BAX-HTN:
Baxdrostat v léčbě nekontrolované a rezistentní hypertenze

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OSTRAVSKÁ UNIVERZITA LÉKAŘSKÁ FAKULTA

FAKULTNÍ NEMOCNICE OSTRAVA

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy and Safety of Baxdrostat in Uncontrolled and Resistant Hypertension

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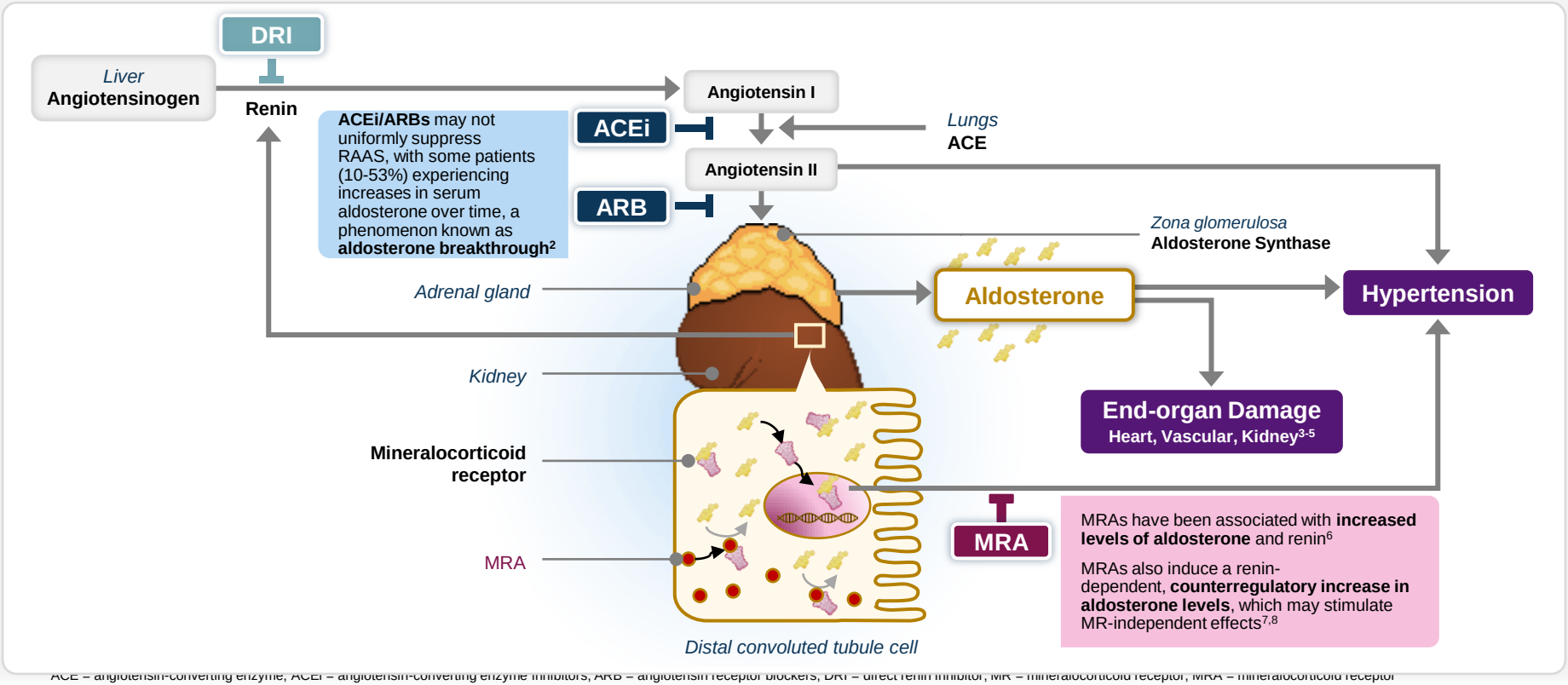
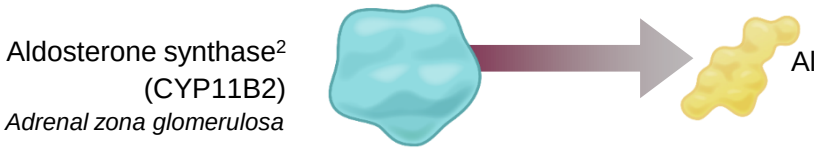
Existing Therapies Do Not Directly Target Aldosterone Synthesis and Therefore Fail to Fully Address the Effects of Excess Aldosterone[1]

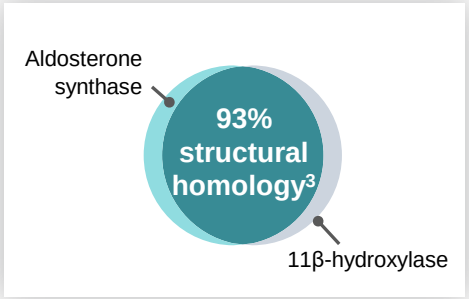


ACE = angiotensin-converting enzyme; ACEi = angiotensin-converting enzyme inhibitors; ARB = angiotensin receptor blockers; DRI = direct renin inhibitor; MR = mineralocorticoid receptor; MRA = mineralocorticoid receptor antagonists;
RAAS = renin-angiotensin-aldosterone system.

1. Leopold JA et al. *N Engl J Med*. 2023;388(5):464-467; 2. Bomback AS et al. *Nat Clin Pract Nephrol.* 2007;3(9):486-492; 3. Hargovan M et al. *JRSM Cardiovasc Dis*. 2014;3:2048004014522440; 4. Muñoz-Durango N et al. Int *J Mol Sci.* 2016;17(7):797; 5. Briones AM et al. Aldosterone/MR Signaling. *AMR - Cell Biology to Translational Medicine.* 2019; 6. Kobayashi M et al. *ESC Heart Fail.* 2020;7(3):953-963; 7. Azizi M. *N Engl J Med.* 2023;388(5):461-463; 8. Agarwal R et al. *Eur Heart J.* 2021;42(2):152-161.

