2. SYNOPSIS

Sponsor: Celltrion Inc.

Study Drug: Azilsartan medoxomil and Amlodipine besylate

Title of study: A Multicentre, Randomized, Double-blind Study to Evaluate and Compare the Efficacy and Safety of 8-week Treatment with Azilsartan Medoxomil and Amlodipine Besylate Combined and Alone in Mild-to-moderate Essential Hypertensive Subjects

Investigators: The study was conducted at 64 sites located in Korea, Poland, and Taiwan. List of investigators: KR-01: Sung-Ha Park; KR-02: Sang-Ho Jo; KR-03: Jin Oh Na and Chang-Gyu Park; KR-04: Seung-Hwan Han; KR-05: Joon-Han Shin; KR-06: Doo Sun Sim and Myung Ho Jeong; KR-07: Moo-Hyun Kim; KR-08: Soon Jun Hong; KR-09: Dong-Ju Choi; KR-10: Kyung-Kuk Hwang and Jang-Whan Bae; KR-11: Byung-Su Yoo; KR-12: Moo-Yong Rhee; KR-13: Sang Hyun Kim; KR-14: Deok Kyu Cho; KR-15: Pil-Sung Yang; KR-16: Byung-Ryul Cho; KR-17: Han-Cheol Lee; KR-18: Dae-hee Kim; KR-19: Jino Park and Sang-hoon Seol; KR-20: Sang Hyun Ihm; KR-21: Yun-Hyeong Cho; KR-22: Sang Hyun Lee, Jeong Su Kim, and Min-Ku Chon; KR-23: Chang Hoon Lee; KR-24: Hancheol Lee; KR-25: Ung Kim; KR-26: Seongwoo Han; KR-27: Hyuck Jun Yoon; KR-28: Sung-Ho Her; KR-29: Seung-Uk Lee; KR-30: Woo-Shik Kim; KR-31: Kyung Ah Han; KR-32: Jun Hwa Hong; KR-33: Kyu Jeung Ahn; KR-34: Jae-Myung Yu; KR-35: Sang-Yong Kim; KR-36: Sung Uk Kwon; PL-01: Krzysztof Milewski; PL-02: Aleksander Zurakowski; PL-03: Pawel Bogdanski; PL-04: Adam Janas; PL-05: Grzegorz Kania; PL-07: Maciej Kosmider; PL-08: Pawel Miekus; PL-09: Lukasz Artyszuk; PL-10: Grazyna Glanowska; PL-11: Marcin Grabowski; PL-12: Nader Elmasri and Przemyslaw Wilczewski; PL-13: Wojciech Czochra; PL-14: Teresa Rusicka; PL-15: Katarzyna Piatkowska; PL-16: Ryszard Serafin; PL-17: Katarzyna Szymczyk; TW-01: Tzung-Dau Wang; TW-02: I-Chang Hsieh; TW-03: Ching-Pei Chen; TW-04: Tsung-Hsien Lin; TW-05: Chern-En Chiang; TW-06: Kuan-Cheng Chang; TW-07: Ming-Hsiung Hsieh; TW-08: Kuan-Chun Chen; TW-09: Chi-Hung Huang; TW-10: Mu-Yang Hsieh and Chih-Cheng Wu; TW-11: Cheng-I Cheng; TW-12: Chun-Yao Huang.

Publications: None.

Period of study: 08 July 2022 (date of first informed consent) to 19 July 2024 (date of last subject's last visit/contact).

Phase of development: Clinical Phase 3

Background and rationale for the study:

Hypertension is one of the most common causes of preventable death in developed nations. Despite the availability of antihypertensive drugs, blood pressure (BP) is uncontrolled in an estimated half of all subjects with hypertension and this is an important worldwide public-health challenge. Most major guidelines including Korea, USA, and Europe recommend that in hypertensive subjects BP be controlled to levels of 140/90 mmHg or lower. It is known that, approximately 60% of these subjects fail to fall under the safety range in subjects with coronary disease and/or diabetes. Multiple mechanism therapy with angiotensin II subtype 1 receptor blocker and calcium channel blocker has the potential to achieve rapid and additive

BP-lowering efficacy by targeting the 2 key pathways involved in the regulation of BP, and to bring less adverse events (AEs).

