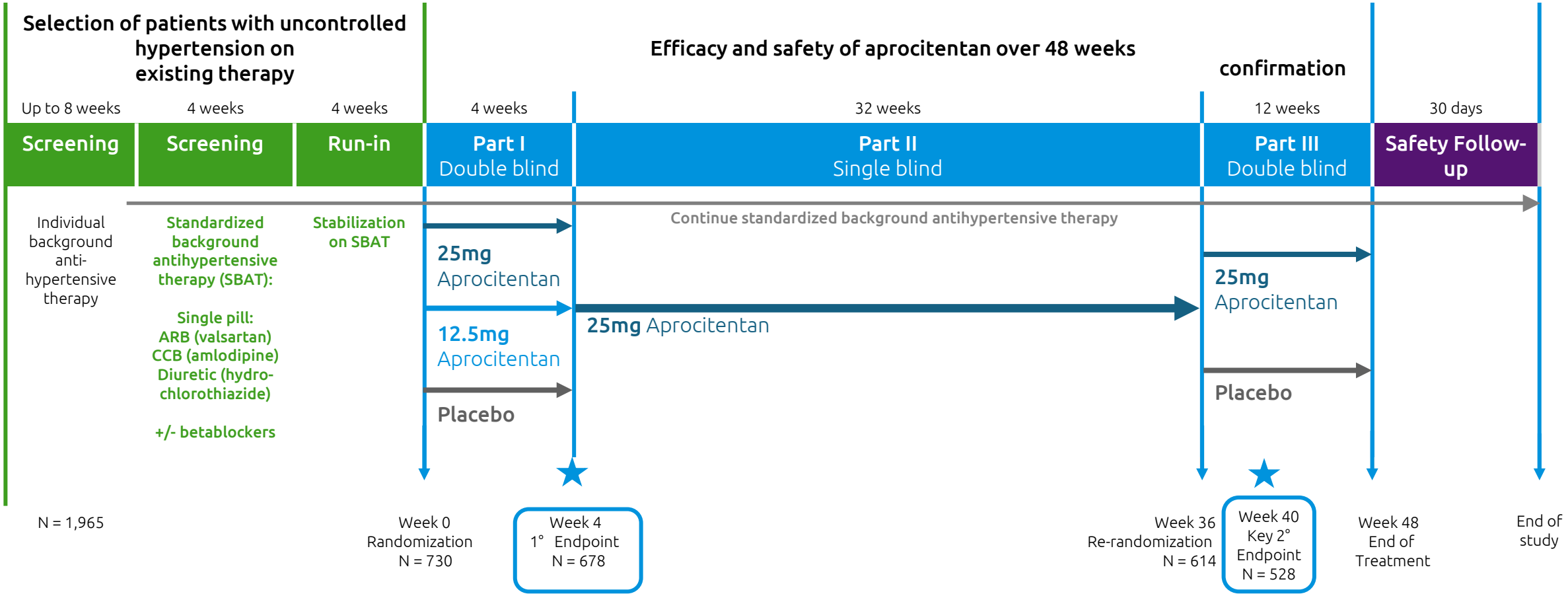
PRECISION: Investigated onset and durability of blood pressure reduction



Schlaich MP, *et al. The Lancet*, 2022

PRECISION population mirrors clinical reality of resistant hypertension with comorbidities and lack of response to prior therapies

Older patients

- **≥65 years old** (34%)
  - Of which, 10% were **≥75 years old**

High-risk and patients with comorbidities

- **North America origin** (29%)
  - Of which 38.9% were **Black or African American**
- **Type 2 Diabetes** (54%)
- **Obese** (55%; 30 to <40) and **severely obese** (15%; ≥40)
- **Congestive heart failure (20%)**
  - Of which, 40% had **elevated NT-proBNP**
- **CKD stage 3 or 4 (22%)**
  - Of which,13% had **macroalbuminuria**

