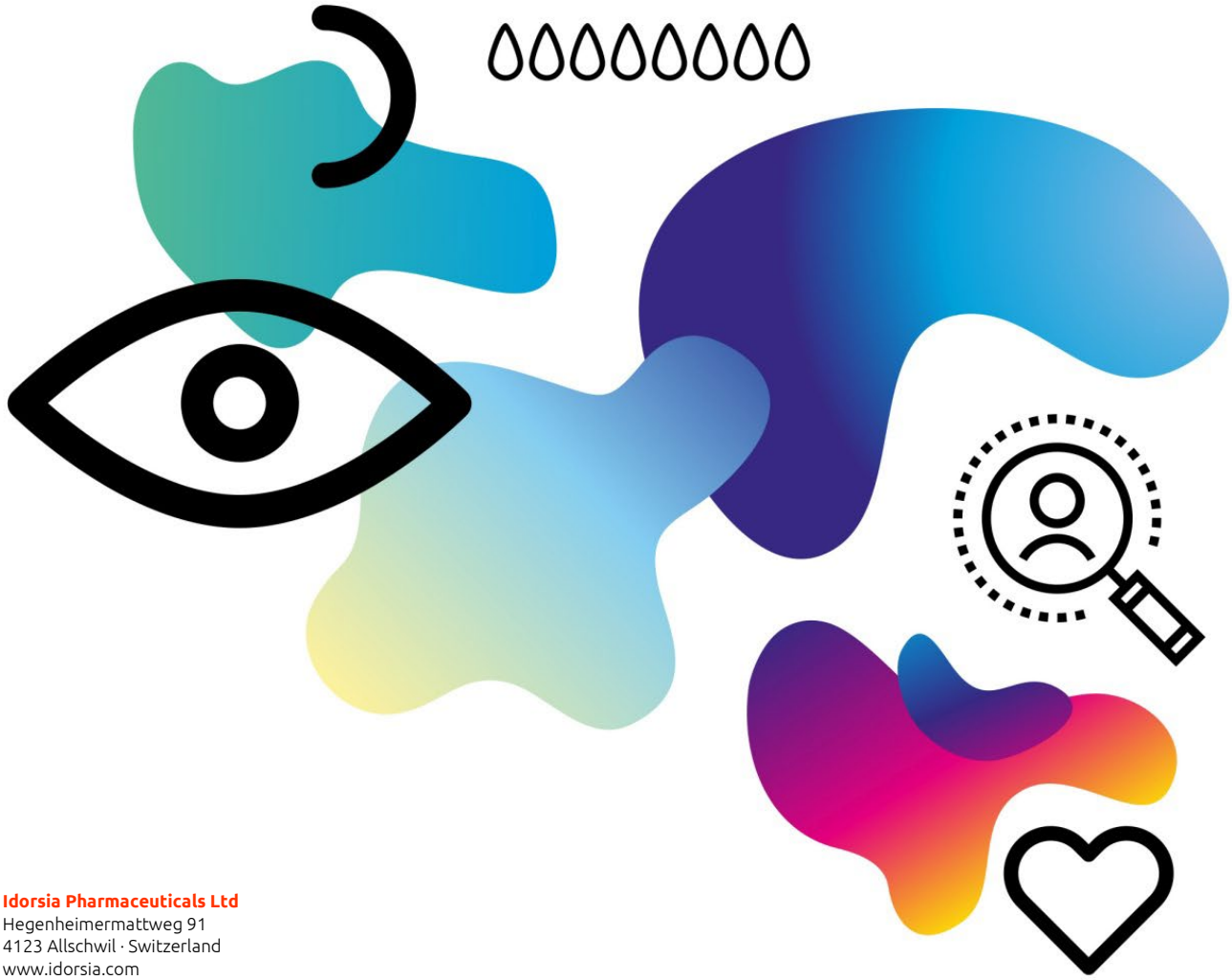
Transcript

August 28, 2025

TRYVIO: The first and only hypertension therapy targeting the endothelin pathway

This document is intended for an investor audience only.



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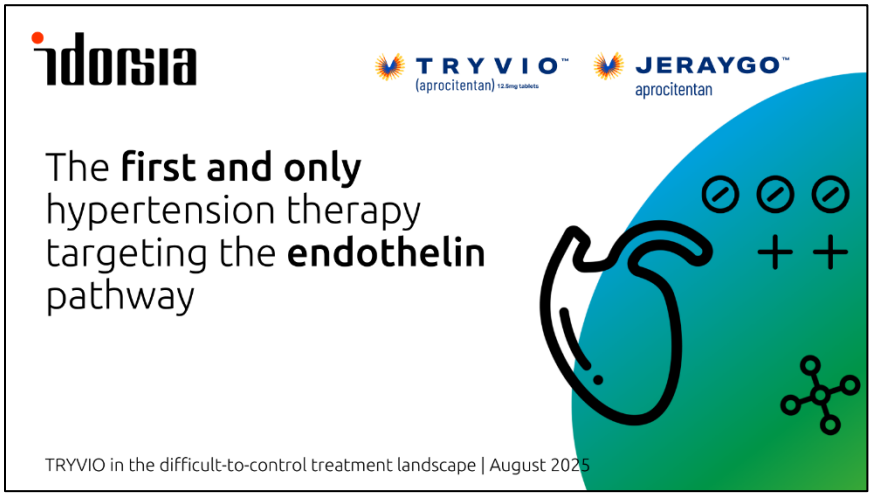
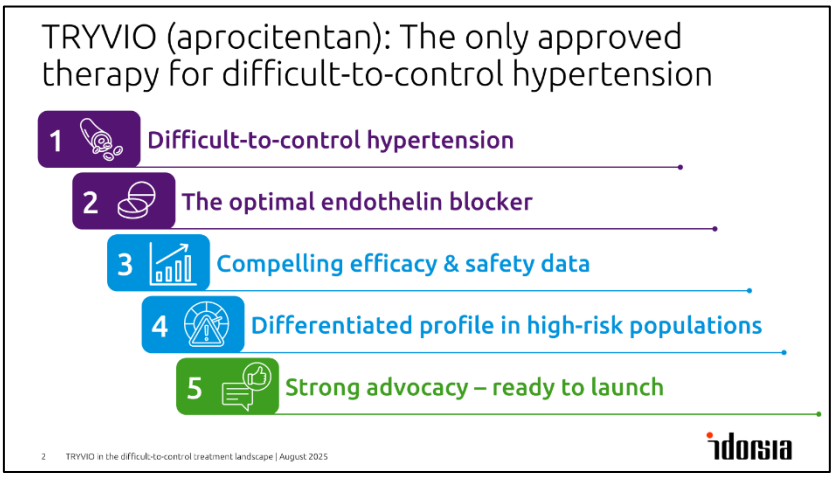


- Thank you for following this presentation of aprocitentan, the first and only hypertension therapy that targets the endothelin pathway.
- Endothelin is a fundamental driver of hypertension initiation, development, and progression, that until the approval of aprocitentan, remained unaddressed by hypertension therapies.
- Endothelin is elevated in hypertension and its role corresponds to many of the pathogenic facets of hypertension and its consequences.
- Aprocitentan is available as TRYVIO in the US and will be launched in Europe as JERAYGO. It is set to transform the treatment landscape for patients with difficult-to-control hypertension and has blockbuster market potential.
- Idorsia is currently engaging with potential partners to launch this outstanding product and maximize the opportunity.



