Dual Endothelin Antagonist:
Evaluating Aprocitentan for Hypertension
A Review of Phase 2 and Phase 3 Clinical Trial Data

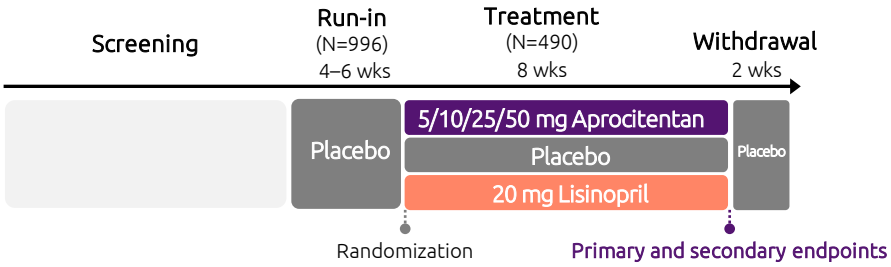
1. Hypertension

- **The endothelin pathway** is implicated in hypertension and represents a unique pathway that has not been targeted with previous antihypertensive agents[1,2]

- **Aprocitentan** is the first and only dual endothelin receptor antagonist to be investigated in patients with uncontrolled hypertension in a **Phase 2 dose-finding study as monotherapy** and in a **Phase 3 study evaluating its efficacy and durability** in patients not adequately controlled in combination with other medications[1,2]

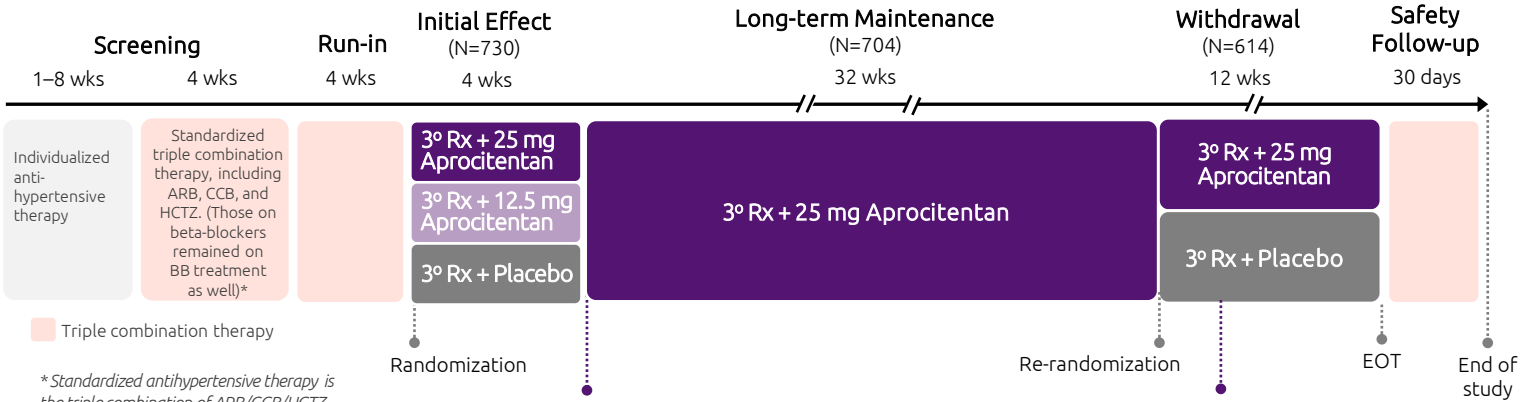
2. Study Design and Methods

- Monotherapy: **Aprocitentan only:** Phase 2 dose-response study in treatment of essential hypertension[1]



Endpoints
Change in mean trough SiDBP (primary) and SiSBP (secondary) from baseline to wk 8

- Combination Therapy: **Aprocitentan + Triple Combination:** Phase 3 PRECISION trial is a multicenter, blinded, randomized, parallel-group study of aprocitentan in patients with uncontrolled hypertension despite being on ≥3 antihypertensives within 1 year of screening[2]



** Standardized antihypertensive therapy is the triple combination of ARB/CCB/HCTZ that is started, as background for study drug or placebo to be added onto*

Short-term efficacy
Primary endpoint: Change in mean sitting office SBP from baseline to wk 4

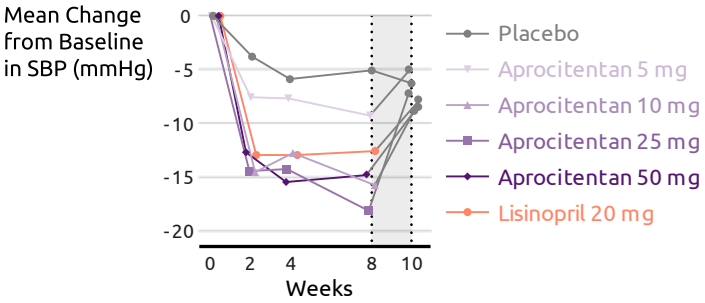
Long-term efficacy
Key secondary endpoint: Change in mean sitting office SBP from wk 36 to 40

3º Rx, triple therapy; **ARB**, angiotensin receptor blocker (i.e. valsartan); **CCB**, calcium channel blocker (i.e. amlodipine); **EOT**, end of treatment; **HCTZ**, hydrochlorothiazide; **SiDBP**, sitting diastolic blood pressure; **SiSBP**, sitting systolic blood pressure; **wk**, week.