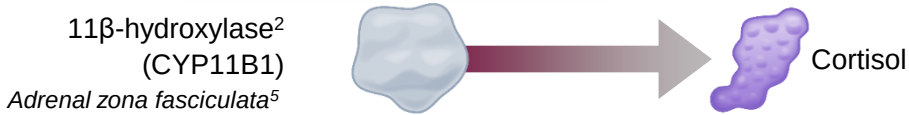
Selective Inhibition of Aldosterone Synthase Has Been a Challenge in the Development of ASIs in the Past[1,2]





The chemical sequence of aldosterone synthase shares 93% structural similarity to the enzyme that controls cortisol synthesis, 11β-hydroxylase, making it difficult to develop ASI compounds that do not also inhibit cortisol synthesis.[1-3]

Selective inhibition of aldosterone synthase avoids unwanted off-target side effects due to reduced cortisol production[4]



ASI = aldosterone synthase inhibitor; CYP = cytochrome P450.

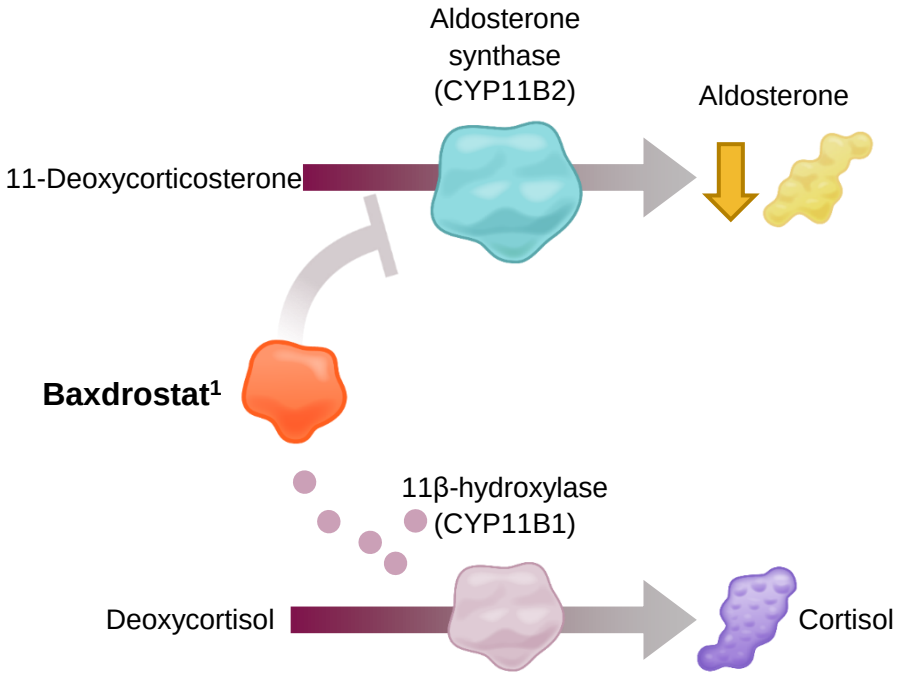
1. Freeman MW et al. *Hypertens Res.* 2023;46:108-118; 2. Leopold JA et al. *N Engl J Med.* 2023;388:464-467; 3. Bogman K et al. *Hypertension*. 2017;69(1):189-196; 4. Freeman MW et al. *N Engl J Med*. 2023;388(5):395-405; 5. Hargovan M et al. *JRSM Cardiovasc Dis*. 2014;3:1-9.

Baxdrostat is a Highly Selective Inhibitor of Aldosterone Synthase[1,2]

Baxdrostat Selectivity for Aldosterone Synthase versus 11β-hydroxylase[2]

HIGH SELECTIVITY
for aldosterone synthase

Selectivity ratio:
100:1



CYP = cytochrome P450.

1. Leopold JA et al. *N Engl J Med.* 2023;388:464-467. 2. Bogman K et al. Hypertension. 2017;69(1):189-196.

BaxHTN: Phase 3 Trial of Baxdrostat in Patients with uHTN or rHTN

Multicenter, multinational, double-blind, randomized, placebo-controlled trial[1]

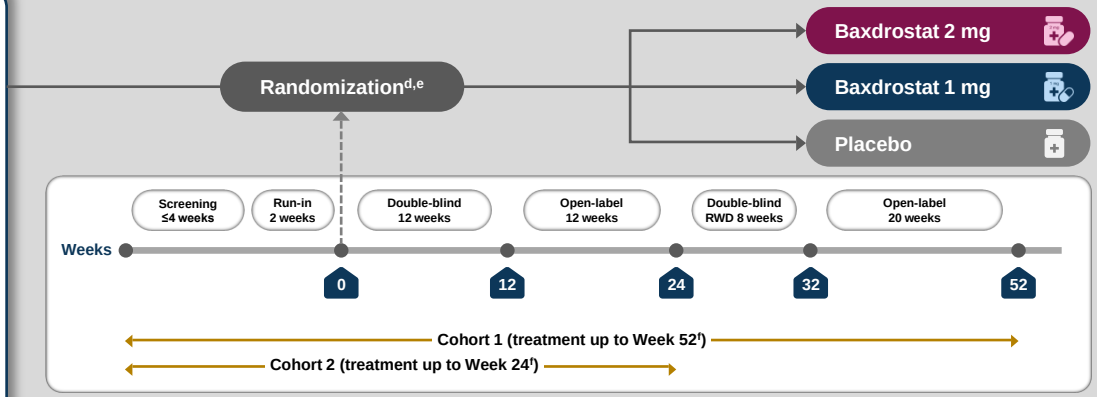
Key Inclusion Criteria[1,2]

- ≥18 years of age
- Mean seated SBP ≥140 and <170 mm Hg
- 1 of the following:
  - uHTN - Stable regimen of 2 antihypertensives[c] from different classes[b]
  - rHTN - Stable regimen of ≥3 antihypertensives[a] from different classes[b]
- eGFR ≥45 mL/min/1.73 m^2
- Serum K^+ ≥3.5 & <5.0 mmol/L

796 Patients

Key Exclusion Criteria[1,2]

- Mean seated SBP ≥170 mm Hg or DBP ≥110 mm Hg
- Use of MRA or K^+-sparing diuretics
- Uncontrolled diabetes[c]
- Renal artery stenosis, uncontrolled/untreated hypo- or hyperthyroidism, pheochromocytoma, Cushing's syndrome, aortic coarctation
- Persistent AF
- NYHA Class IV HF at screening