- Today, we will highlight
  - the urgent unmet medical need and significant market opportunity in difficult-to-control hypertension,
  - the fundamental role of endothelin in hypertension,
  - and the clinical evidence that secured TRYVIO's approval and its place in the recently updated ACC/AHA treatment guidelines.

- In addition, we will go through the details of its differentiated profile, data in several specific patient populations, including elderly and those with chronic kidney disease or CKD.
- Finally, we will share some of the real-world evidence and market preparation activities currently underway to secure access to this important therapy.

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.

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

- This presentation contains forward-looking statements based on our research, prescriber feedback, advisory boards and primary quantitative market research. Please consider both risks and opportunities before investing in Idorsia.

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

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

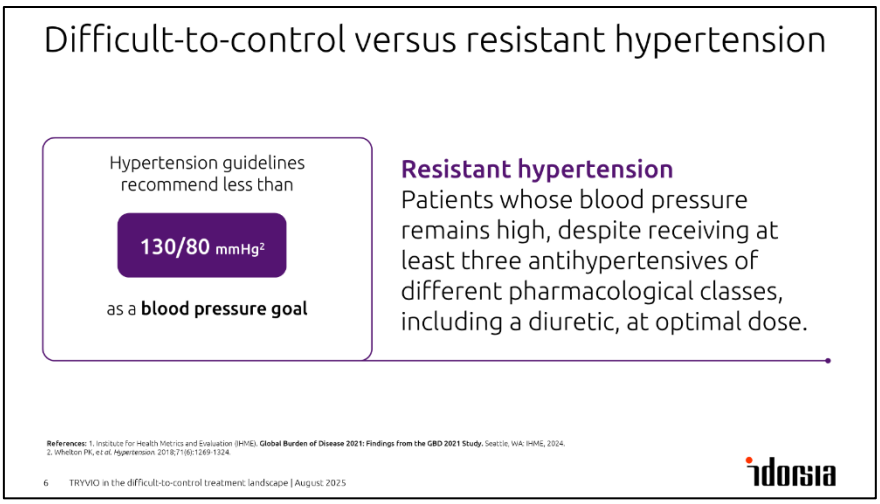
1 Difficult-to-control hypertension

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

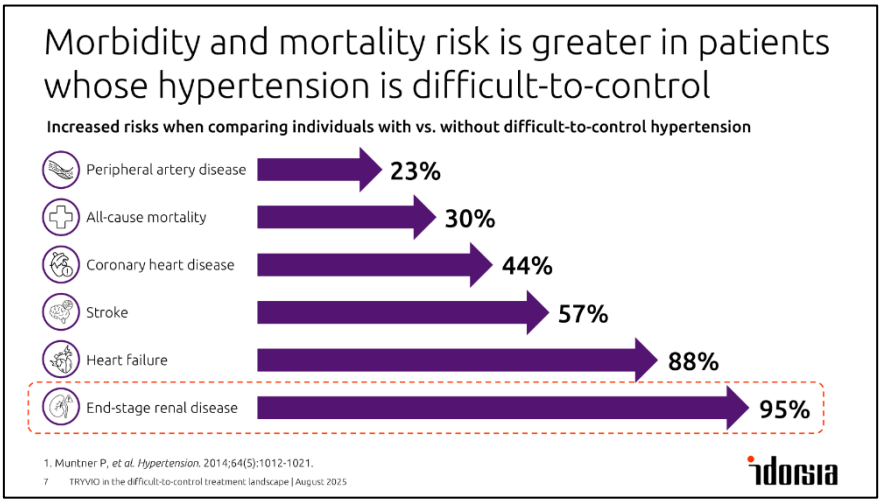
The Global Burden of Disease 2021, The Lancet 2024

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

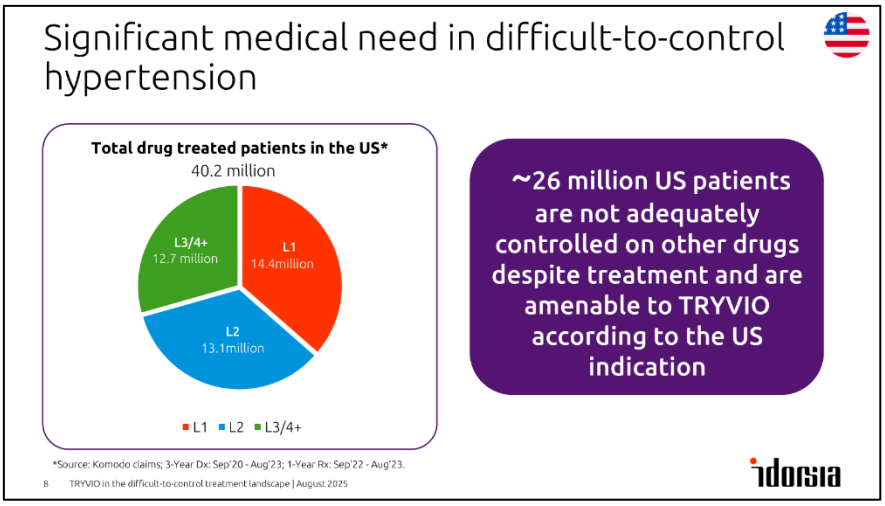
- Hypertension is the number one modifiable risk factor for cardiovascular morbidity and premature death. The risk is even higher for patients with difficult-to-control hypertension.



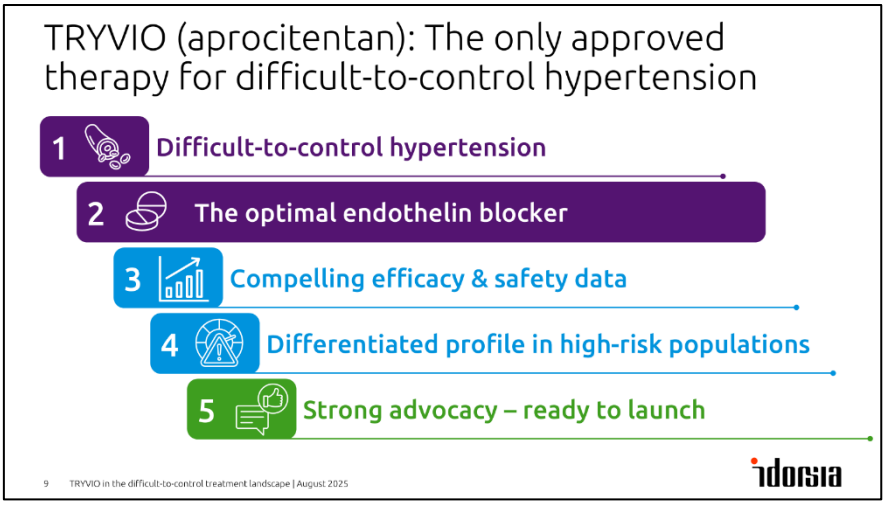
- Difficult-to-control hypertension is generally defined as high blood pressure that remains above 130/80 mmHg despite the use of appropriate therapy. This definition is broad compared to resistant hypertension where blood pressure remains uncontrolled despite treatment with three or more antihypertensive drugs of different classes, including a diuretic, at optimal dose.