In this study CT-L05-301, Celltrion evaluated the efficacy of Azilsartan Medoxomil (AZM)/Amlodipine Besylate (AML) combination for the treatment of hypertension in subjects whose BP was not adequately controlled with AML alone or with AZM alone.

Objectives:

The primary objective of the study was to evaluate antihypertensive efficacy of a combination of AZM and AML, in mild-to-moderate essential hypertensive subjects not adequately controlled by AZM monotherapy or AML monotherapy.

The secondary objectives were:

- to evaluate the safety and tolerability of a combination of AZM and AML, in mild-to-moderate essential hypertensive subjects not adequately controlled by AZM monotherapy or AML monotherapy
- to determine the dose-response relationship of AZM or AML monotherapy and AZM/AML combination therapy in subjects with mild-to-moderate essential hypertension.

Methodology:

This was an 8-week, randomized, double-blind Phase 3, multicenter study to determine the optimal dose of AZM and AML in combination therapy and to compare efficacy and tolerability of the combination therapy to each of the monotherapy in essential hypertensive subjects who were not adequately controlled on AZM 40 and 80 mg or AML 5 and 10 mg monotherapy.

This study was composed of 4 study parts, including screening period, single-blind run-in period, double-blind treatment period, and safety follow-up period. The total duration of the study was to be up to 16 weeks for each subject who completed the entire study.

Potential subjects underwent an onsite screening visit to determine their eligibility for the study. Subjects who qualified for enrollment following a 2-week screening were to start a 4-week single-blind pre-treatment baseline run-in period. An estimated total of 804 subjects were to be randomized in a ratio of 1:1:1:1 to AZM 40 mg, AZM 80 mg, AML 5 mg, and AML 10 mg with 201 subjects in each treatment group. During the run-in period, subjects received AZM or AML for 4 weeks and attended 2 scheduled visits.

After the single-blind run-in period, 201 qualified subjects in each group (those not responding to treatment in the run-in period) were to be randomized in a double-blind manner with a ratio of 1:1:1 to 1 control group (AZM monotherapy or AML monotherapy) and 2 test groups (AZM and AML combination therapy, low or high dose) with at least 67 subjects in each treatment group. During the treatment period, subjects received treatment for 8 weeks.

Subjects who were randomized were to be contacted for a follow-up telephone call 2 weeks after the final study visit for recording any new or ongoing AEs and any changes from a concomitant medication.

Number of subjects (planned and analyzed):

Approximately 804 subjects were planned for enrollment in the run-in period, with 201 subjects in each group. At least 67 subjects were to be randomized to each treatment group in the treatment period.

A total of 1295 subjects were randomized for the run-in period (325 subjects in the AZM 40 mg group, 325 subjects in the AZM 80 mg group, 324 subjects in the AML 5 mg group, and 321 subjects in the AML 10 mg group).

Of the 1295 subjects randomized for the run-in period, 890 subjects remained eligible to be randomized in the double-blind treatment period.

A total of 225 subjects were randomized to the treatment period in the AZM 40 mg non-responder group, along with 211 subjects in the AZM 80 mg non-responder group, 241 subjects in the AML 5 mg non-responder group, and 213 subjects in the AML 10 mg non-responder group.

Among the 890 randomized subjects, 879 subjects received at least 1 dose of study drug, 833 subjects completed the study, and 46 subjects prematurely withdrew.

Diagnosis and criteria for inclusion and exclusion:

The following were the inclusion criteria for subjects in this study:

At screening:

1. Subjects voluntarily agreed to participate in the trial and sign the written Informed Consent Form (ICF), after listening to the purpose, method, and effect of clinical trial.

2. Male or female adult subjects below the age of 75 years, inclusive.

   Note: Legal minimum age of adult requirement is country-specific, and requirements of current country-specific regulations were applied. The legal ages of adult in Korea, Taiwan, and Poland were ≥19, ≥18, and ≥18 years, respectively.

3. Subjects with mild-to-moderate essential hypertension:

   a. Previously untreated subjects who had not received any antihypertensive medication in the 28 days prior to Visit 1 with mean sitting systolic BP (msitSBP) ≥140 mmHg and ≤180 mmHg

      OR

   b. Subjects with msitSBP ≥130 mmHg and ≤180 mmHg who had not been controlled with antihypertensive drugs.