Primary Endpoint[1,g,h]

- Change in seated SBP from baseline to Week 12

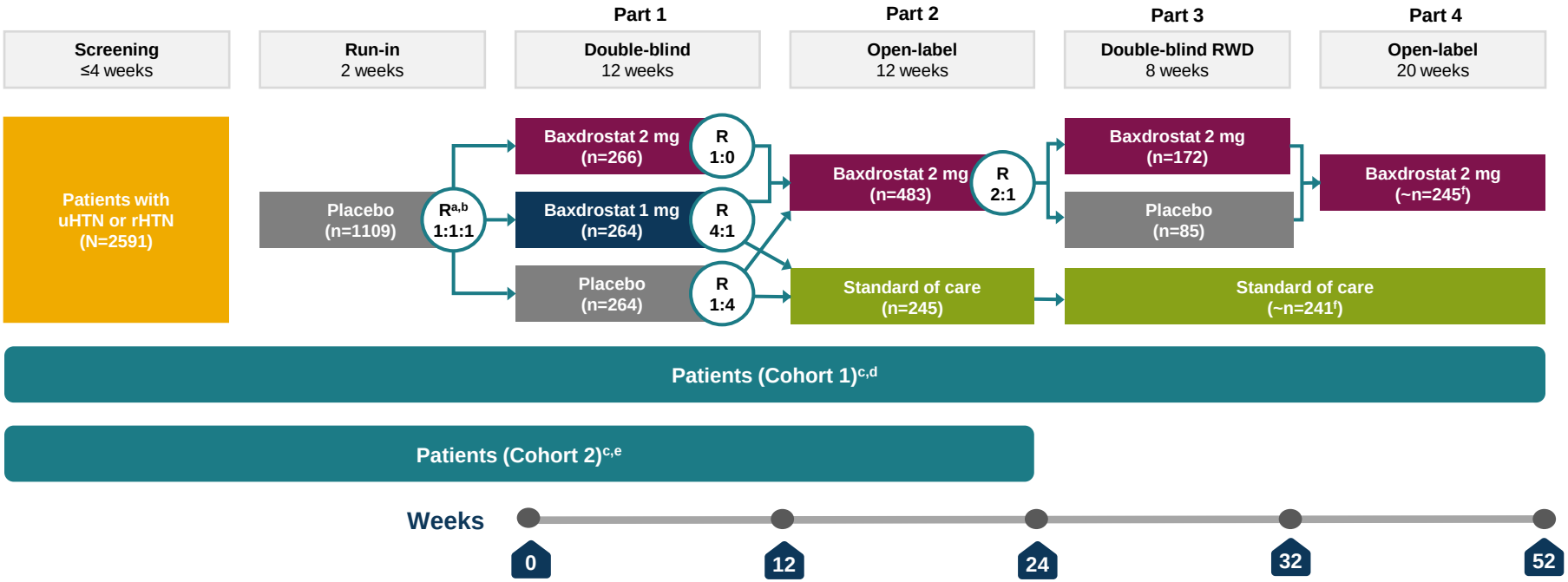
Secondary Endpoints in Hierarchical Order[1,2,g]

1. Change in seated SBP from RWD (Week 24) to Week 32 (2 mg dose only)
2. Change in seated SBP from baseline to Week 12 in the rHTN subgroup[h]
3. Change in seated DBP from baseline to Week 12[h]
4. Percentage achieving SBP <130 mm Hg at Week 12[h]

AF = atrial fibrillation; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HF = heart failure; HTN = hypertension; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; rHTN = resistant hypertension; RWD = randomized withdrawal; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

BaxHTN Study Design Scheme[1,2]



Note: Patients were grouped into two cohorts based on when they were randomized.[1] The first 450 randomized patients (Cohort 1) participated in all four study phases, while those randomized afterward (Cohort 2) took part only in the first two phases. This ensured enough power for the primary endpoint and limited unnecessary placebo exposure during the RWD phase (part 3).

[a]After a 2-week single-blind run-in period on placebo added to stable background therapy, patients with seated SBP ≥135 mm Hg and good adherence to background antihypertensives (seated SBP ≥130 mm Hg after directly observed therapy) and placebo (≥80% adherence by pill count) were randomized;[1,2] [b]Randomization was stratified by baseline HTN status (uHTN, rHTN) and baseline SBP (<145 mm Hg, ≥145 mm Hg);[1] [c]Treatment period will be followed by a 2-week safety follow-up;[2] [d]Treatment up to Week 52;[1,2] [e]Treatment up to Week 24;[1,2] [f]At the time of the primary data lock, some patients from Cohort 2 were still in the first open-label phase (part 2), while the two randomized parts (parts 1 and 3) of the study were complete for efficacy.[1,2]

HTN = hypertension; R = randomization; rHTN = resistant hypertension; RWD = randomized withdrawal; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Baseline Characteristics

Patient Demographics and Clinical Characteristics at Baseline (N=794):[1,2,a]
baxdrostat 1 mg (n=264), baxdrostat 2 mg (n=266) and placebo (n=264)

Age, years
59.8 (11.8)
61.8 (11.7)
61.9 (11.6)

Male, %
64.0%
61.3%
61.4%

BMI, kg/m²
31.5 (6.4)
31.2 (6.2)
31.1 (6.0)

Potassium, mmol/L
4.2 (0.4)
4.2 (0.4)
4.2 (0.5)

Sodium, mmol/L
139.9 (2.6)
139.8 (2.5)
139.6 (2.5)

eGFR, mL/min/1.73 m²
86.6 (18.5)
84.3 (17.9)
84.1 (18.0)

Seated SBP/DBP, mm Hg
Baxdrostat 1 mg (n=264): 149.7 (10.1)/88.0 (10.5)
Baxdrostat 2 mg (n=266): 149.1 (9.1)/85.8 (10.5)
Placebo (n=264): 149.0 (8.7)/85.8 (10.5)