- Patients with difficult-to-control hypertension face up to a 95% higher risk of major cardiovascular events, such as stroke and heart failure, and end-stage renal disease, compared with patients whose blood pressure is responding to first-line anti-hypertensives. In this patient population there is therefore a clear and urgent need for therapies that can lower blood pressure in order to decrease the risk of end-organ complications.



- In the US, nearly half of adults – around 120 million people – have hypertension.
- According to claims data, approximately 40 million US patients, are currently treated with antihypertensive drugs. Seen here in L2 – patients on 2 lines of hypertensive therapy, and L3/4+, patients on 3 or more lines of hypertensive therapy – 26 million patients could potentially be treated under TRYVIO's US indication for patients "not adequately controlled on other drugs".
- The addressable patient population is large and will continue to grow, underpinned by an increase in the elderly population and age-related comorbidities, and greater recognition of the consequences of uncontrolled disease.
- TRYVIO is at the forefront of this growth as it is the only therapy to target a novel pathway – on the market or in development.
- Since TRYVIO is uniquely placed in the hypertension market we believe that global aprocitentan peak sales could reach up to 5 billion dollars.



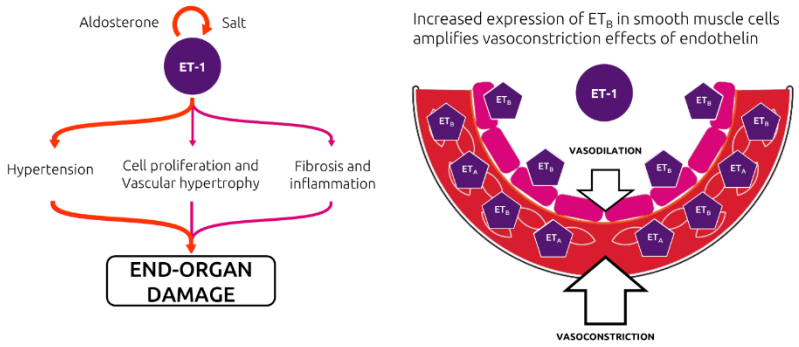
2 The optimal endothelin blocker

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

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

- Our team's deep expertise in endothelin science created a unique opportunity to design the ideal endothelin receptor antagonist (ERA): one with the optimal efficacy and safety profile for use in systemic hypertension.

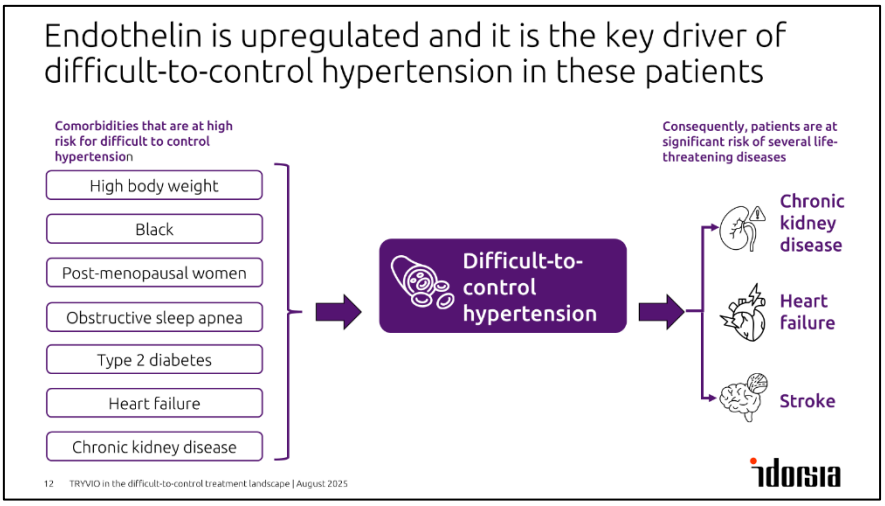
The endothelin system



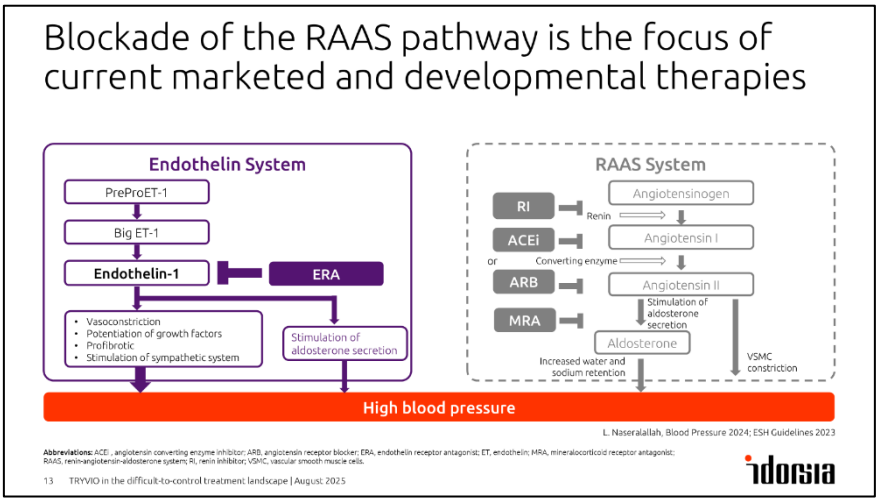
Abbreviations: ET_A and ET_B, endothelin receptor A and B; ET, endothelin

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

- Our extensive research led to the recognition that endothelin is far more than "just" a potent vasoconstrictor. It is a multifunctional peptide that promotes cell proliferation, vascular hypertrophy, fibrosis, inflammation, and the secretion of aldosterone, cytokines, and catecholamines – thereby influencing fundamental pathological processes in a variety of diseases that are also highly prevalent in hypertension.
- The endothelin system is not just present in the circulation – where it is only the spill-over from the tissues – it is produced and active, locally within tissues, such as the heart, blood vessels, kidneys, and lungs.
- In the setting of hypertension, the endothelin peptides (mostly endothelin-1) and the receptors, ET_A and ET_B, become upregulated, meaning their levels and activity are increased. This upregulation amplifies the pathological processes that contribute to high blood pressure, vascular damage, and organ damage, creating a vicious cycle that drives disease progression.