4. Subjects who were capable of understanding and complying with protocol requirements.

Post-4 week, AZM or AML monotherapy treatment:

5. Subjects who did not achieve target BP (defined as clinic systolic BP [SBP] <140 mmHg as determined by the mean of 3 sitting, trough, measurements; for subjects who had diabetes mellitus or cardiovascular disease [CVD] or chronic kidney disease [CKD] with albuminuria [or proteinuria] target BP was defined as clinic SBP <130 mmHg) following 4 weeks run-in treatment with AZM or AML monotherapy, prior to randomization to double-blind treatment.

6. Subjects who were compliant (>70% and <130%) with the study medication during run-in treatment period.

The following were the exclusion criteria for subjects in this study:

At screening:

1. Subjects who had msitSBP >180 mmHg or mean sitting diastolic BP (msitDBP) >110 mmHg.

2. The differences of msitSBP >20 mmHg or msitDBP >10 mmHg between 2 arms.

3. A history or any suspected history of secondary hypertension, including but not limited to any of the following: coarctation of the aorta, primary hyperaldosteronism, unilateral or bilateral renal artery stenosis, Cushing's syndrome, pheochromocytoma, polycystic kidney disease, CKD on dialysis, etc.

4. Symptomatic orthostatic hypotension (a sudden fall in standing SBP of at least 20 mmHg or standing diastolic BP (DBP) of at least 10 mmHg after standing compared with BP from the sitting or supine position).

5. Type 1 or 2 diabetes mellitus with poor glucose control which is defined as history of poorly controlled diabetes mellitus (fasting blood glucose >11.1 mmol/L [200 mg/dL]) (excluding subjects who did not need diabetes medication control during the study period).

6. Severe heart disease (congestive heart failure [New York Heart Association Class 3 or 4]), ischemic heart disease (unstable angina, myocardial infarction), peripheral arterial vascular disease/endovascular intervention for peripheral artery disease, history of percutaneous transluminal coronary angioplasty or coronary artery bypass grafting within the past 6 months.

7. Clinically significant ventricular tachycardia, atrial fibrillation, atrial flutter, or other clinically significant arrhythmia, or clinically significant QT interval corrected using Fridericia formula for heart rate interval >450 milliseconds (male) and >470 milliseconds (female), or symptomatic bradycardia.

8. Clinically significant electrocardiogram (ECG) abnormalities including third-degree atrioventricular block, sick sinus syndrome, sinus-atrial block.

9. Hypertrophic obstructive cardiomyopathy, severe obstructive coronary artery disease, aortic stenosis, hemodynamically relevant stenosis of the aortic or mitral valve.

10. Severe cerebrovascular disease (history of stroke, cerebral infarction, or cerebral hemorrhage) within the past 6 months.

11. Known moderate or malignant retinopathy (history of retinal signs of hemorrhage, visual impairment, retinal microaneurysm, etc.) within the past 6 months.

12. A history of or ongoing: wasting disease, autoimmune diseases (rheumatoid arthritis, systemic lupus erythematosus, etc.), hepatic impairment defined as Child-Pugh Class A and above or connective tissue disease.

13. Subjects who had the following clinically significant laboratory abnormalities: either creatinine clearance <30 mL/min or serum creatinine >2 mg/dL or >200 μmol/L, serum potassium >5.5mmol/L, alanine aminotransferase or aspartate aminotransferase >3 × upper limit normal (ULN).

14. Significant thyroid disease (thyroid stimulating hormone >1.5 × ULN).

15. History of unexplained syncope within the prior 2 years, or a known syncopal disorder.

16. Any surgical or medical condition of the gastrointestinal tract that could significantly alter the absorption, distribution, metabolism, or excretion of the drug; current active gastritis, gastrointestinal/rectal bleeding, active inflammatory bowel disease within the last 12 months, etc.

17. Positive for human immunodeficiency virus, hepatitis C virus antibody, and/or positive for hepatitis B surface antigen that required antiviral treatment.

18. History of drug or alcohol abuse within the past 1 year.

19. Subjects who were pregnant or lactating women, women suspected of being pregnant, women who wished to be pregnant during the study, or women of child-bearing potential who were not using medically acceptable methods of contraception.

20. Any chronic inflammatory condition needing chronic anti-inflammatory therapy.

21. A known hypersensitivity to any main excipients and components of the investigational drugs or other drugs in the same class.