Key clinical characteristics, %

	uHTN[b]	rHTN[b]	eGFR <60 mL/min/1.73 m²	Diabetes	BMI ≥30 kg/m²
Baxdrostat 1 mg (n=264)	29.2%	70.8%	10.2%	31.4%	51.1%
Baxdrostat 2 mg (n=266)	25.2%	74.8%	11.3%	41.4%	52.6%
Placebo (n=264)	26.9%	73.1%	11.0%	41.7%	51.1%

Number of background antihypertensive medications, %[2]

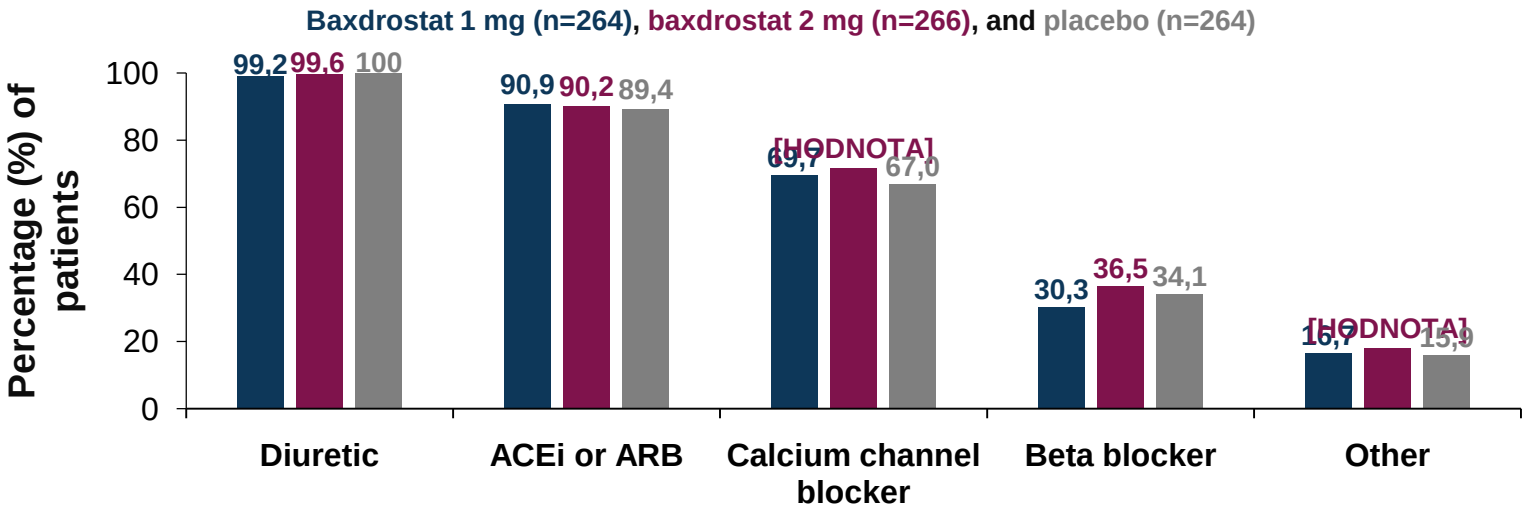
	2	3	4	5+
Baxdrostat 1 mg (n=264)	29.2%	40.2%	21.2%	9.5%
Baxdrostat 2 mg (n=266)	24.8%	39.8%	27.1%	8.3%
Placebo (n=264)	26.5%	41.7%	26.9%	4.9%

[a]Data are mean (SD) unless otherwise stated;[1] [b]Based on information collected in the medication case report form.[1]
BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Baseline Antihypertensive Medications

Prevalence of background antihypertensive medications at baseline[1,2,a]



The median number of background antihypertensive medications at baseline was 3 in each arm[1]

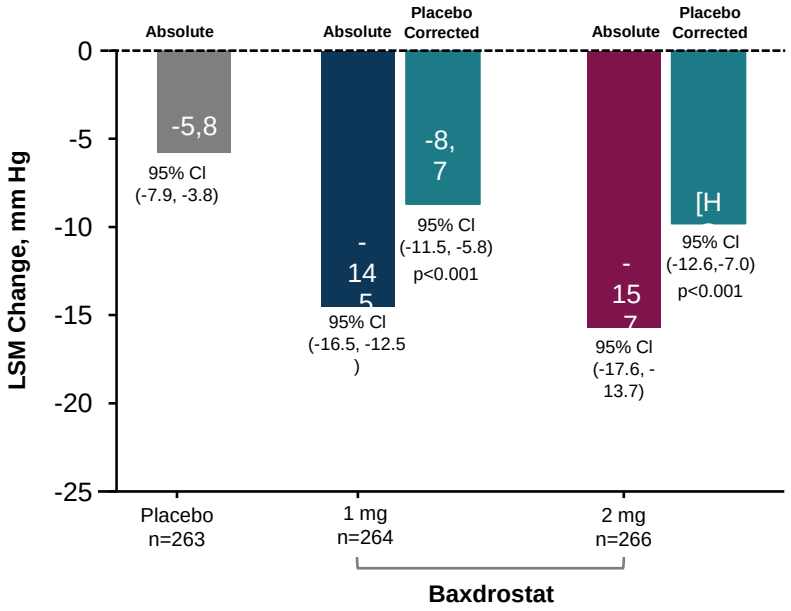
[a]Patients continued background antihypertensive therapy throughout the trial.[2] During double-blind periods, background therapy was to remain unchanged unless seated SBP >170 mm Hg or DBP >105 mm Hg, permitting rescue therapy as needed. In open-label phases, background therapy adjustments were permitted at investigator discretion, except for addition of MRAs or K^+-sparing diuretics.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; DBP = diastolic blood pressure; K^+ = potassium; MRA = mineralocorticoid receptor antagonist; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

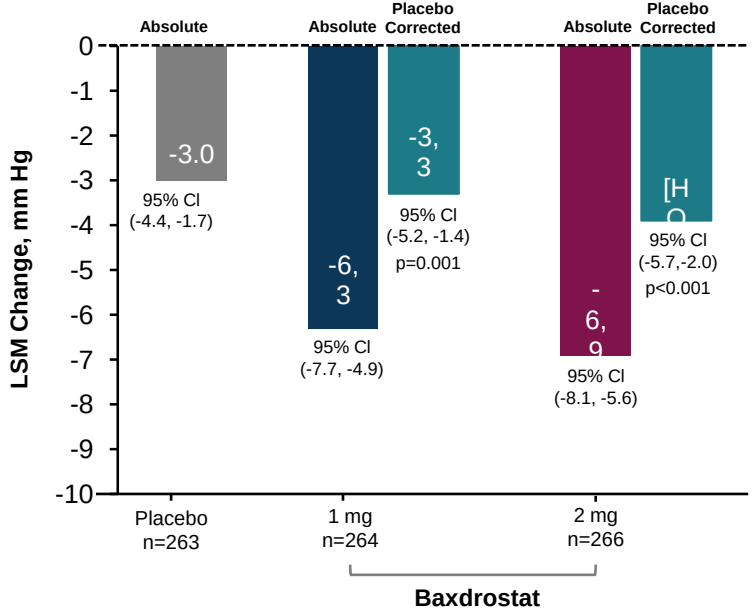
1. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025.