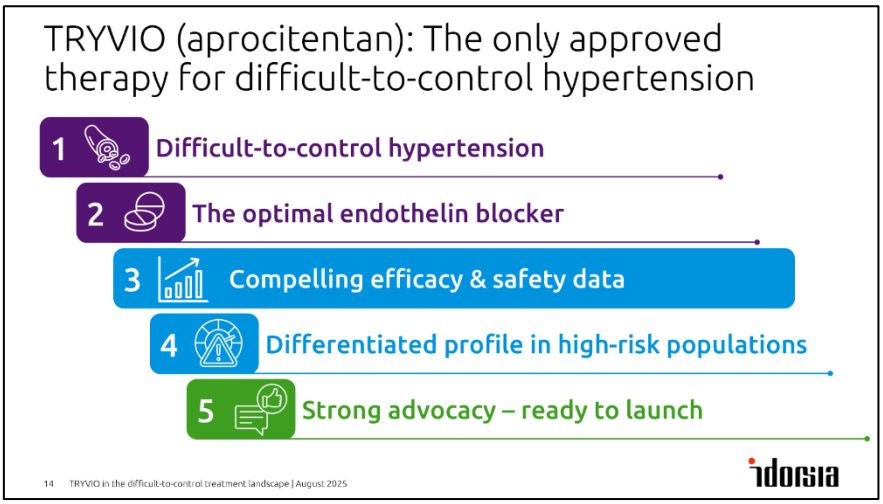
- It is well known that certain groups of patients face a particularly high risk of hypertension that is difficult-to-control with existing therapies. These include Black patients, individuals with higher body weight, older age and postmenopausal women, and those with conditions such as obstructive sleep apnea, type 2 diabetes, heart failure, or chronic kidney disease.
- In all these patient populations, the endothelin system is upregulated – providing a clear scientific rationale for understanding why hypertension is often resistant to treatment.
- The early studies of aprocitentan confirmed the central role of endothelin in the pathology of hypertension. In healthy volunteers with no underlying disease, even doses 50 times higher than the therapeutic level – up to 600 mg – had no effect on blood pressure. This evidence makes clear that aprocitentan is only active when the pathology is driven by endothelin.
- Moreover, endothelin likely contributes not only to the cause of hypertension, but also to its consequences – including end-organ damage to the kidneys and heart, as well as the heightened risk of stroke in these vulnerable patients, providing further clinical rationale to use aprocitentan as the next therapy to be added to patients that continue to struggle to meet their target blood pressure.

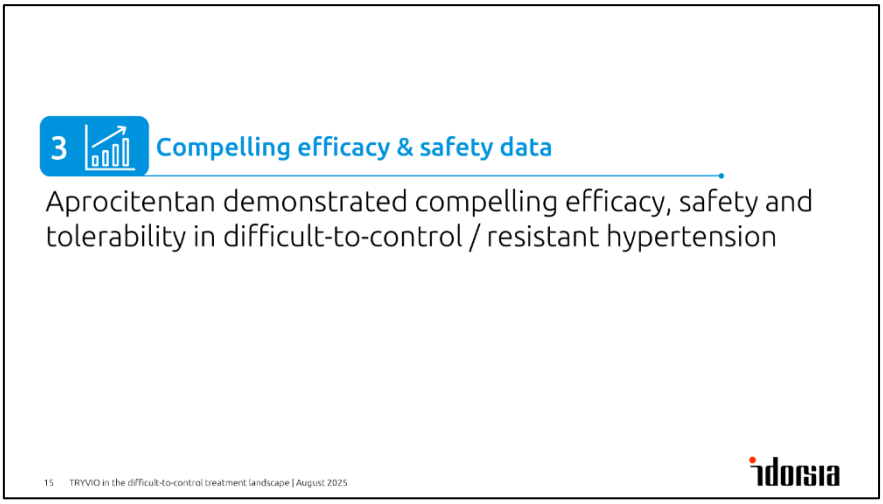


- Current marketed and developmental therapies focus on blockade of the Renin-Angiotensin-Aldosterone System (RAAS), including ACE inhibitors, ARBs, mineralocorticoid receptor antagonists

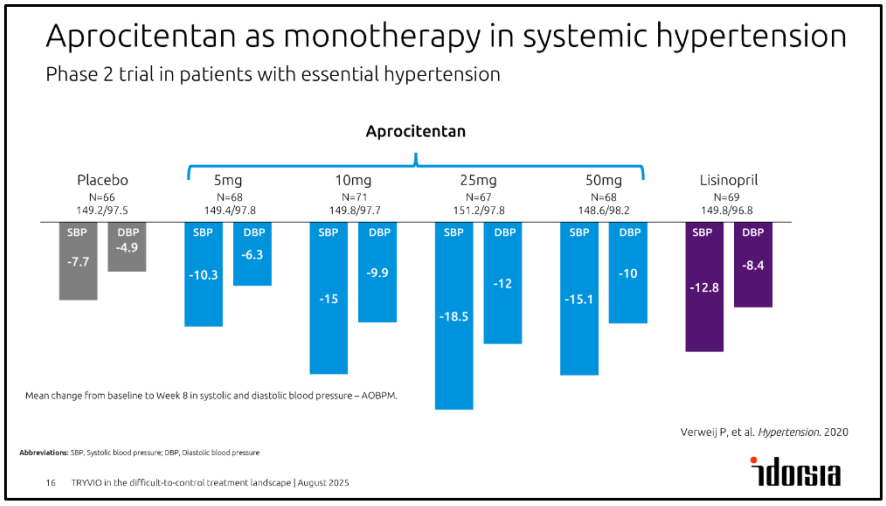
(MRAs) and even the emerging aldosterone synthase inhibitors, as well as angiotensinogen RNA interference.

- While new treatments are emerging, they carry risks such as the excessive blockade of the renin–angiotensin–aldosterone system and potential interactions with other pathways like steroid production.

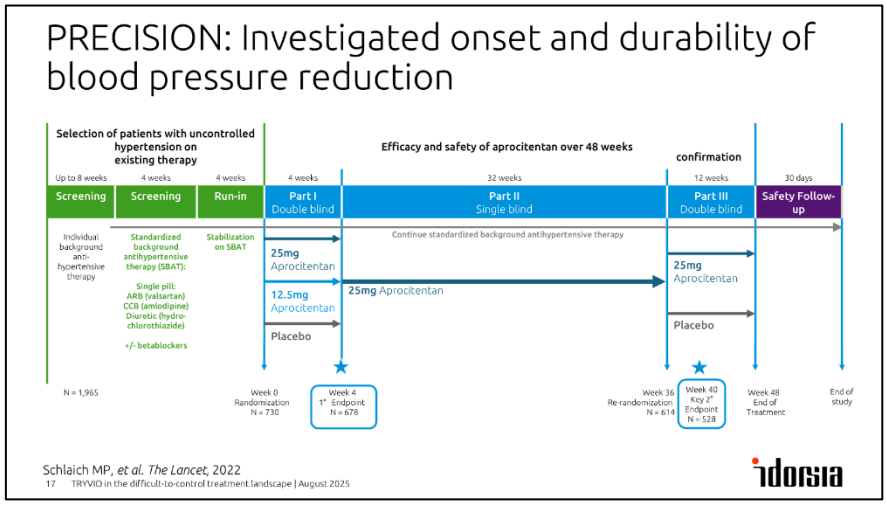




- The compelling clinical data with aprocitentan are well established –published in several peer-reviewed journals, included in TRYVIO's product information and FDA-approved materials, and most recently recognized in the ACC/AHA joint clinical practice guidelines for systemic hypertension.