Schlaich MP, *et al. The Lancet,* 2022

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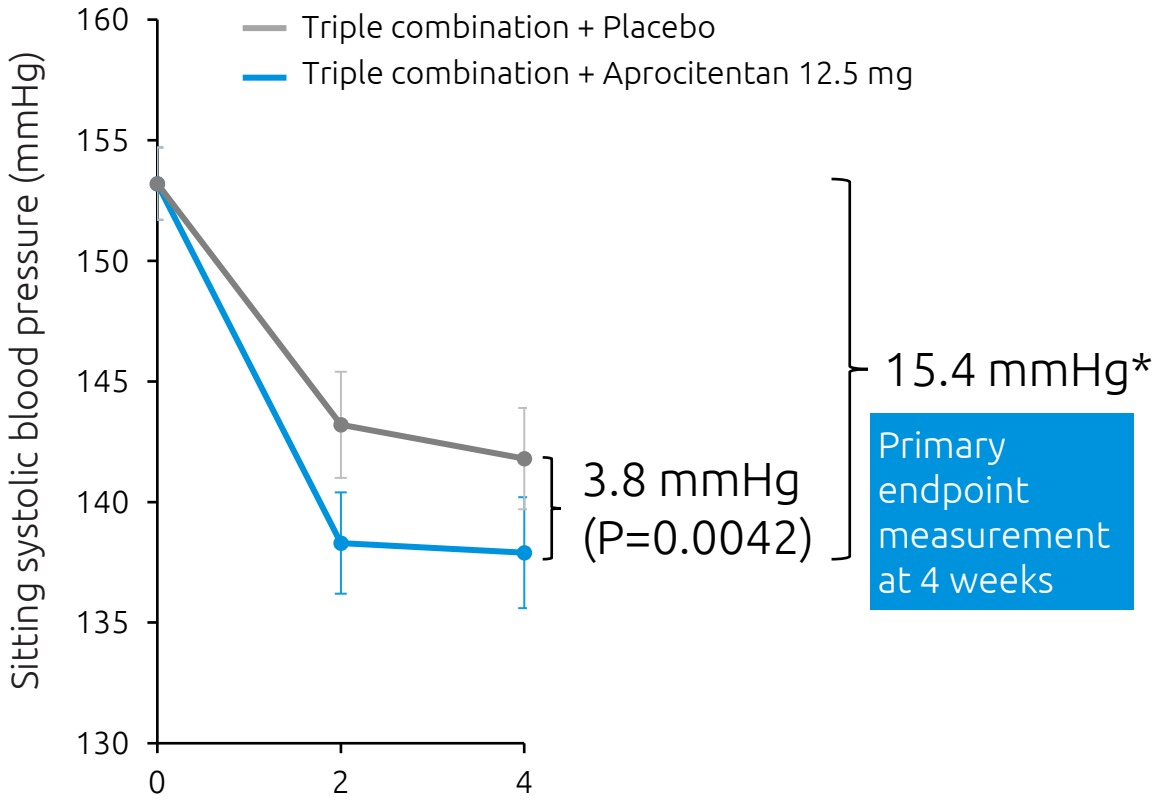
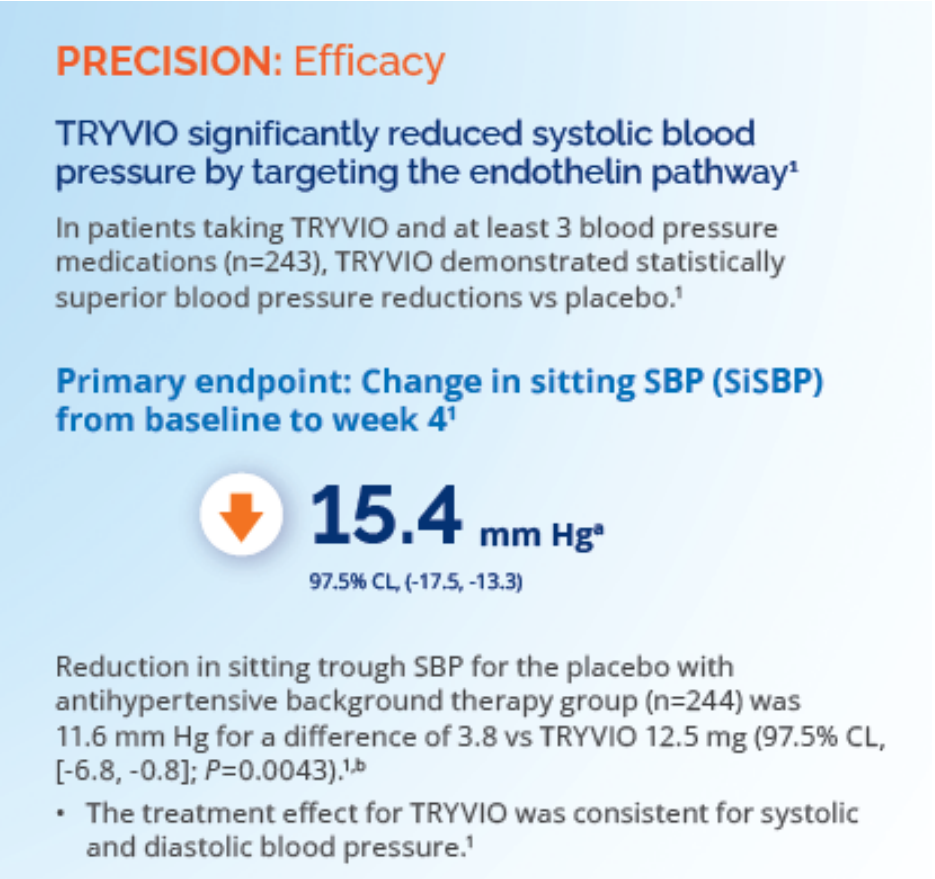
Rapid double-digit reduction in BP seen as early as 2 weeks with continued benefit over time