Baxdrostat Demonstrated Significant Placebo-Corrected Reductions in Seated SBP and DBP in Patients With uHTN or rHTN[1,2]

Primary Endpoint - Change in Seated SBP from Baseline to Week 12[1,a,c]



Secondary Endpoint - Change in Seated DBP from Baseline to Week 12[1,2,b,c]



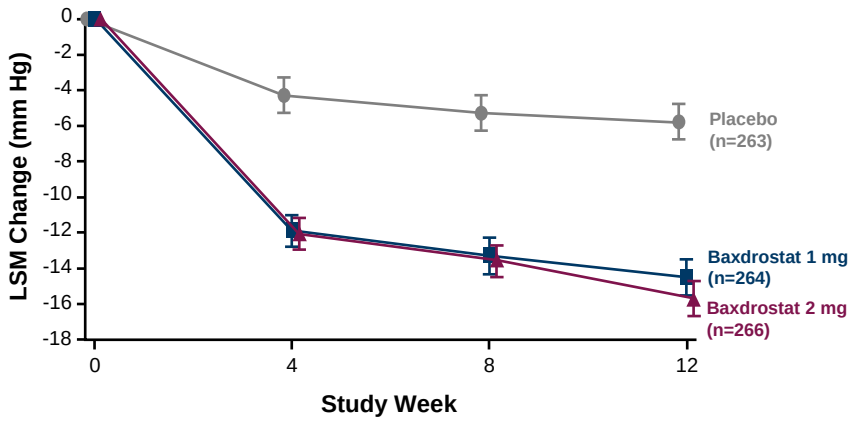
[a]The analysis was performed on the full analysis set (all randomized patients who received at least one dose of study intervention) using an ANCOVA model with treatment and HTN at baseline (uHTN, rHTN) as factors, and baseline seated SBP value as a covariate;[1] [b]The analysis was performed on the full analysis set using an ANCOVA model with treatment and HTN at baseline (uHTN, rHTN) as factors, and baseline seated DBP value as a covariate;[1] [c]Missing data at week 12 following treatment discontinuation were imputed using a multiple imputation retrieved dropout method and missing data at week 12 following initiation of rescue medication were imputed using a multiple imputation washout method. Intercurrent events of deaths were handled using the hypothetical strategy (i.e., as if the subject had not died).[1]

ANCOVA = analysis of covariance; CI = confidence interval; DBP = diastolic blood presure; HTN = hypertension; LSM = least-squares mean; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

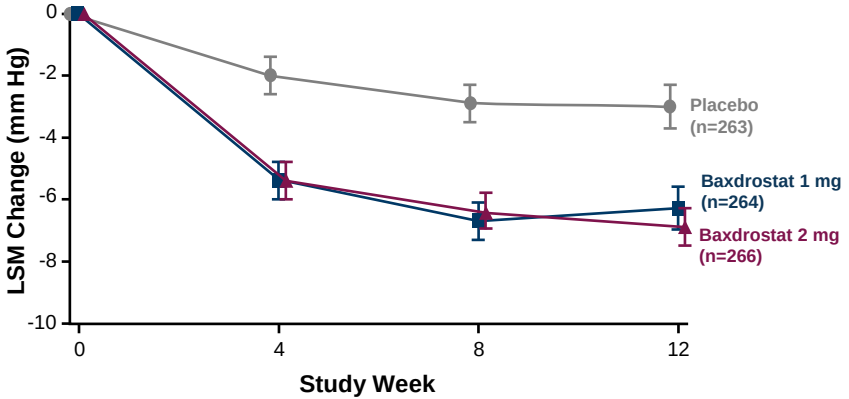
1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Sustained Reductions in Seated SBP and DBP were Observed Over Time With Baxdrostat in Patients With uHTN or rHTN[a]

Time Course of Change in Seated SBP from Baseline to Week 12



Time Course of Change in Seated DBP from Baseline to Week 12



A reduction in seated SBP and DBP was observed as early as Week 4 with baxdrostat

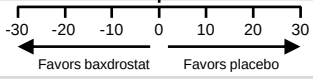
[a]The line graphs show time courses for LSM mean change from baseline in seated SBP up to week 12 (left) and seated DBP up to week 12 (right). Bars on the line graphs indicate the standard error.
DBP = diastolic blood presure; LSM = least-squares mean; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension

Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025.

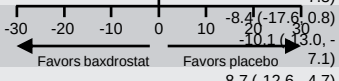
Effect of Baxdrostat on SBP Across Pre-specified Subgroups[1,2]

The effect of baxdrostat on seated SBP was consistent across all pre-specified subgroups[1,2,a]