- In the phase 2 monotherapy trials with patients with systemic hypertension, aprocitentan at a dose of 12.5 mg, reduced systolic blood pressure by 15 mmHg – a reduction comparable or superior to that achieved by lisinopril, a cornerstone ACE inhibitor that has been used for more than 30 years in the treatment of hypertension, and with no sign of fluid retention.
- With the efficacy and safety of aprocitentan established in patients with general systemic hypertension, our next step was to demonstrate efficacy and safety of this novel mechanism in patients with the greatest unmet medical need.



- The Phase 3 PRECISION study was designed to demonstrate both the blood pressure-lowering effect of aprocitentan in patients with confirmed resistant hypertension and the durability, safety, and tolerability of that effect over the long term.
- A key innovation of the study was the rigorous patient selection process. Patients were first observed for eight weeks to confirm that their hypertension remained uncontrolled on their existing treatment regimen.
- All patients were transitioned to a standardized fixed-dose triple therapy of an angiotensin receptor blocker, calcium channel blocker and diuretic – the standard of care for resistant hypertension – this ensured a homogeneous background therapy.
- Patients were followed for another eight weeks. Only patients whose hypertension remained uncontrolled were randomized to receive aprocitentan or placebo.

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**

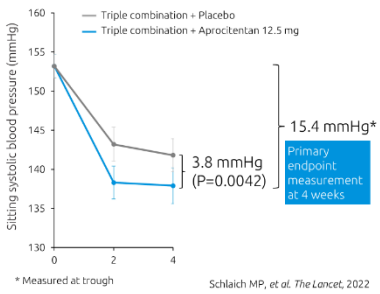
Schlaich MP, *et al. The Lancet*, 2022

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

- PRECISION was an inclusive study. By selecting patients with proven resistant hypertension and not excluding specific comorbidities, the study enrolled a real-world patient population, with comorbidities and treatment resistance that reflect daily clinical practice. 54 % of patients had type 2 diabetes, 55% were obese and 15% severely obese, 20% had congestive heart failure and 22% had chronic kidney disease stage 3 or 4.
- These are the very patients with the greatest clinical need – where even modest reduction in blood pressure can translate into meaningful reductions in cardiovascular risk.

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

PRECISION: Efficacy

TRYVIO significantly reduced systolic blood pressure by targeting the endothelin pathway[a]

In patients taking TRYVIO and at least 3 blood pressure medications (n=243), TRYVIO demonstrated statistically superior blood pressure reductions vs placebo.[1]

Primary endpoint: Change in sitting SBP (SiSBP) from baseline to week 4[1]

15.4 mm Hg*

97.5% CI, (-17.5, -13.3)

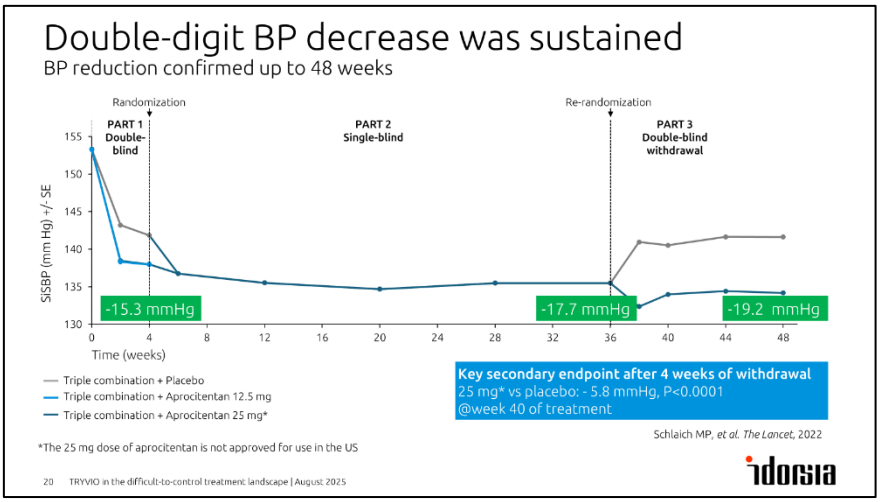
Reduction in sitting trough SBP for the placebo with antihypertensive background therapy group (n=244) was 11.6 mm Hg for a difference of 3.8 vs TRYVIO 12.5 mg (97.5% CI, [-6.8, -0.8]; *P*=0.0043).[1,b]

- The treatment effect for TRYVIO was consistent for systolic and diastolic blood pressure.[1]

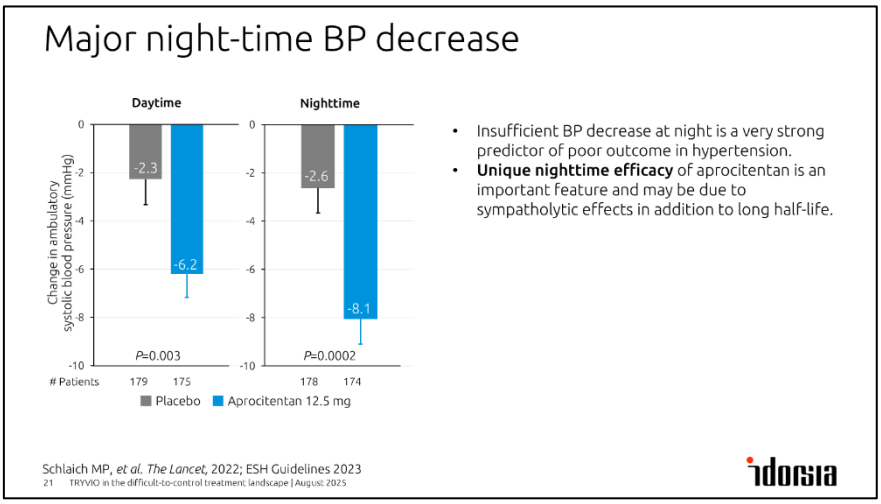
Regulatory approved promotional material

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

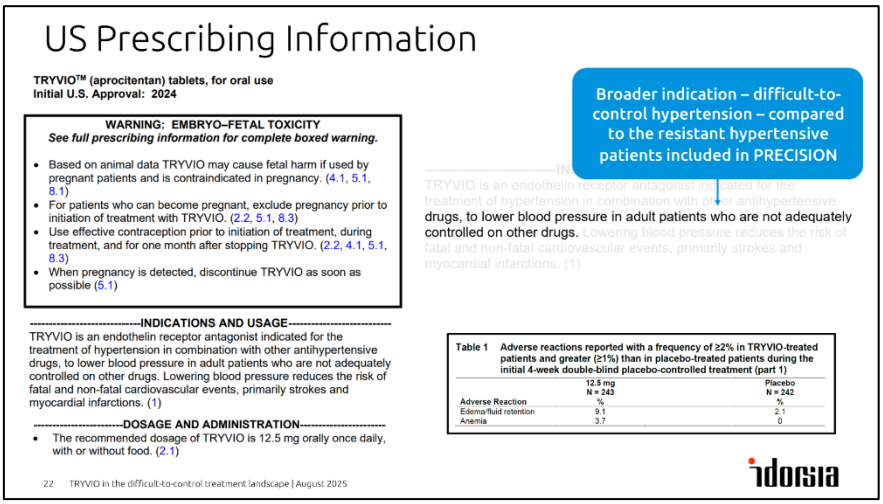
- Once-daily treatment with TRYVIO achieved a rapid, double-digit reduction in systolic blood pressure, seen as early as two weeks in patients still hypertensive despite 3 or more anti-hypertensive medications taken at their optimal doses.
- PRECISION is the ONLY trial that all patients included met the strict clinical definition of resistant hypertension.
- While the PRECISION trials clinical end point was the measurement of decrease in blood pressure at 4 weeks, data supports that patients continued to derive meaningful clinical benefit beyond this timepoint.