On top of three antihypertensives: valsartan, amlodipine and hydrochlorothiazide



* Measured at trough

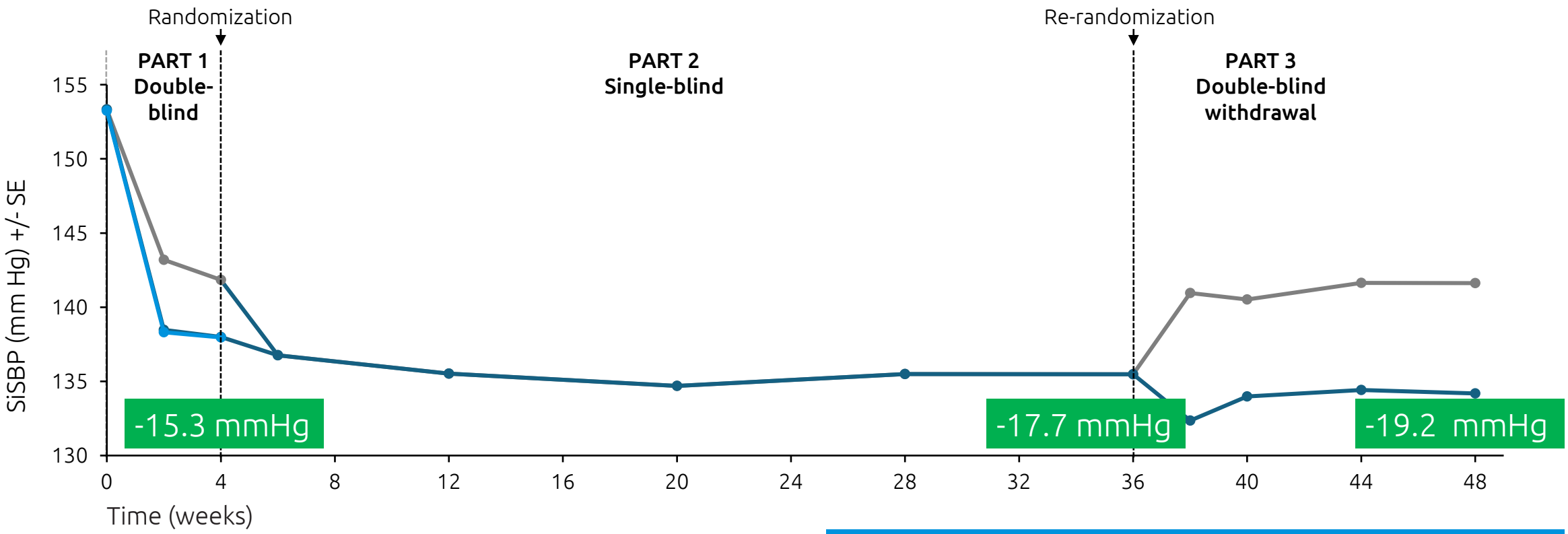
Schlaich MP, *et al. The Lancet*, 2022



Regulatory approved promotional material

Double-digit BP decrease was sustained

BP reduction confirmed up to 48 weeks



- Triple combination + Placebo
- Triple combination + Aprocitentan 12.5 mg
- Triple combination + Aprocitentan 25 mg*

Key secondary endpoint after 4 weeks of withdrawal
25 mg* vs placebo: - 5.8 mmHg, P<0.0001
@week 40 of treatment

Schlaich MP, *et al. The Lancet*, 2022

*The 25 mg dose of aprocitentan is not approved for use in the US

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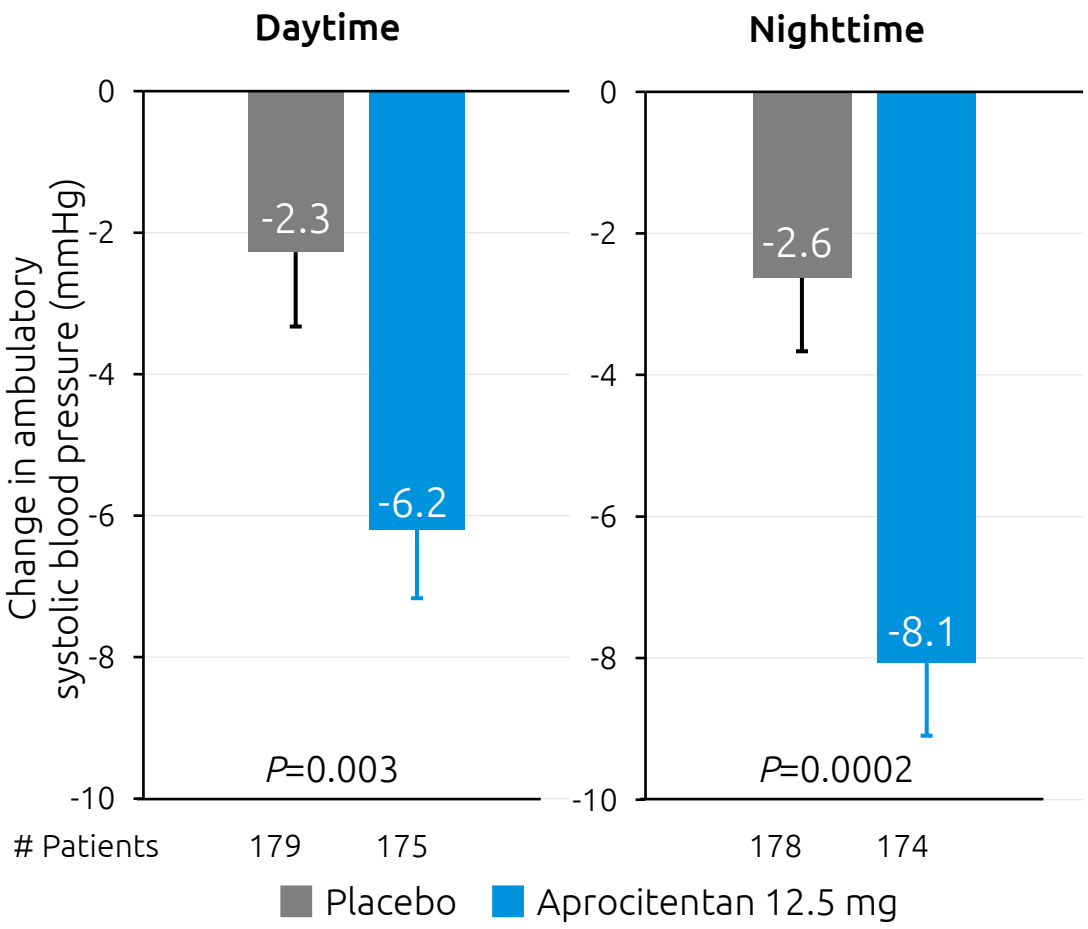
Major night-time BP decrease



- Insufficient BP decrease at night is a very strong predictor of poor outcome in hypertension.
- **Unique nighttime efficacy** of aprocitentan is an important feature and may be due to sympatholytic effects in addition to long half-life.

