Efficacy Subgroup Analysis: KBP-5074, a Novel Non-Steroidal, Highly Selective, Mineralocorticoid Receptor Antagonist (MRA) for the Treatment of Uncontrolled Hypertension in CKD Stage 3b/4

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ABSTRACT

TITLE:
Subgroup Analysis of the Efficacy of KBP-5074, a Non-Steroidal, Highly Selective, Mineralocorticoid Receptor Antagonist (MRA) in uncontrolled hypertension and CKD Stage 3b/4

BACKGROUND:
KBP-5074, a novel highly protein-bound and highly selective non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development, for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD). KBP-5074 selectively binds to recombinant human mineralocorticoid receptor (MR) with much higher affinity then to recombinant human glucocorticoid, progesterone, and androgen receptors and has a higher antagonistic activity to the MR than steroidal MRAs (ie, spironolactone and eplerenone) and non-steroidal finerenone (1-3). Phase 2b clinical trial BLOCK-CKD (4) with subjects having CKD stage 3b/4 (eGFR 15-44 mL/min/1.73 m^2) demonstrated statistically significant blood pressure lowering and that neither hyperkalemia nor reductions in kidney function were limiting factors to the use of KBP-5074.

OBJECTIVES:
To evaluate the efficacy of KBP-5074 in exploratory subgroups with uncontrolled hypertension in stage 3b/4 CKD.

METHODS:
BLOCK-CKD is a phase 2b, international, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. It evaluates the safety, efficacy, and pharmacokinetics of the nonsteroidal MRA KBP-5074 for uncontrolled hypertension in patients with stage 3b/4 CKD already receiving background antihypertensive medications.

BASELINE CHARACTERISTICS:
A total of 162 patients were randomized. One hundred thirty-eight (138) of 162 (85.2%) patients enrolled completed the study, including 47 patients in the placebo group, 47 patients in the KBP-5074 0.25-mg group, and 44 patients in the KBP-5074 0.50-mg group. Upon the completion of enrollment, 162 stage 3b/4 CKD patients randomized in the clinical trial had a mean SBP at baseline of 155.3 mm Hg, and a DBP of 87.7 mm Hg; 64 (39.5%) patients had stage 4 CKD and 125 (77.2%) patients had proteinuria as defined by UACR ≥30 mg/g and 85 (52.5%) patients having albuminuria (UACR >300 mg/g). Baseline eGFR was similar across treatment groups at baseline was 31.9 mL/min/1.73 m^2. 144 (88.9%) patients were taking at least 3 antihypertensive medications and 81 (50.0%) patients were taking at least 4 antihypertensive medications. A subject was considered to be diabetic if the Investigator determined that diabetes was the etiology of the subject's renal disease; overall, 51 (31.5%) patients were considered diabetic.

RESULTS:
Subgroup analyses for placebo-corrected change from Baseline to Day 84 in SBP resulted in consistent and clinically meaningful reductions from Baseline in SBP (i.e., the placebo-corrected LS mean reduction from Baseline to Day 84 in SBP was >5 mmHg) were observed in subgroups analyzed. In subgroup evaluation of SBP over different age categories (≤65 or >65 years), baseline eGFR (<30 or ≥30 mL/min/1.73 m^2), baseline SBP (≥ 160 vs < 160 mm Hg), baseline antihypertensive medications (3 or more or 2 or less), gender, albuminuria, ethnicity, or diabetic status, consistent results were observed.

CONCLUSIONS:
KBP-5074 demonstrated consistent efficacy across numerous subgroups.