22. Subjects who had previously experienced symptoms characteristic of angioedema during treatment with angiotensin-converting enzyme inhibitors or angiotensin II subtype I receptor blocker.

23. Subjects who had received any investigational product within 4 weeks (28 days) prior to screening or were participating in another investigational study.

    Note: Subjects participating in observational studies (per local definition) could enter screening provided that the last intervention or invasive procedure was > 28 days prior to Visit 1.

24. Subjects who were required to take excluded medications at any point during the study.

25. Subjects who were judged unsuitable to participate in the study in the opinion of the investigator.

Post 4-week of AZM or AML monotherapy treatment:

26. Subjects who had a clinic msitSBP >180 mmHg and/or msitDBP >110 mmHg.

Investigational product, dose and mode of administration, batch number:

Dose levels of AZM were 40 mg (one 40-mg tablet) and 80 mg (two 40-mg tablets). Doses were administered orally once a day; lot numbers 12009099 and 12174283.

Dose levels of AML were 5 mg (one 5-mg tablet) and 10 mg (two 5-mg tablets). Doses were administered orally once a day; lot numbers EG9003, FM5877, GA1265, FX8304, and FJ7553.

Reference therapy, dose and mode of administration, batch number:

Placebo tablets of AZM; lot numbers CFHBC01C, CFHBC02E, and CFHBC03F.

Placebo tablets of AML; lot numbers CFKBC01C, CGNBC02A, and CGNBC01B.

Duration of treatment:

The study drugs were administered once a day during a run-in period of 4 weeks and a treatment period of 8 weeks.

Endpoints and/or estimand:

Primary Efficacy Endpoint

The primary efficacy endpoint was change from baseline in msitSBP after 8 weeks of treatment.

Estimand for the Primary Endpoint

Efficacy estimand for the primary objective was defined through the following aspects:

A: Treatments: Treatments of interest were:

- AZM: 40 mg, 80 mg
- AML: 5 mg, 10 mg
- AZM 40 mg and AML 5 mg combined
- AZM 80 mg and AML 5 mg combined
- AZM 40 mg and AML 10 mg combined
- AZM 80 mg and AML 10 mg combined.

B: Population: The population was defined through the inclusion and exclusion criteria per Full Analysis Set (FAS).

C: Variable: For each subject in the study, the variable to address the clinical question was the msitSBP change from baseline.

D: Handling of Intercurrent Events: Intercurrent events, such as the use of additional medication and discontinuation of study medication, were handled through a treatment policy strategy.

E: Population-level Summary: The treatment effect was quantified by the estimated difference in least squares (LS) means of treatment groups at Week 8.

An analysis of covariance (ANCOVA) model of msitSBP change from baseline values at Week 8 was used.

Secondary Endpoints

The secondary efficacy endpoints were:

1) Key secondary efficacy endpoint:

- Change from baseline in msitDBP after 8 weeks of treatment.

2) Other secondary efficacy endpoints:

- Change from baseline in msitSBP after 4 weeks of treatment
- Change from baseline in msitDBP after 4 weeks of treatment
- Proportion of subjects who achieved below response criteria:
    - Clinic msitSBP <140 mmHg (but subjects having diabetes mellitus or CVD or CKD with albuminuria [or proteinuria] <130 mmHg) and/or reduction of ≥20 mmHg from baseline after 4 and 8 weeks of treatment
    - Clinic msitDBP <90 mmHg (but subjects having diabetes mellitus or CVD or CKD with albuminuria [or proteinuria] <80 mmHg) and/or reduction of ≥10 mmHg from baseline after 4 and 8 weeks of treatment
    - (a) and (b).

The safety endpoints were:

- Incidence of AEs and serious AEs (SAEs)
- Change in clinical laboratory parameters (biochemistry, haematology, coagulation, and urinalysis, etc.)
- Change in vital signs measurements (BP, heart rate, body temperature, and respiratory rate)
- Change in 12-lead ECG parameters
- Change in physical examination findings.

Statistical methods:

Sample Size

Assuming a standard deviation (SD) of 8.51 mmHg, 60 subjects per arm would have at least 90% power to detect the difference of 5.08 mmHg based on a 2-sample t-test of the mean change from baseline in sitSBP at a 5% two-sided significance level. A total of 67 subjects per arm were to be enrolled in this study to account for 10% dropouts (total 804 subjects).