Schlaich MP, *et al. The Lancet,* 2022; ESH Guidelines 2023

US Prescribing Information

TRYVIO™ (aprocitentan) tablets, for oral use
Initial U.S. Approval: 2024

WARNING: EMBRYO–FETAL TOXICITY
See full prescribing information for complete boxed warning.

- Based on animal data TRYVIO may cause fetal harm if used by pregnant patients and is contraindicated in pregnancy. (4.1, 5.1, 8.1)
- For patients who can become pregnant, exclude pregnancy prior to initiation of treatment with TRYVIO. (2.2, 5.1, 8.3)
- Use effective contraception prior to initiation of treatment, during treatment, and for one month after stopping TRYVIO. (2.2, 4.1, 5.1, 8.3)
- When pregnancy is detected, discontinue TRYVIO as soon as possible (5.1)

----------INDICATIONS AND USAGE----------

TRYVIO is an endothelin receptor antagonist indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of TRYVIO is 12.5 mg orally once daily, with or without food. (2.1)

Broader indication – difficult-to-control hypertension – compared to the resistant hypertensive patients included in PRECISION

----------INDICATIONS AND USAGE----------
TRYVIO is an endothelin receptor antagonist indicated for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions. (1)

Table 1 Adverse reactions reported with a frequency of ≥2% in TRYVIO-treated patients and greater (≥1%) than in placebo-treated patients during the initial 4-week double-blind placebo-controlled treatment (part 1)

Adverse Reaction	12.5 mg N = 243 %	Placebo N = 242 %
Edema/fluid retention	9.1	2.1
Anemia	3.7	0

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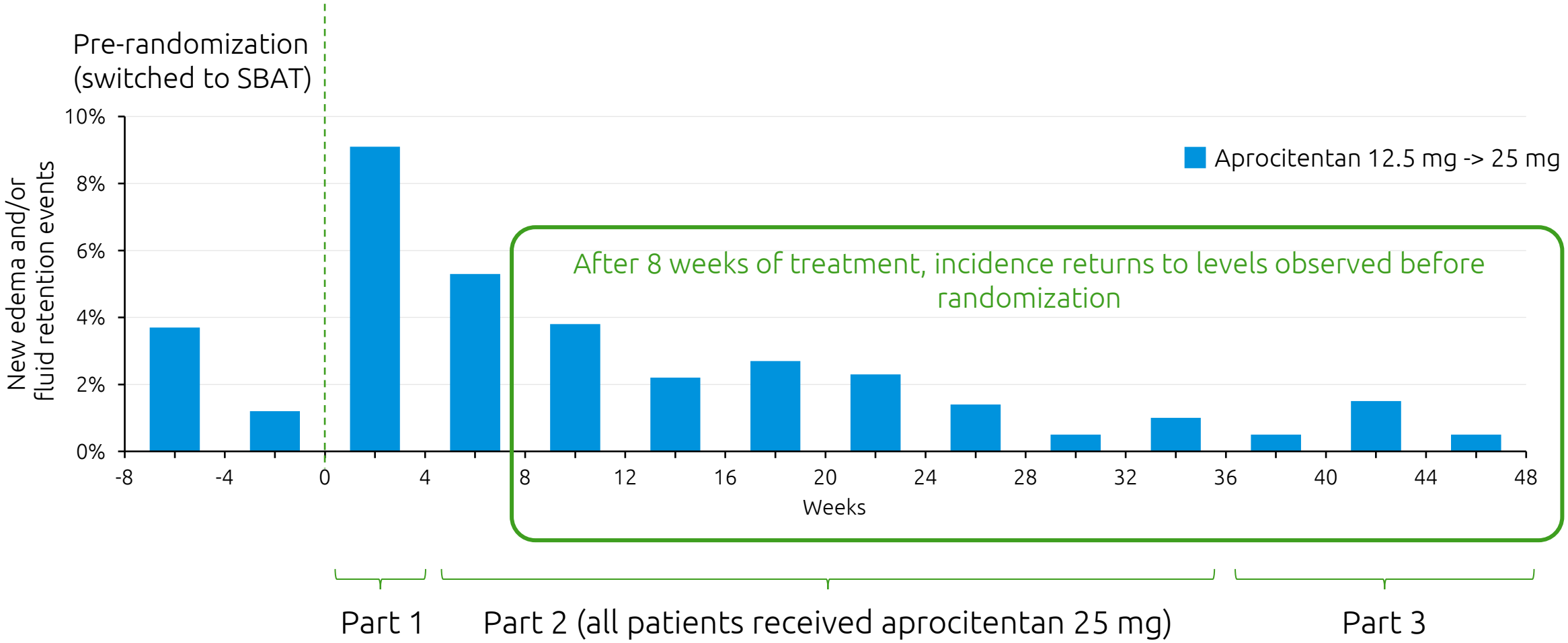
Edema: mild, peripheral, early and transient