References: 1. Verweij P, et al. *Hypertension.* 2020;75(4):956-965. **2.** Schlaich MP, et al. *Lancet.* 2022;400(10367):1927-1937.

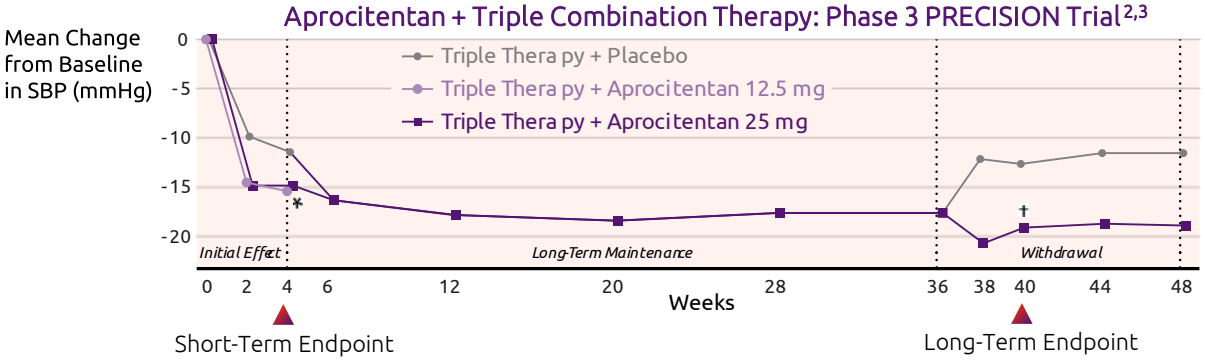
3. Results

Aprocitentan as Monotherapy: Phase 2 Study[1]



- In patients with essential hypertension, **aprocitentan as monotherapy** led to **dose-dependent reductions** in mean office **sitting SBP** compared to that of placebo after 8 weeks of treatment
- Similar reductions were observed in **sitting DBP**, which was the primary endpoint
- **Incidence of adverse events were similar** in the **aprocitentan** groups and the **placebo** group. Aprocitentan produced dose-dependent decreases in hematocrit, albumin, and uric acid, increase in est. plasma volume, and no change in weight.

Aprocitentan + Triple Combination Therapy: Phase 3 PRECISION Trial[2,3]

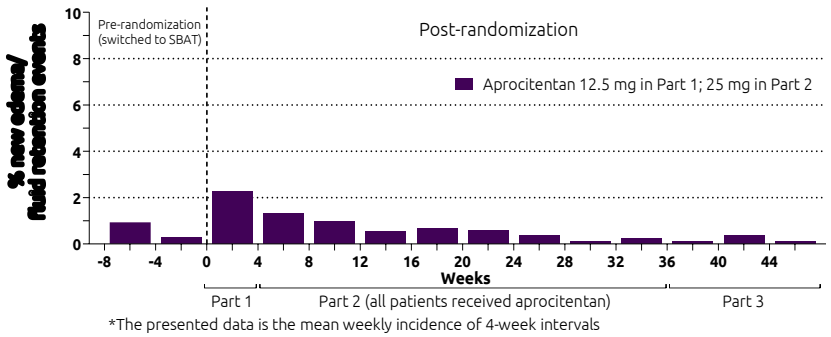


	Baseline[3] Randomization Week 0 Mean SBP	Short-Term Treatment[3] Week 4 Mean SBP (LS Mean Δ mmHg vs BL)	Long-Term Treatment[3] Rerandomization [RR] Week 36 Mean SBP	Withdrawal[3] Week 40 Mean SBP (LS Mean Δ mmHg vs RR)
Placebo	153.3	141.8 (**-11.5**)	136.4	140.5 (**+4.4**)
Aprocitentan 12.5 mg	153.2	138.0 (**-15.3**)		
Aprocitentan 25 mg	153.3	138.0 (**-15.2**)	135.3	134.0 (**-1.5**)

3.1. Safety and Tolerability

- Aprocitentan was **well-tolerated** with the most frequent adverse events being anemia and mild to moderate **edema or fluid retention;** most of these events were **clinically manageable with diuretic therapy** during the study.

% of New Edema/Fluid Retention Events per Week across Phase 3 PRECISION Study[3]



*The presented data is the mean weekly incidence of 4-week intervals

4. Key Takeaways

In patients with untreated hypertension, **aprocitentan monotherapy** led to **clinically meaningful[4] reductions** in blood pressure without serious adverse events.

In **combination** with standard triple therapy, **aprocitentan** led to **clinically meaningful[4] reductions** in SBP in the first 4 weeks and **sustained** over 48 weeks.

Mild to moderate edema or fluid retention was **manageable with diuretic therapy.**

References: 1. Verweij P, et al. *Hypertension.* 2020;75(4):956-965. **2.** Schlaich MP, et al. *Lancet.* 2022;400(10367):1927-1937. **3.** Data on File. PRECISION CSR. Idorsia Pharmaceuticals. 2024. **4.** Canoy D, et al. *Curr Cardiol Rep.* 2022;24(7):851-860.