Overall effects of sitSBP mean change from baseline were calculated based on the meta-analysis provided in the protocol. Meta-analysis was based on a fixed effect model, and weights were calculated using inverse variance. The overall effects were calculated for each AML and telmisartan non-responder groups and the results are shown in the protocol.

With a conservative approach, it was decided to enroll 60 subjects, assuming that the difference in sitSBP mean change from baseline between combination therapy and monotherapy was 5.08 mmHg and pooled SD was 8.51 mmHg.

Analysis Populations

The following analysis populations were used for this study:

Enrolled Set: All subjects who had signed the ICF. The Enrolled Set was used for summaries of disposition and the associated listing.

Intent-to-Treat Set (ITT): All randomized subjects. Intent-to-Treat Set subjects were analyzed according to their randomized treatment.

Full Analysis Set: All randomized subjects in ITT who had at least one dose of double-blind study medication, had baseline and at least one post-baseline msitSBP value. FAS subjects were analyzed according to their randomized treatment. The FAS was the primary analysis set for the primary, key-secondary, non-key secondary, and exploratory efficacy endpoints.

Per Protocol Set (PPS): All subjects in the FAS who did not have any important protocol deviations leading to exclusion from the PPS. Per Protocol Set subjects were analyzed according to their randomized treatment. The PPS was used for the analyses of primary, key-secondary, and non-key secondary efficacy endpoints.

Safety Set: All subjects treated with at least one dose of double-blind study medication. Safety Set subjects were analyzed according to the actual treatment they received. This population was the primary population for all safety parameters and demographic and baseline characteristics.

Safety Set Expanded: All subjects treated with at least one dose of single-blind (run-in period) study medication. The Safety Set Expanded subjects were analyzed according to the actual treatment they received. This population was used for the exploratory safety analysis.

Primary Efficacy Analysis

After 8 weeks of study administration, the mean change from baseline in msitSBP was evaluated using ANCOVA with administration group as a group variable and its baseline msitSBP as a covariate. The administration group was set as a monotherapy (control group) or combination therapy (test group [high or low dose]).

The msitSBP and its change from baseline at Week 8 were summarized descriptively on FAS.

The following hypotheses were tested to compare the therapeutic effect of combination therapy of high-dose group to that of the monotherapy group at Week 8:

H_0: Mean ΔmsitSBP of combination therapy (test group [high dose]) = Mean ΔmsitSBP of monotherapy (control group)

H_1: Mean ΔmsitSBP of combination therapy (test group [high dose]) ≠ Mean ΔmsitSBP of monotherapy (control group)

where Δ signifies change from baseline. A similar hypothesis test was done for a comparison of combination therapy of low-dose group to its corresponding monotherapy group. Difference of LS means between combination therapy of high- or low-dose group and monotherapy group and its two-sided 95% confidence interval (CI) were provided.

Comparisons were made between monotherapy and combination therapy according to a fixed sequential test procedure to control for Type 1 error.

For each non-responder group, 2 ANCOVA models were used with one model for the first step (superiority test of high dose combination therapy to monotherapy) and the other model for the second step (superiority test of low dose combination therapy to monotherapy; conducted if two-sided P-value was not greater than 5% in step 1).

The primary analysis was based on FAS. Additional analysis was performed with PPS in a similar manner to primary analysis. All other sensitivity analyses were based on FAS.

Secondary Efficacy Analysis

The mean change from baseline in msitDBP after Week 8 was analyzed using the same ANCOVA models as used for the primary efficacy variable. The same two-step testing procedure was used. Standard descriptive statistics for continuous variable were provided for msitDBP and its change from baseline at Week 8 by treatment group.

The mean change from baseline in msitSBP and msitDBP after Week 4 was analyzed using the similar ANCOVA models as used for the primary efficacy variable. Standard descriptive statistics for continuous variable were provided for msitSBP and msitDBP and their change from baseline at Week 4 by treatment group. Mean changes from baseline at Weeks 4 and 8 were plotted by treatment.