Edema discontinuation rate <1% over 48 weeks



Schlaich MP, *et al. The Lancet*, 2022

Demonstrated safety and tolerability profile

No drug-drug interactions

No increased incidence of hyperkalemia

No hypotension,
No heart rate increase,
No headaches

with or without food

No dose adjustments

Very low overall discontinuation rate due to adverse events over 48 weeks: only 7.3%

Half-life of 41 hours

One dose can be missed

Schlaich MP, *et al. The Lancet,* 2022; L. Nasaralallah, Blood Pressure 2024

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4 Differentiated profile in high-risk populations

The blood pressure-lowering effect of TRYVIO was consistent among subgroups – defined by age, sex, race, body mass index, baseline eGFR, baseline UACR, and medical history of diabetes

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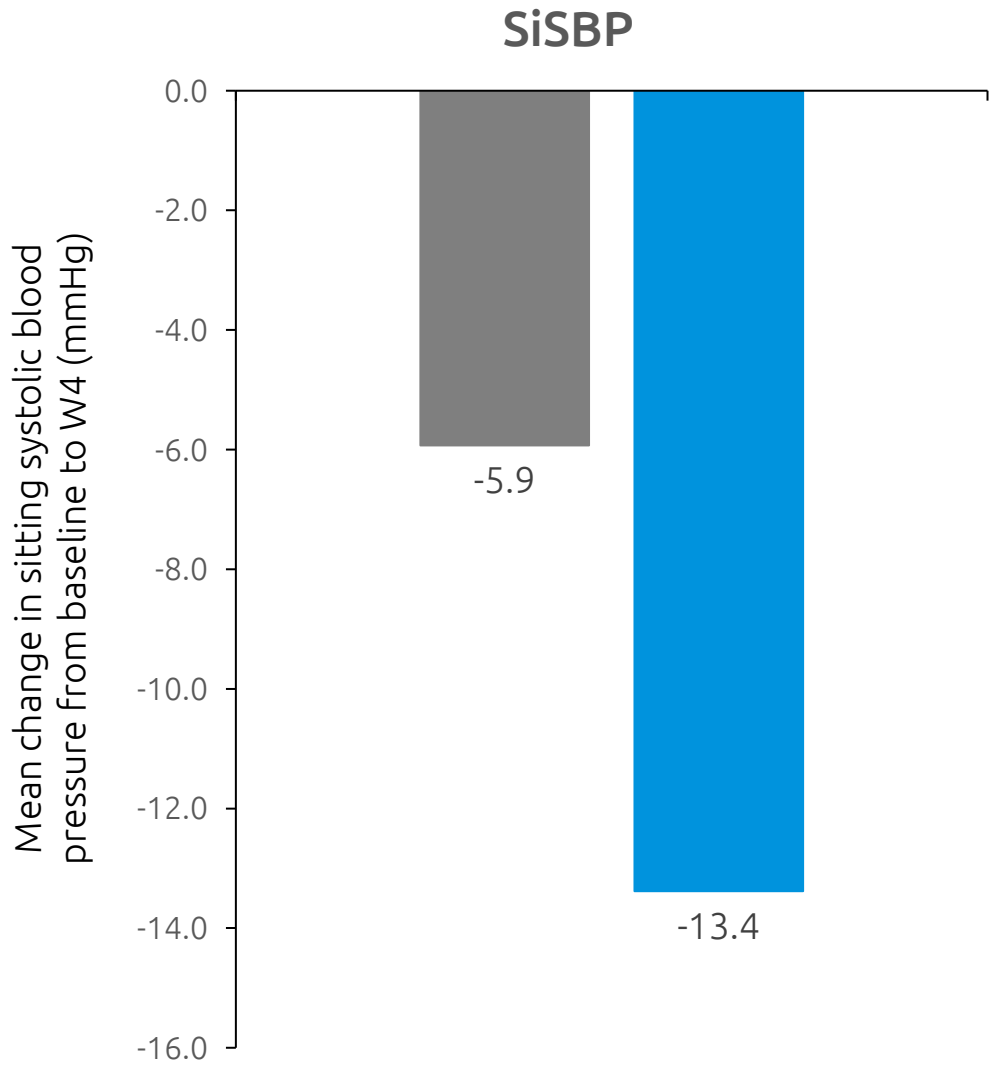
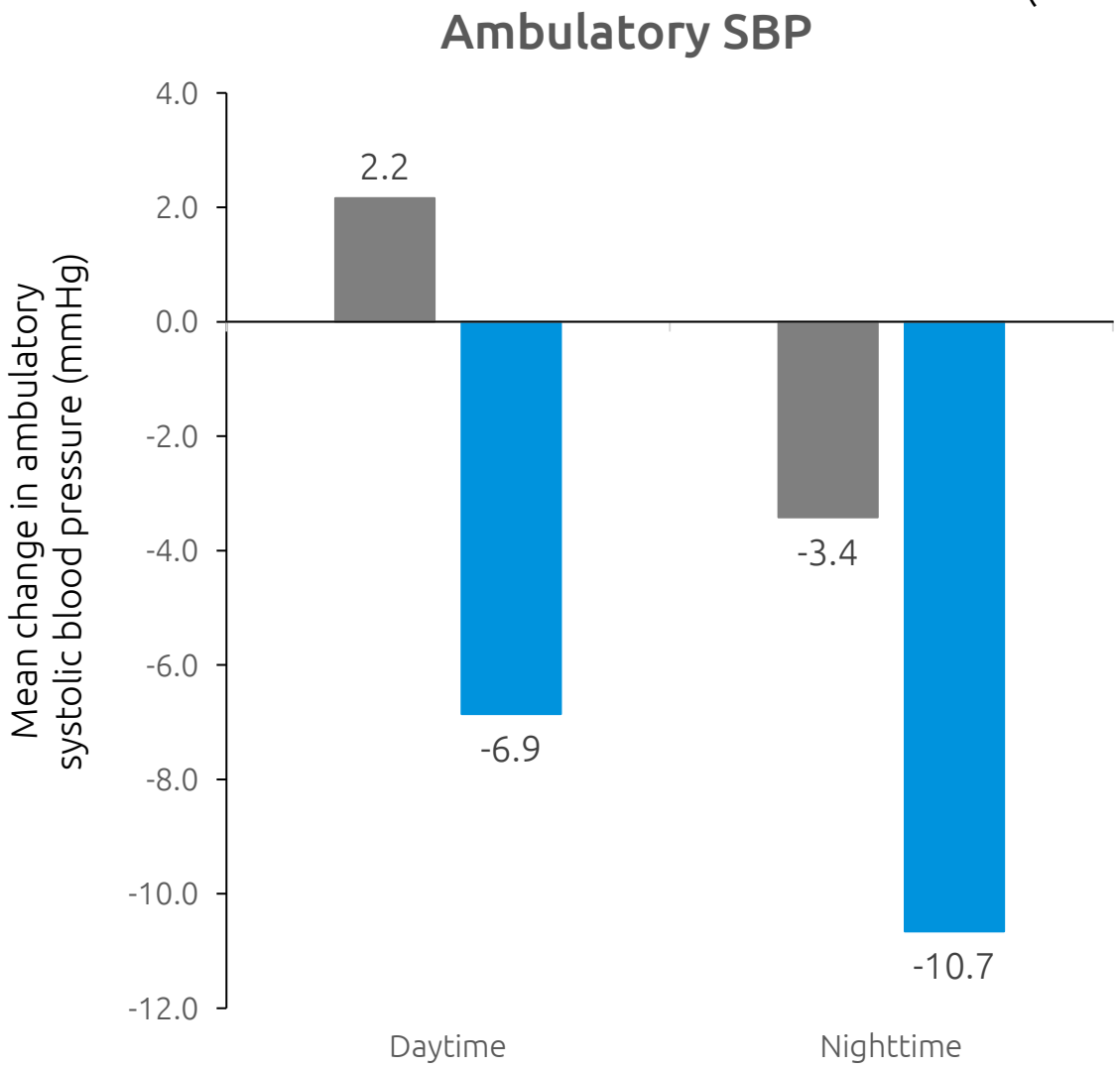
Unprecedented BP reduction in CKD 3/4 patients