For additional information please contact:

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BACKGROUND

- KBP-5074, a novel highly protein-bound and highly selective non-steroidal mineralocorticoid receptor antagonist (MRA), is currently under development, for the treatment of uncontrolled hypertension in patients with chronic kidney disease (CKD).
- KBP-5074 selectively binds to recombinant human mineralocorticoid receptor (MR) with much higher affinity then to recombinant human glucocorticoid, progesterone, and androgen receptors and has a higher antagonistic activity to the MR than steroidal MRAs (ie, spironolactone and eplerenone) and non-steroidal finerenone (1-3).
- Phase 2b clinical trial BLOCK-CKD (4) with subjects having CKD stage 3b/4 (eGFR 15-44 mL/min/1.73 m^2) demonstrated statistically significant blood pressure lowering and that neither hyperkalemia nor reductions in kidney function were limiting factors to the use of KBP-5074

METHODS

- Overall, of 455 screened subjects, a total of 162 subjects were randomized to either placebo (57 [35.2%] subjects), KBP-5074 0.25-mg (51 [31.5%] subjects) or KBP-5074 0.5-mg (54 [33.3%] subjects) group.
- The randomized subjects were stratified based on their baseline eGFR <30 or > 30 mL/min/1.73 m^2 and SBP <160 or > 160 mm Hg.
- The primary efficacy endpoint was the change in trough cuff seated SBP from Baseline to Day 84.
- Although blood pressure was measured in triplicate, only the average of the last 2 triplicate measurements were used in the analyses.

BASELINE CHARACTERISTICS

- A total of 162 patients were randomized. The baseline demographics and characteristics are shown in Table 1.
- 138 of 162 (85.2%) patients enrolled completed the study, including 47 patients in the placebo group, 47 patients in the KBP-5074 0.25-mg group, and 44 patients in the KBP-5074 0.50-mg group.

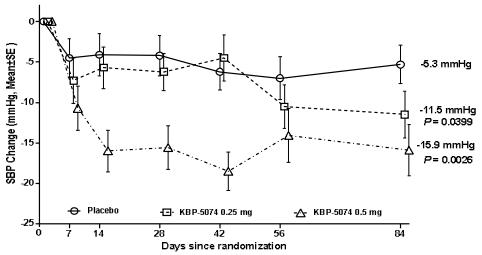
Table 1. Baseline Demographics and Characteristics

Baseline Demographics and Characteristics	Overall (N=162)
SBP (mmHg): Mean (SD)	155.3 (13.55)
DBP (mmHg): Mean (SD)	87.7 (12.23)
Background antihypertensive medication: n (%) • 3 or more • 2 or less	 144 (88.9) 18 (11.1)
Baseline eGFR (mL/min/1.73 m^2): mean (SD)	31.9 (9.90)
Baseline eGFR: n (%) • CKD Stage 3b: 30-44 mL/min/1.73 m^2 • CKD Stage 4: 15-29 mL/min/1.73 m^2	 98 (60.5) 64 (39.5)
Baseline Proteinuria: n (%) • UACR >300 mg/g • UACR 30-300 mg/g • UACR <30 mg/g	 85 (52.5) 40 (24.7) 35 (21.6)

PRIMARY EFFICACY ANALYSIS

- The primary analysis showed statistically significant decreases in mean trough cuff seated SBP from Baseline to Day 84 between the KBP-5074 0.25-mg and 0.5-mg groups compared to placebo (Figure 1).
- The decreases in mean trough cuff seated SBP from Baseline to Day 84 were greater in the KBP-5074 0.5-mg (-15.9 mm Hg) and 0.25-mg (-11.5 mm Hg) groups than in the placebo group (-5.3 mm Hg).
- The LS mean treatment differences in change from Baseline to Day 84 between the KBP-5074 0.5-mg and placebo groups (-10.2 mm Hg [95.01% CI: -16.7, -3.6]) and between the KBP-5074 0.25-mg and placebo groups (-7.0 mm Hg [95.01% CI: -13.6, -0.3]) were statistically significant (p=0.0026 and p=0.0399, respectively).

Figure 1. Line Plot of Mean Change in Trough cuff Seated SBP from Baseline to Post-Baseline Visits (LOCF Analysis) (Intent-to-Treat Population)



Note: Baseline was defined as the last non-missing value before the subject received the first dose of study drug.