Count and percent of responders were provided for the visit of Weeks 4 and 8 by treatment group. A responder (specific to type a, b, and c) was defined as a subject who satisfied one of the following criteria:

a. Clinic msitSBP <140 mmHg (but subjects having diabetes mellitus or CVD or CKD with albuminuria [or proteinuria] <130 mmHg) and/or reduction of ≥20 mmHg from baseline after 4 and 8 weeks of treatment
b. Clinic msitDBP <90 mmHg (but subjects having diabetes mellitus or CVD or CKD with albuminuria [or proteinuria] <80 mmHg) and/or reduction of ⩾10 mmHg from baseline after 4 and 8 weeks of treatment
c. (a) and (b).

The probability of response "a" and "c" were modelled using a logistic regression model with administration group as a group variable and its baseline msitSBP as a covariate. The probability of response "b" was modelled using a logistic regression model with administration group as a group variable and its baseline msitDBP as a covariate. The administration group was set as a monotherapy (control group) or combination therapy (test group [high or low dose]). Odds ratio and its 95% CI were calculated for combination therapy of high- or low-dose group relative to the monotherapy group. Proportion of responders was plotted. Only for the subjects in Korea, additional subgroup analysis was performed in a similar way as above.

Subgroup Analyses

Subgroup analyses were conducted using FAS, for the main analysis of primary endpoint in the following subgroups:

- Age (<65, ≥65 years of age)
- Baseline body mass index (BMI) (<30, ≥30 kg/m^2)
- Baseline renal function (calculated glomerular filtration rate [GFR] ≥90, ≥60 to<90, ≥30 to <60 mL/min/1.73 m^2)
- Sex (male, female)
- Race (Caucasian, Black, Other)
- Baseline msitSBP (<median, ≥median) (median msitSBP in mmHg of the FAS for a particular non-responder group)
- Country (Korea, Poland, Taiwan).

The msitSBP change from baseline at Week 8 was summarized descriptively by subgroup levels.

Exploratory Analysis

The mean change from Week -4 in msitSBP after Week 8 was analyzed using ANCOVA. The ANCOVA model included msitSBP at Week -4 as the covariate, and treatment (a monotherapy and 2 combination therapies) as factors. Comparison of each dose was conducted within each non-responder group.

Standard descriptive statistics for continuous variable were provided for mean change from Week -4 in msitSBP at Week 8 by treatment group. The mean change from Week -4 in msitSBP after Week 8 was also plotted.

For further exploratory comparisons between monotherapy versus combination therapy, and between the lower and higher dose of combination therapies, mean change from Week -4 in msitSBP after Week 8 were analyzed using ANCOVA. The ANCOVA model included msitSBP at Week -4 as the baseline covariate, treatment (AZM 40 mg + AML 10 mg, AZM 40 mg + AML 5 mg, AZM 80 mg + AML 10 mg, AZM 80 mg + AML 5 mg, AZM 80 mg, AZM 40 mg, AML 10 mg, AML 5 mg), non-responder group (4 levels) as factors.

All analyses described above for the msitSBP change from Week -4 at Week 8 were repeated for the msitDBP change from Week -4 at Week 8.

Safety Analysis

Safety assessments included incidence of AEs in the run-in and treatment periods, and findings from clinical laboratory evaluations, vital signs, ECG, and physical examination assessments.

Adverse events were summarized by default descriptive summary statistics for categorical variables for the Safety Set by treatment group and overall. An overview of AEs summarized the number and percentage of subjects with at least one of each mentioned AE type: any AEs (including those leading to interruption/discontinuation of study treatment or death, AEs by maximum severity, AEs by relationship to treatment, and AEs by relationship and maximum severity), any study treatment-related AEs (including those leading to interruption/discontinuation of study treatment), any SAEs (including those leading to interruption/discontinuation of study treatment or death), and any study treatment-related SAEs (including those leading to interruption/discontinuation of study treatment or death).

The number and percentage of subjects reporting each AE and the count of number of events was summarized by system organ class (SOC) and preferred term (PT). Subjects with more than one AE within a particular SOC were counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT were counted only once for that PT.

Summary - Conclusions: Subject disposition:

In the AZM 40 mg non-responder group, a total of 225 subjects were randomized to treatment with AZM/AML 40/10 mg (75 subjects), AZM/AML 40/5 mg (75 subjects), or AZM 40 mg monotherapy (75 subjects). Overall, 2 subjects were not treated and 7 subjects discontinued the study treatment, being “voluntary withdrawal” the most common reason (3 subjects).