(n = 162)





Triple combination + Placebo

Triple combination + Aprocitentan 12.5 mg

Schlaich MP, *et al. The Lancet,* 2022; Data on file

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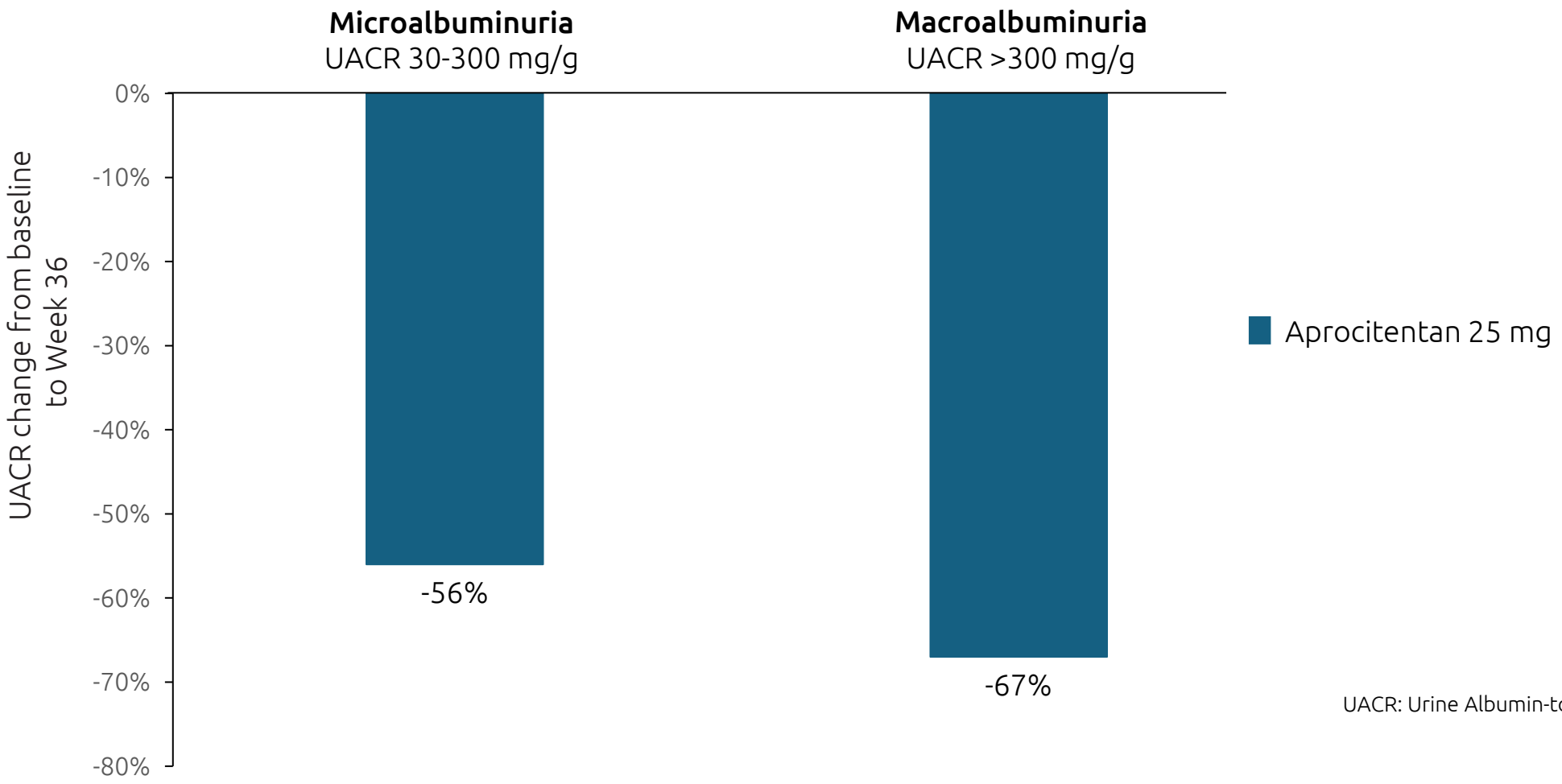
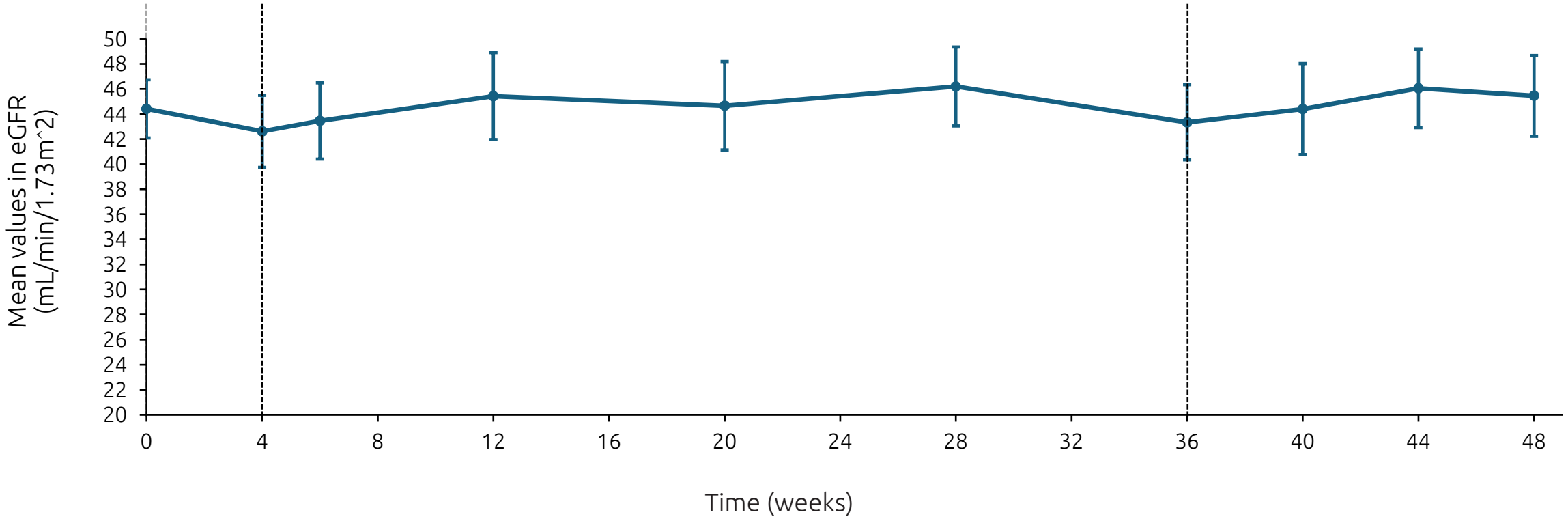
Major reduction of UACR at week 36



UACR: Urine Albumin-to-Creatinine Ratio

Schlaich MP, *et al. The Lancet,* 2022; Data on file

Stable eGFR in CKD 3/4 at 25 mg over 48 weeks



Aprocitentan 25 mg

eGFR mean observed values for patients treated with aprocitentan 25 mg over 48 weeks – CKD stage 3/4 (eGFR = 15 to <60 ml/min/1.73m^2) subgroup (n = 162)