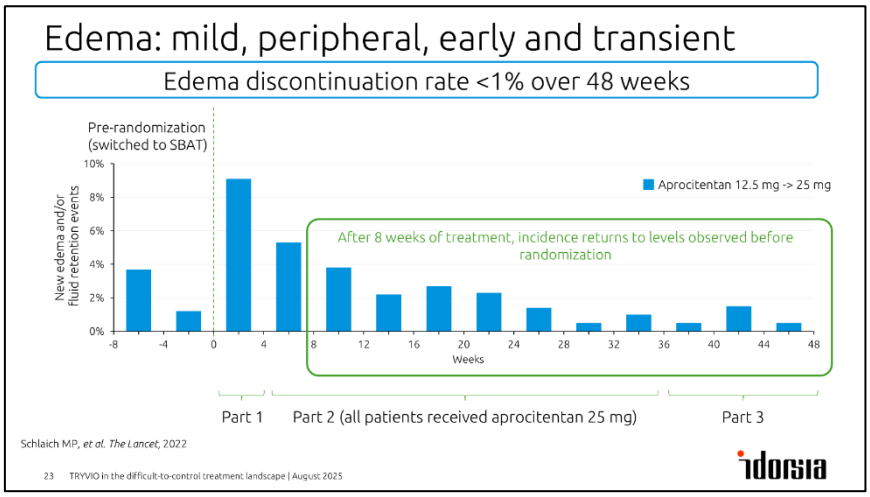
- Of significant importance, the double-digit blood pressure decrease was sustained over the 48-week study duration with a blood pressure reduction of 19.2 mmHg.



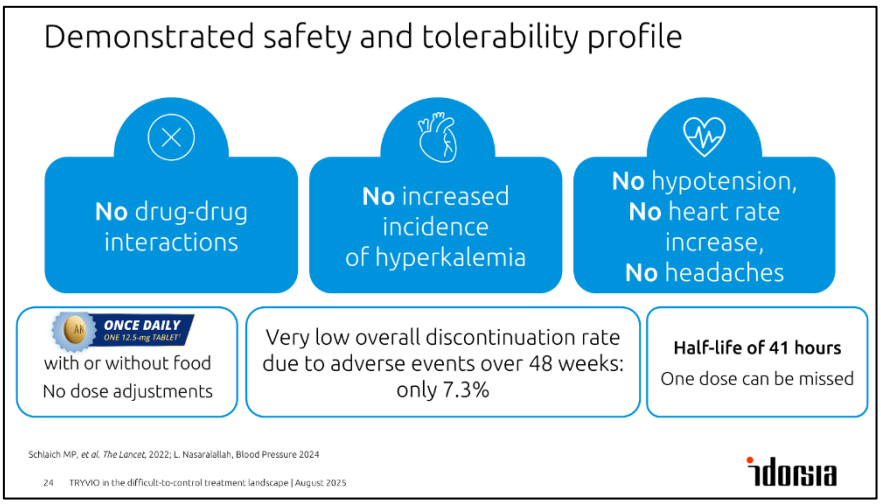
- The effect was consistent across all forms of measurement: office systolic and diastolic readings at trough, as well as 24-hour ambulatory monitoring, which is considered the gold standard.
- TRYVIO has a half-life of 41 hours which is of specific importance, if a patient misses a dose, but also for nighttime coverage. People who have a lack of nighttime dipping of their blood pressure have a much higher cardiovascular risk.



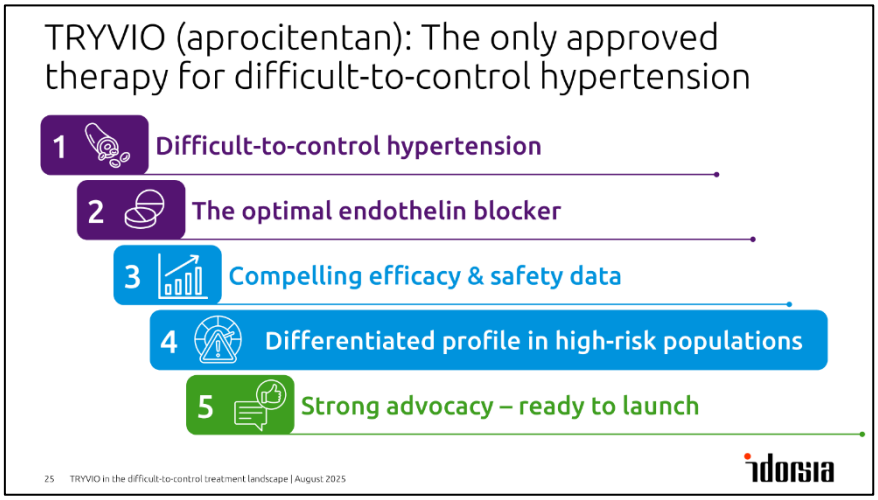
- The US label indication for TRYVIO is for the treatment of hypertension in combination with other antihypertensive drugs, to lower blood pressure in adult patients who are not adequately controlled on other drugs. This is the broader – difficult-to-control hypertension population, compared to the resistant hypertensive patients included in PRECISION.
- The label also draws attention to the impact lowering blood pressure has for patients with the following outcomes statement: "Lowering blood pressure reduces the risk of fatal and non-fatal cardiovascular events, primarily strokes and myocardial infarctions."
- Based on data from animal reproduction studies with endothelin receptor antagonists, the FDA product information carries a warning that TRYVIO may cause fetal harm when administered during pregnancy and is contraindicated for use in patients who are pregnant. The label also notes that the available human data for endothelin receptor antagonists do not establish the presence or absence of fetal harm related to the use of TRYVIO.
- Otherwise, based on the 48-week treatment period, the TRYVIO product information lists two treatment-related side effects – edema at 9% vs 2% with placebo – and a mild, expected decrease in hemoglobin from plasma volume expansion.