Subgroup		Bax 1 mg n	Placebo n	LSM difference (95% CI) in seated SBP (mm Hg)
Overall		264	263	-8.7 (-11.5, -5.8)
Age - years	<65	168	138	-10.3 (-14.3, -6.4)
	≥65 to <75	71	91	-7.4 (-12.5, -2.4)
	≥75	25	34	-5.5 (-12.5, 1.5)
Sex	Female	95	102	-9.0 (-14.1, -3.9)
	Male	169	161	-8.6 (-12.0, -5.2)
Race	Black	23	15	-0.5 (-11.5, 10.6)
	Asian	65	72	-7.8 (-13.1, -2.4)
	White	165	166	-9.7 (-13.2, -6.1)
Ethnicity	Hispanic/Latino	27	38	-14.0 (-21.5, -6.6)
	Not Hispanic/Latino	231	215	-7.6 (-10.7, -4.4)
Geographic region	APAC, Middle East, Africa	80	80	-9.9 (-15.0, -4.8)
	Americas	72	74	-9.2 (-14.3, -4.1)
	Europe	112	109	-7.5 (-12.0, -3.0)
HTN Subtype	uHTN	77	71	-7.3 (-12.4, -2.3)
	rHTN	187	192	-9.1 (-12.6, -5.7)
Baseline SBP (mm Hg)	<145	92	92	-8.5 (-13.4, -3.5)
	≥145	172	171	-8.9 (-12.4, -5.4)
Baseline eGFR (mL/min/1.73 m^2)	<60	27	29	-7.3 (-16.6, 2.1)
	≥60	237	234	-8.8 (-11.8, -5.9)
Baseline BMI (kg/m^2)	<30	129	128	-8.1 (-12.1, -4.1)
	≥30	135	135	-9.1 (-13.2, -5.0)



Subgroup		Bax 2 mg n	Placebo n	LSM difference (95% CI) in seated SBP (mm Hg)
Overall		266	263	-9.8 (-12.6, -7.0)
Age - years	<65	145	138	-11.4 (-15.5, -7.4)
	≥65 to <75	88	91	-7.9 (-12.6, -3.2)
	≥75	33	34	-7.7 (-14.0, -1.4)
Sex	Female	103	102	-11.6 (-16.4, -6.7)
	Male	163	161	-9.0 (-12.4, -5.6)
Race	Black	21	15	-9.5 (-21.1, 2.1)
	Asian	72	72	-8.9 (-14.1, -3.6)
	White	168	166	-9.6 (-13.1, -6.2)
Ethnicity	Hispanic/Latino	39	38	-12.7 (-19.8, -5.6)
	Not Hispanic/Latino	216	215	-9.1 (-12.3, -6.0)
Geographic region	APAC, Middle East, Africa	80	80	-10.7 (-15.8, -5.6)
	Americas	68	74	-10.9 (-16.2, -5.6)
	Europe	118	109	-8.5 (-12.8, -4.1)
HTN Subtype	uHTN	67	71	-10.1 (-15.3, -4.9)
	rHTN	199	192	-9.8 (-13.1, -6.4)
Baseline SBP (mm Hg)	<145	92	92	-8.3 (-13.3, -3.3)
	≥145	174	171	-10.7 (-14.1, -7.3)
Baseline eGFR (mL/min/1.73 m^2)	<60	30	29	-8.4 (-17.6, 0.8)
	≥60	236	234	-10.1 (-13.0, -7.1)
Baseline BMI (kg/m^2)	<30	126	128	-8.7 (-12.6, -4.7)
	≥30	140	135	-10.8 (-14.8, -6.7)



[a]Forest plot shows LSM difference versus placebo for change from baseline in seated SBP at week 12 with baxdrostat 1 mg (left) and 2 mg (ri
baseline HTN (uHTN, rHTN) as factors, and baseline seated SBP value as a covariate. For the baseline HTN subgroup analysis, the baseline
handled via multiple imputation. Circle denotes the point estimate. The widths of CI have not been adjusted for multiplicity and cannot be used to infer treatment effects.

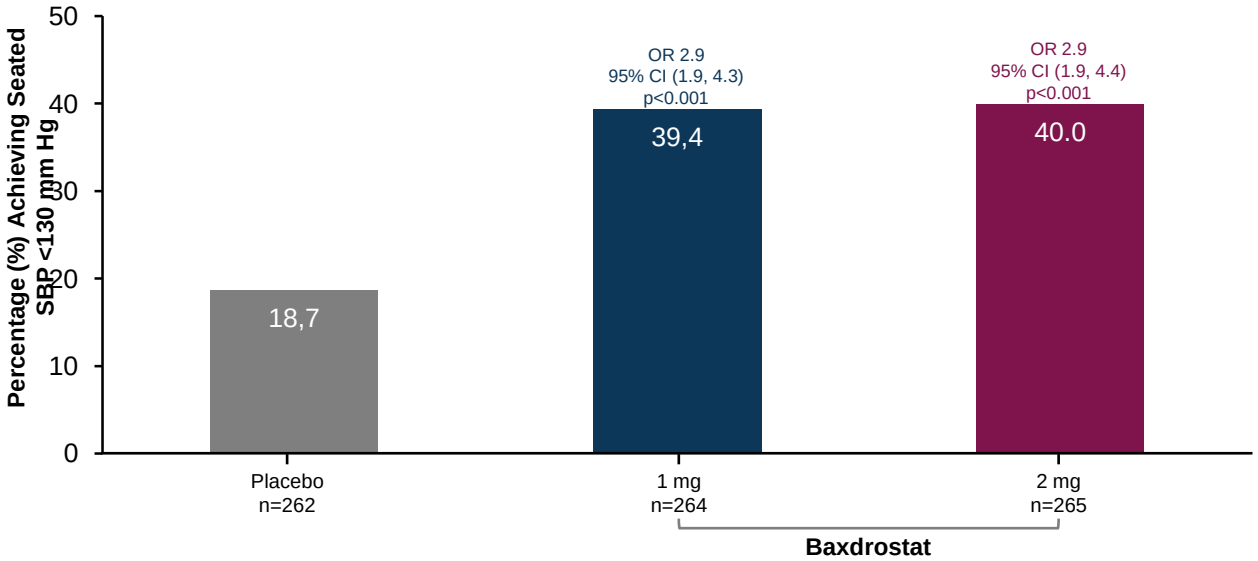
ANCOVA = analysis of covariance; APAC = Asia Pacific; Bax = baxdrostat; BMI = body mass index; CI = confidence interval; DBP = diastolic blood presure; eGFR = estimated glomerular filitration rate; HTN = hypertension; LSM = least-squares mean; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Percentage of Patients Achieving Target SBP <130 mm Hg[1,2]

Baxdrostat demonstrated approximately a 3-fold increase in the odds of patients achieving SBP <130 mm Hg compared to placebo