Schlaich MP, *et al. The Lancet,* 2022; Data on file

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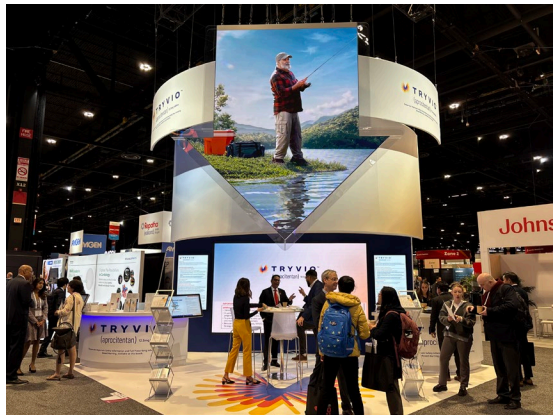
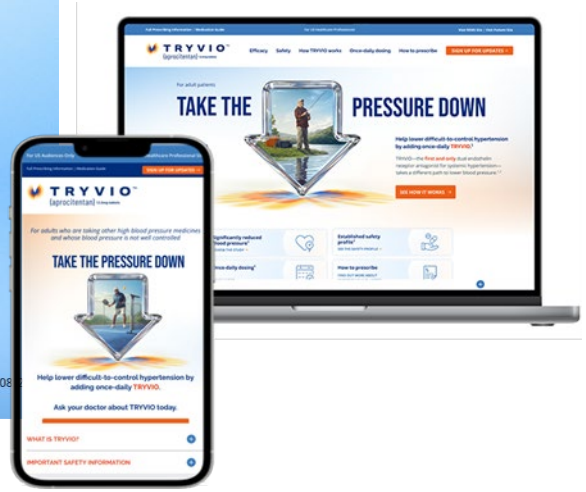
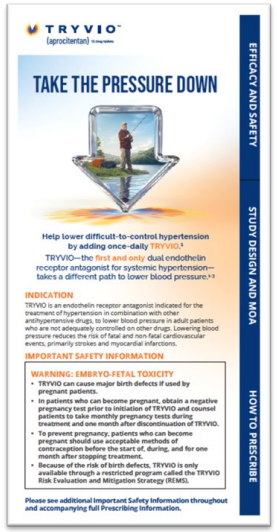
5 Strong advocacy – ready to launch

Prescribers are seeing the benefits of TRYVIO in real-world practice.

Commercially available in the US and ready for launch with the right partner







TRYVIO™ (aprocitentan) 12.5mg tablets

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Early positive outcomes with TRYVIO in US

Strong advocacy and interest for patients with difficult-to-control hypertension

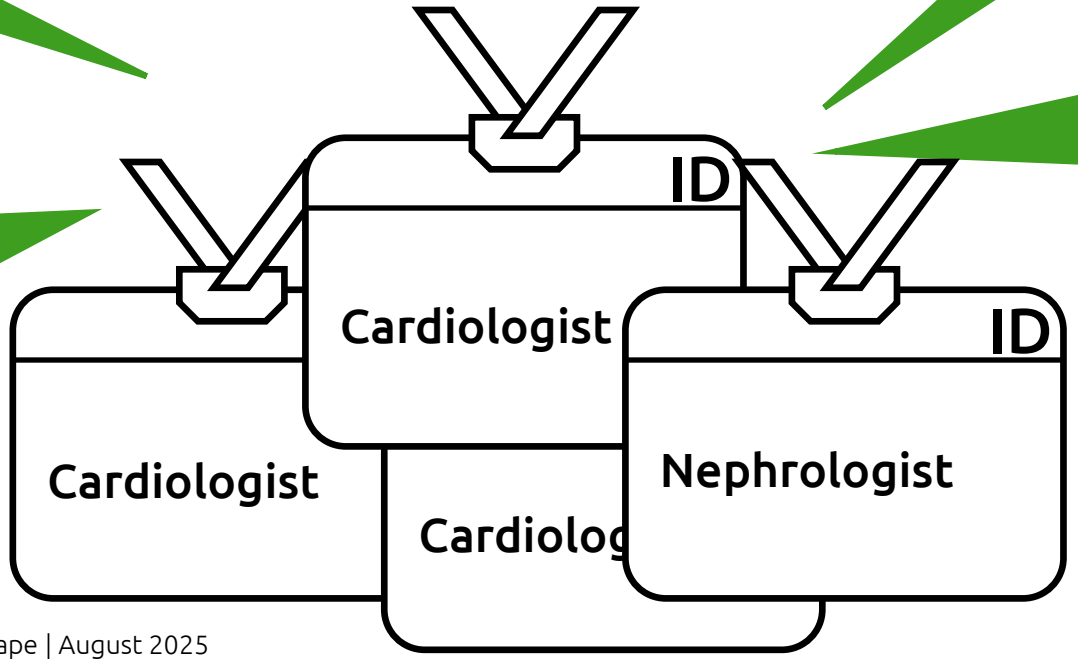
- **~10 to 15 mmHg drop** in BP
- **Well tolerated**, plans to expand use within **CKD population**
- **Endothelin MOA is needed** for these difficult to treat patients

We continue to build advocacy and real-world evidence

Key institutions we are engaged with on these efforts include **Columbia, Cedars Sinai, Stanford, and Duke**

"Resistant hypertension has complexities... One patient had a clear need for additional medication, **he normalized with adding TRYVIO!**"

- **~10 to 15 mmHg drop** in BP
- Patients on **multiple other medications** are **tolerating TRYVIO well**



- **~5 to 20 mmHg drop** in BP
- Close monitoring based on patient type, **preferred in CKD**

TRYVIO: first systemic hypertension treatment to target a new pathway in over 30 years

TRYVIO is the *first and only* dual endothelin receptor antagonist (ERA) approved for systemic hypertension

The endothelin pathway is a key driver in difficult-to-control hypertension

TRYVIO is well tolerated and delivers rapid, durable blood pressure reduction when added on top of any existing treatment regimen for patients with difficult-to-control hypertension

Once daily, single dose tablet

eGFR down to 15

No risk of hyperkalemia, hypotension and no clinically relevant drug-drug interactions

TRYVIO™ (aprocitentan) 12.5mg tablets

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