In the AZM 80 mg non-responder group, a total of 211 subjects were randomized to treatment with AZM/AML 80/10 mg (69 subjects), AZM/AML 80/5 mg (70 subjects), or AZM 80 mg monotherapy (72 subjects). Overall, a total of 5 subjects were not treated and 13 subjects discontinued the study treatment, being “voluntary withdrawal” the most common reason (7 subjects).

In the AML 5 mg non-responder group, a total of 241 subjects were randomized to treatment with AZM/AML 80/5 mg (80 subjects), AZM/AML 40/5 mg (80 subjects), or AML 5 mg monotherapy (81 subjects). Overall, a total of 3 subjects were not treated and 13 subjects discontinued the study treatment, being “did not meet inclusion criteria or did meet exclusion criteria” the most common reason (7 subjects and 6 subjects, respectively).

In the AML 10 mg non-responder group, a total of 213 subjects were randomized to treatment with AZM/AML 80/10 mg (72 subjects), AZM/AML 40/10 mg (70 subjects), or AML 10 mg monotherapy (71 subjects). Overall, 1 subject was not treated and 13 subjects discontinued the study treatment, being “voluntary withdrawal” the most common reason (6 subjects).

Demography and baseline characteristics:

In general, treatment groups within each non-responder group were well balanced with respect to demographic and baseline disease characteristics.

Overall, the majority of subjects were male and Asian in all non-responder groups. In the AZM 40 mg, AZM 80 mg, and AML 5 mg non-responder groups, most subjects were Asian

(>54%), while in the AML 10 mg non-responder group, 50.2% of subjects were White. All subjects in all non-responder groups were of not Hispanic or Latino ethnicity.

Mean age was 60.4 years and most subjects were ≥45 years of age (772/868, 88.9%, including 398 subjects [45.9%] ≥65 years of age). Subjects' BMI ranged from 16.8 to 54.3 kg/m^2 across the non-responder groups.

Overall, mean (SD) SBP at baseline was 147.588 (9.1040) mmHg in the AZM 40 mg non-responder group, 148.821 (9.5910) mmHg in the AZM 80 mg non-responder group, 146.963 (9.0013) mmHg in the AML 5 mg non-responder group, and 146.225 (8.5357) mmHg in the AML 10 mg non-responder group. Mean (SD) DBP at baseline ranged from was 90.407 (8.5305) mmHg, 90.767 (9.4797) mmHg, 90.777 (9.1750) mmHg, and 87.820 (7.5563) mmHg, respectively.

Efficacy results:

In subjects with essential hypertension who did not achieve target BP after 4 weeks of treatment with monotherapy, treatment with AZM/AML as combination therapy doses of 40/5 or 40/10 or 80/5 or 80/10 mg for 8 weeks resulted in statistically significant greater reductions in BP from double-blind baseline to Week 8 compared to continued monotherapy, as demonstrated by the primary, secondary, and other efficacy endpoints.

Primary Efficacy Endpoint

For the primary efficacy endpoint of change from baseline to Week 8 in msitSBP, AZM/AML low-dose and high-dose treatments were significantly better than the control group (monotherapy) in reducing the msitSBP. Treatment differences and the corresponding 95% CIs were:

- AZM 40 mg non-responder group:
    - High-dose AZM/AML 40/10 mg compared to AZM 40 mg – LS mean difference (SE) of -7.761 (2.3479) (95% CI: -12.4 to -3.12; p-value = 0.0012)
    - Low-dose AZM/AML 40/5 mg compared to AZM 40 mg – LS mean difference (SE) of -5.242 (2.3455) (95% CI: -9.88 to -0.606; p-value = 0.0270).
- AZM 80 mg non-responder group:
    - High-dose AZM/AML 80/10 mg compared to AZM 80 mg – LS mean difference (SE) of -8.992 (2.6636) (95% CI: -14.3 to -3.72; p-value = 0.0010)
    - Low-dose AZM/AML 80/5 mg compared to AZM 80 mg – LS mean difference (SE) of -7.593 (2.4791) (95% CI: -12.5 to -2.69; p-value = 0.0027).
- AML 5 mg non-responder group:
    - High-dose AZM/AML 80/5 mg compared to AML 5 mg – LS mean difference (SE) of -7.359 (1.9946) (95% CI: -11.3 to -3.42; p-value = 0.0003)
    - Low-dose AZM/AML 40/5 mg compared to AML 5 mg – LS mean difference (SE) of -7.190 (1.8716) (95% CI: -10.9 to -3.49; p-value = 0.0002).
- AML 10 mg non-responder group:

- High-dose AZM/AML 80/10 mg compared to AML 10 mg – LS mean difference (SE) of -6.649 (2.1481) (95% CI: -10.9 to -2.40; p-value = 0.0024)
- Low-dose AZM/AML 40/10 mg compared to AML 10 mg – LS mean difference (SE) of -8.984 (2.2169) (95% CI: -13.4 to -4.60; p-value <0.0001).