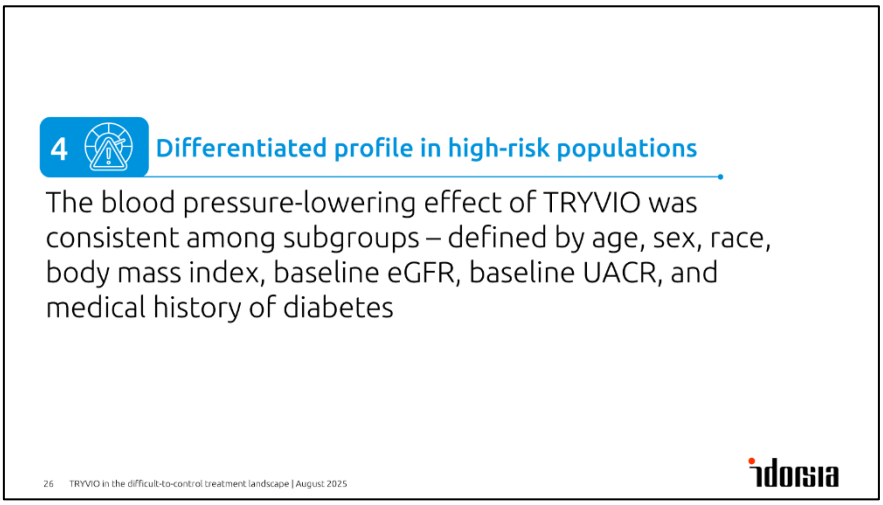


- Importantly, edema was:
  - Mild and transient, leading to less than 1% discontinuation,
  - Occurred early and returned to baseline within 8 weeks, and
  - Was manageable in clinical practice.

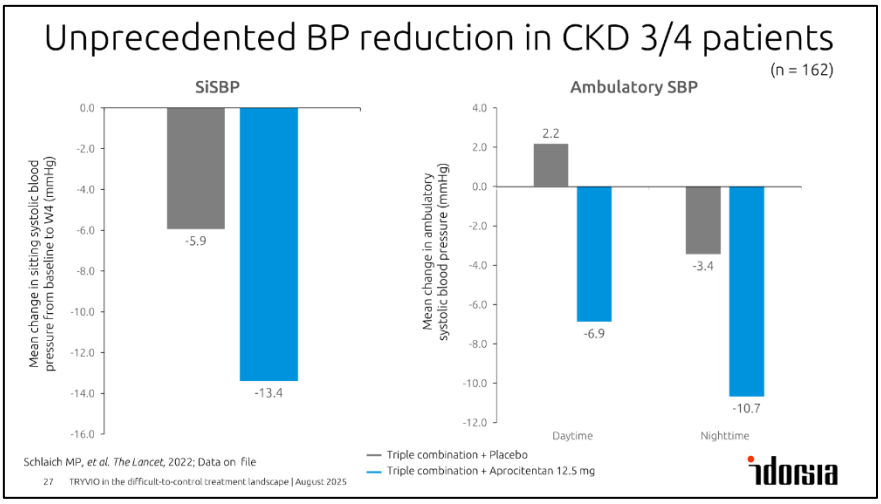


- Crucially, TRYVIO showed no drug-drug interactions, an important advantage and differentiating feature when selecting additional therapy for patients with difficult-to-control hypertension and comorbidities who often have a very complex treatment regimens with many different drugs beyond their antihypertensives.
- This differentiation makes TRYVIO an uncomplicated decision for prescribers when adding a new therapy on top of a patient's current therapies.
- There was no signal for hyperkalemia, hypotension, headache, or tachycardia.
- TRYVIO is uniquely positioned to help address a critical unmet need in resistant and difficult-to-control hypertension, offering durable efficacy, a manageable safety profile, and the potential to transform care in cardiovascular populations worldwide.

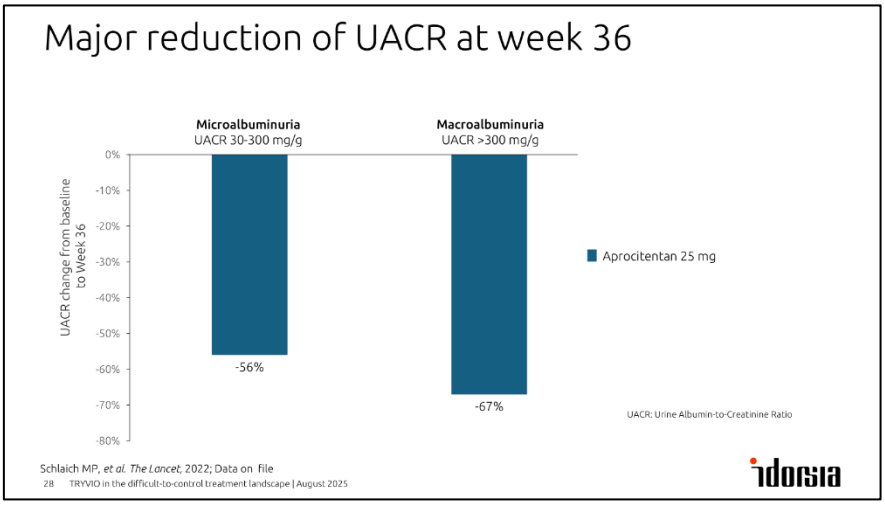




- The blood pressure-lowering effect of TRYVIO was consistent among subgroups – defined by age, sex, race, body mass index, baseline eGFR, baseline UACR, and medical history of diabetes.
- Patients with both hypertension and CKD, even as low as an eGFR of 15ml/min, represent a group with particularly urgent needs, as many current antihypertensive therapies carry risks of hyperkalemia or worsening renal function.

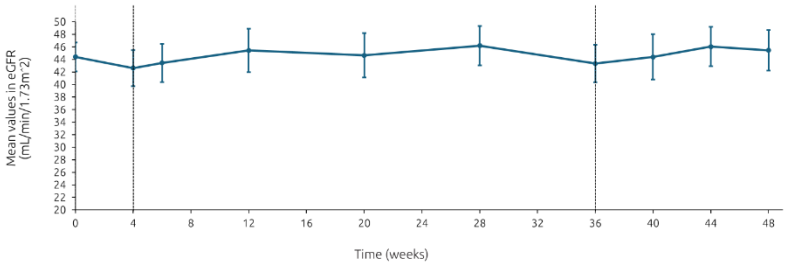


- The efficacy in the subgroup of CKD stage 3 and 4 patients is exceptional. TRYVIO achieved robust reductions in office systolic blood pressure as well as in ambulatory daytime and nighttime measurements – all on top of triple background therapy.



- We also observed a remarkable improvement in renal biomarkers.
- TRYVIO produced a rapid and sustained reduction in urinary albumin-to-creatinine ratio (UACR):
- 56% reduction in patients with baseline microalbuminuria,
- 67% reduction in patients with baseline macroalbuminuria.
- And again, this was on top of standard background therapy, including valsartan.

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



eGFR mean observed values for patients treated with aprocitentan 25 mg over 48 weeks – CKD stage 3/4 (eGFR = 15 to <60 ml/min/1.73m²) subgroup (n = 162)

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

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

- These improvements occurred alongside a stable eGFR over 48 weeks, further underscoring the renal safety and protective profile of TRYVIO.