Secondary Endpoint – Percentage (%) Achieving Seated SBP <130 mm Hg at Week 12[a]



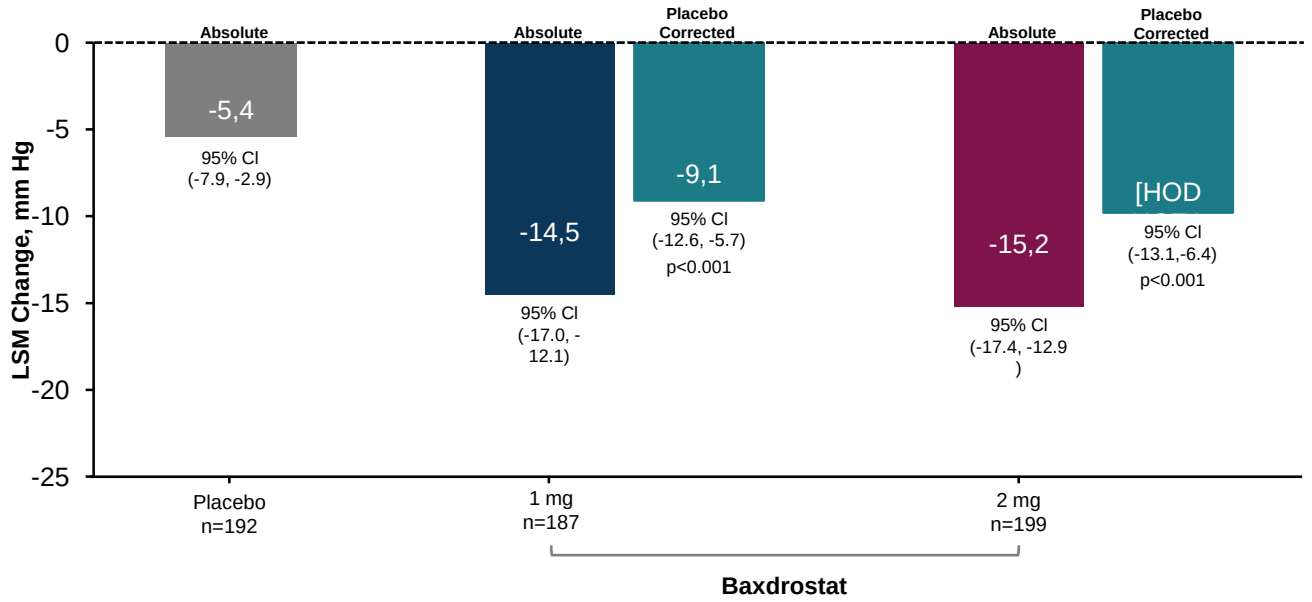
[a]The analysis was performed using a logistic regression model with baseline seated SBP value as a covariate and treatment and HTN at baseline (uHTN, rHTN) as factors.[2] The analysis included patients with baseline seated SBP of ≥130 mm Hg. An OR greater than 1 favors baxdrostat. Missing data at week 12 following treatment discontinuation were imputed using a multiple imputation retrieved dropout method and missing data at week 12 following initiation of rescue medication were imputed using a multiple imputation washout method. Intercurrent events of deaths were handled using the hypothetical strategy (i.e., as if the subject had not died).

CI = confidence interval; HTN = hypertension; OR = odds ratio; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension.

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Baxdrostat Demonstrated Significant Placebo-Corrected Reductions in Seated SBP in the resistant HTN Subpopulation at Week 12[1,2]

Secondary Endpoint – Change in Seated SBP from Baseline to Week 12 in the rHTN Subgroup[a]

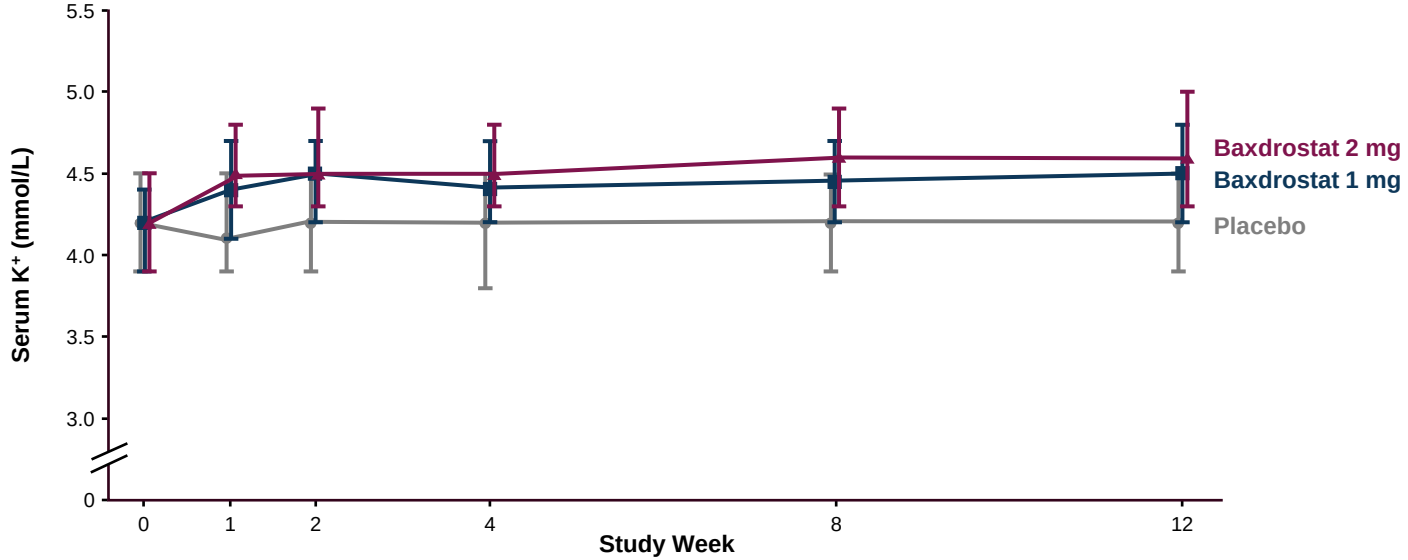


[a]The analysis was performed on the full analysis set (all randomized patients who received at least one dose of study intervention) using an ANCOVA model with treatment as factor, and baseline seated-SBP value as a covariate. Only patients with rHTN at baseline were included in the analysis.[1] Missing data at week 12 following treatment discontinuation were imputed using a multiple imputation retrieved dropout method and missing data at week 12 following initiation of rescue medication were imputed using a multiple imputation washout method. Intercurrent events of deaths were handled using the hypothetical strategy (i.e., as if the subject had not died).
ANCOVA = analysis of covariance; CI = confidence interval; LSM = least-squares mean; rHTN = resistant hypertension; SBP = systolic blood pressure; uHTN = uncontrolled hypertension