Abbreviations: SBP, systolic blood pressure; SE, standard error

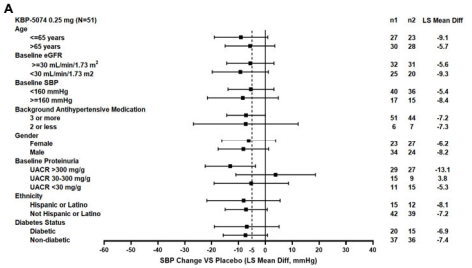
Source: Table 14.2.1.1

EXPLORATORY SUBGROUP ANALYSES

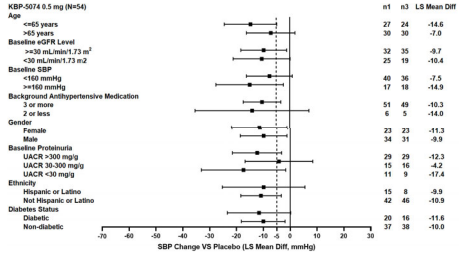
- Subgroup analyses for placebo-corrected change from Baseline to Day 84 in SBP are shown in Figure 2A and B.
- In general, consistent and clinically meaningful reductions from Baseline in SBP (i.e., the placebo-corrected LS mean reduction from Baseline to Day 84 in SBP was >5 mm Hg) were observed in subgroups analyzed.
- The subgroup analysis showed no differences in reduction from baseline SBP with different age categories (≤65 or >65 years), including group cut off (18 to ≤45 years, >45 to ≤65 years, >65 to ≤75 years, >75 years), baseline eGFR (<30 or ≥30 mL/min/1.73 m^2), baseline SBP (≥160 vs < 160 mm Hg), baseline antihypertensive medications (3 or more or 2 or less), gender, ethnicity, or diabetic status, consistent results were observed.
- KBP-5074 resulted in a consistent, dose-dependent and statistically significant lowering of SBP in subjects with albuminuria (UACR >300 mg/g). In subjects with UACR <30 mg/g, a dose-dependent trend towards lower SBP was observed with statistically significant lowering of SBP in the KBP-5074 0.5-mg group compared to placebo (p=0.0301).

Figure 2. Subgroup analyses for placebo-corrected mean change from Baseline to Day 84 in SBP for KBP-5074 treatment groups (Intent-to-Treat Population)

A



B



Abbreviations: eGFR, estimated glomerular filtration rate; LS Mean Diff, least squares mean difference; n1, number of subjects on placebo; n2, number of subjects on KBP-5074 0.25-mg QD; n3, number of subjects on KBP-5074 0.5-mg QD; SBP, systolic blood pressure; UACR, urinary albumin creatinine ratio; VS, versus

Note: The dotted line indicates a 5 mm Hg placebo-corrected reduction from Baseline.

Source: Table 14.2.1.7b, Table 14.2.1.8, Table 14.2.1.9, Table 14.2.1.10, Table 14.2.1.12, Table 14.2.1.13 and Table 14.2.1.14

CONCLUSIONS

- This study showed clinically meaningful and statistically significant effects on primary outcome, decreases in trough cuff seated SBP from Baseline to Day 84, for both doses of KBP-5074 compared to placebo in subjects with advanced CKD (eGFR ≥15 to ≤44 mL/min/1.73 m^2) and uncontrolled hypertension (average baseline 155.3 mm Hg) even with multiple background antihypertensive medications (88.9% of subjects on at least 3 antihypertensive medications).
- Subgroup analysis showed consistent SBP reduction across various subgroups such as age, baseline eGFR, baseline SBP, baseline antihypertensive medications, gender, albuminuria, ethnicity, or diabetic status.

References

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3. Pitt B, Jaisser F, Bakris GL. An evaluation of KBP-5074 in advanced chronic kidney disease with uncontrolled hypertension. Expert Opinion on Investigational Drugs. 2021;30(10):1017–1023.
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