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

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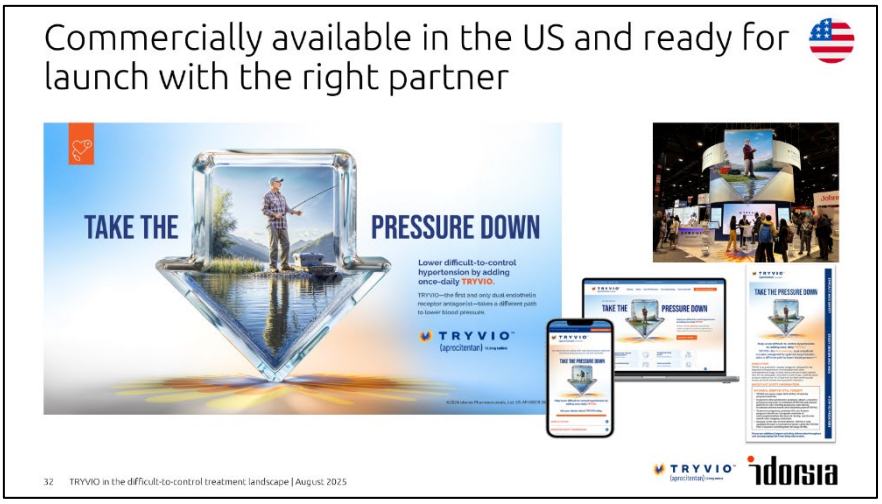
30 TRYVIO in the difficult-to-control treatment landscape | August 2025

5 Strong advocacy – ready to launch

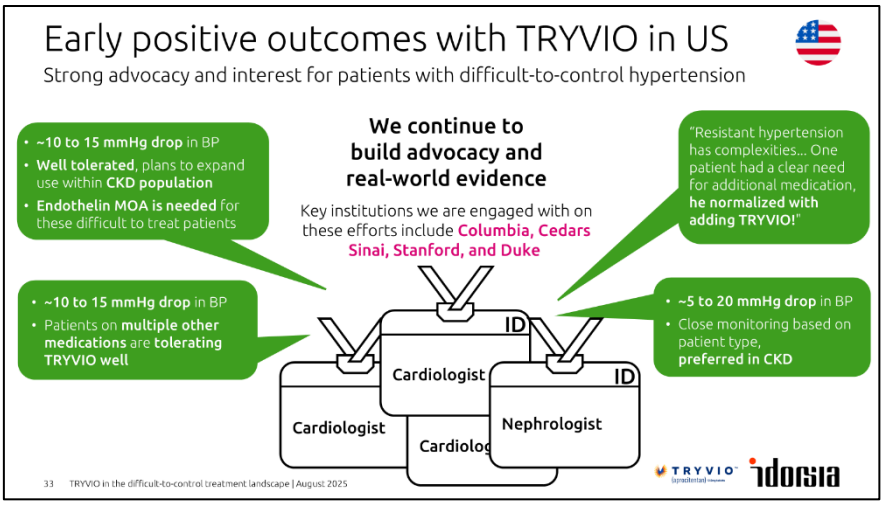
Prescribers are seeing the benefits of TRYVIO in real-world practice.

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

- We are moving with urgency to ensure patients with the highest need have access to TRYVIO by educating healthcare practitioners and payers regarding the important benefit that could be gained by treatment with TRYVIO. We continue to engage with potential partners to maximize and accelerate the opportunity we have created.

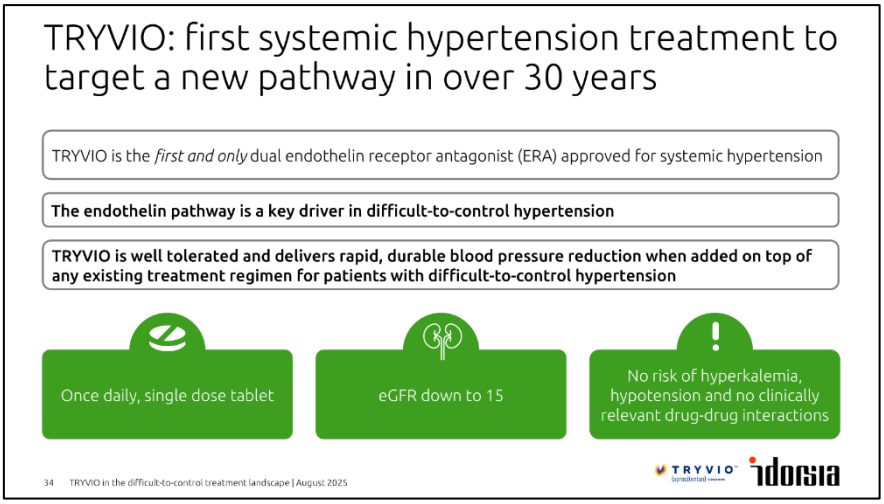


- To maximize TRYVIO's impact, Idorsia is seeking a partner with the scale and capabilities to rapidly bring this innovation to patients in the US and globally.
- A partner could also advance follow-on development, including new indications and fixed-dose combinations with other drugs.
- In parallel, Idorsia is preparing for launch: engaging leading key opinion leaders across specialties including cardiologist, nephrologists, and internal medicine experts at the top hypertension centers to build strong clinical advocacy, ensuring a presence at major congresses focused on providing medical education, and disseminating relevant promotional materials.
- We are also progressing payer discussions to secure inclusive access and reimbursement, so patients can benefit from this important therapy.
- In the U.S., TRYVIO is currently available via Walgreens Specialty Pharmacy and will soon be available through other retail pharmacies nationwide.



- Feedback from prescribers confirm TRYVIO delivers a similar double-digit blood pressure reductions shown in PRECISION in the patients they see in clinical practice regardless of background therapy.
- Physicians are consistently reporting that patients on multiple therapies are tolerating TRYVIO very well.

- Importantly, clinicians are embracing its use in CKD patients, recognizing its unique profile in this high-risk population.
- We conducted quantitative market research surveying approximately 300 Healthcare professionals on the value of TRYVIO, and compared it to baxdrostat, lorundrostat and zilebesiran. TRYVIO was seen as more favorable in the following domains: Mechanism of Action, in a CKD population, route of administration/dosing, efficacy on blood pressure, and efficacy on UACR.



- In conclusion, TRYVIO represents a true breakthrough in the treatment of resistant and difficult-to-control hypertension. By targeting the endothelin pathway – a mechanism long recognized but until now unaddressed – we have introduced a therapy that delivers rapid, durable blood pressure reduction, has a demonstrated safety and tolerability profile.
- The results from the PRECISION study, reinforced by real-world physician feedback, confirm the ability of TRYVIO to achieve outcomes that existing therapies cannot. This positions TRYVIO as not only a differentiated clinical solution, but also a transformative commercial opportunity in one of the largest, most urgent areas of cardiovascular medicine.
- We are confident that TRYVIO is set to become a cornerstone therapy for difficult-to-control hypertension with blockbuster market potential.
- At Idorsia, our mission has always been to push the boundaries of science to improve patient outcomes. With TRYVIO, we are on the cusp of delivering a new standard of care to millions of patients who have long been underserved. We are committed to ensuring innovation reaches those who need it most – transforming lives, shaping clinical practice, and unlocking significant value for all stakeholders.