1. Flack JM et al. Article online ahead of print. *N Engl J Med.* 2025; 2. Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Median Change in Serum K^+ Over the Treatment Period

Serum K^+ from Baseline to Week 12



Placebo	n=264	241	247	254	252	247
Baxdrostat 1 mg	n=264	251	247	257	252	251
Baxdrostat 2 mg	n=266	244	251	256	255	251

Note: Data represent the median serum potassium level. Bars on the line graphs indicates interquartile range.
K^+ = potassium.

Flack JM et al. Supplementary appendix online ahead of print. *N Engl J Med.* 2025.

Select Safety Data

Event, n (%)	Baxdrostat 1 mg n=264	Baxdrostat 2 mg n=266	Placebo n=264
Any SAE[a]	5 (1.9)	9 (3.4)	7 (2.7)
Death	0 (0.0)	0 (0.0)	1 (0.4)
Any AE	125 (47.3)	119 (44.7)	109 (41.3)
AE leading to discontinuation	7 (2.7)	12 (4.5)	5 (1.9)
AESI[b]			
Hyperkalemia	7 (2.7)	21 (7.9)	0 (0.0)
Hyponatremia	2 (0.8)	6 (2.3)	1 (0.4)
Hypotension	5 (1.9)	6 (2.3)	2 (0.8)

Note: Safety data during the 12-week double-blind treatment period. All blood samples were measured at a central laboratory, blinded to randomization. Serum K^+ was measured at both local and central laboratories.

[a]One case of hyperkalemia (baxdrostat 1 mg) and 2 cases of hyponatremia (baxdrostat 1 mg and baxdrostat 2 mg) were deemed by investigators to be possibly related to baxdrostat; [b]Hyperkalemia (serum K^+ >5.0 mmol/L), hyponatremia (serum Na^+ <135 mmol/L), and hypotension requiring clinical intervention were AEs of special interest.

AE = adverse event; AESI = adverse event of special interest; Na^+ = sodium$^+$; K^+ = potassium; SAE = serious adverse event.

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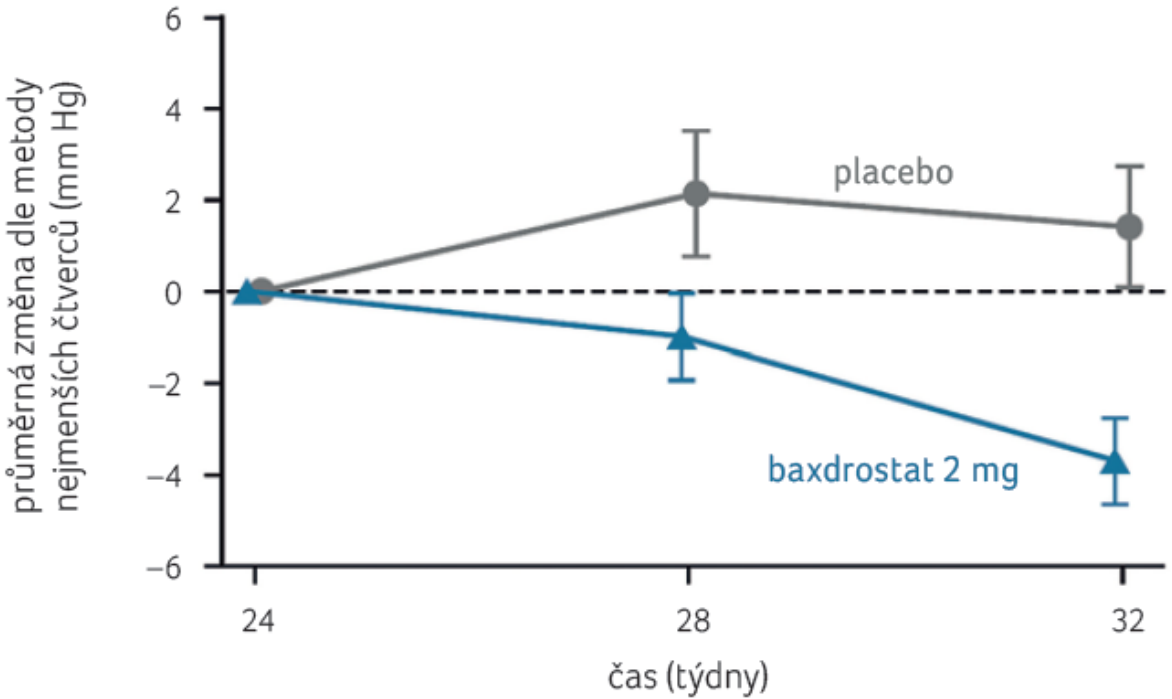
Změna hodnoty systolického krevního tlaku od randomizovaného vysazení studijní léčby (týden 24) do 32. týdne



Pomalé odeznívání účinku léku:

Po randomizovaném vysazení 2mg dávky v další fázi studie zůstal krevní tlak v placebové skupině relativně stabilní až do 32. týdne, což pravděpodobně souvisí s dlouhodobým ovlivněním homeostázy sodíku baxdrostatem

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Závěry

Přidání baxdrostatu v dávkách 1 mg nebo 2 mg k zavedené medikaci vedlo po 12 týdnech k významnému a klinicky relevantnímu poklesu hodnoty systolického krevního tlaku oproti placebu o 8,7 mm Hg a o 9,8 mm Hg

Léčba byla dobře snášena, nejčastějším nežádoucím účinkem souvisejícím s mechanismem působení léku byly hyperkalemie a hyponatremie

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