Key Secondary Efficacy Endpoint

For the key secondary efficacy endpoint of change from baseline to Week 8 in msitDBP, AZM/AML low-dose and high-dose treatments reduced mean DBP statistically greater or numerically larger than control group (monotherapy). Treatment differences and corresponding 95% CIs were:

- AZM 40 mg non-responder group:
  - High-dose AZM/AML 40/10 mg compared to AZM 40 mg – LS mean difference (SE) of -2.753 (1.3730) (95% CI: -5.47 to -0.0389; p-value = 0.0468)
  - Low-dose AZM/AML 40/5 mg compared to AZM 40 mg – LS mean difference (SE) of -1.087 (1.3443) (95% CI: -3.74 to -1.57; p-value = 0.4199)
  - AZM/AML high-dose treatments statistically significantly reduced msitDBP. Additionally, numerically greater reductions in msitDBP were observed with low-dose combination therapy compared to monotherapy, which was considered a clinically relevant reduction.
- AZM 80 mg non-responder group:
  - High-dose AZM/AML 80/10 mg compared to AZM 80 mg – LS mean difference (SE) of -5.706 (1.5585) (95% CI: -8.79 to -2.62; p-value = 0.0004)
  - Low-dose AZM/AML 80/5 mg compared to AZM 80 mg – LS mean difference (SE) of -4.773 (1.3611) (95% CI: -7.47 to -2.08; p-value = 0.0006).
- AML 5 mg non-responder group:
  - High-dose AZM/AML 80/5 mg compared to AML 5 mg – LS mean difference (SE) of -2.913 (1.2580) (95% CI: -5.40 to 0.428; p value = 0.0219)
  - Low-dose AZM/AML 40/5 mg compared to AML 5 mg – LS mean difference (SE) of -5.447 (1.2024) (95% CI: -7.82 to -3.07; p-value <0.0001).
- AML 10 mg non-responder group:
  - High-dose AZM/AML 80/10 mg compared to AML 10 mg – LS mean difference (SE) of -2.596 (1.3185) (95% CI: -5.20 to 0.0110; p-value = 0.0510)
  - Low-dose AZM/AML 40/10 mg compared to AML 10 mg – LS mean difference (SE) of -3.754 (1.3627) (95% CI: -6.45 to -1.06; p-value = 0.0067)
  - The superiority of the high-dose combination therapy compared to monotherapy was confirmed. The results were confirmed in the sensitivity and supplementary analysis.

Other Secondary Efficacy Endpoints

For secondary efficacy endpoints, statistically significantly greater reductions in msitSBP were achieved by combination treatment relative to monotherapy by Week 4 in all non-responder groups (p-value <0.05 for all comparisons).

At Week 4, statistically significantly greater reductions in msitDBP were achieved by combination treatment relative to monotherapy in all non-responder groups (p-value <0.05 for all comparisons) except AZM/AML 40/5 mg group in AZM 40 mg non-responder group (p-value = 0.1098).

Additionally, the proportion of subjects with msitSBP <140 mmHg and/or reduction of ≥20 mmHg from baseline and clinic msitDBP <90 mmHg and/or reduction of ≥10 mmHg from baseline at Weeks 4 and 8 were statistically greater or numerically larger more than control group (monotherapy) in all non-responder groups.

In summary, coadministration of AZM/AML led to potent reductions in msitSBP and msitDBP, and these reductions were larger than those with use of monotherapy.

Safety results:

During the study, AEs were observed across all non-responder groups, with varying frequencies and severities between the run-in and treatment periods. AZM/AML low-dose and high-dose combination treatments were generally safe and well tolerated related to the control group (monotherapy) and the incidence of AEs and clinical laboratory abnormalities did not increase with AZM/AML low-dose and high-dose combination treatments.

Single-blind Monotherapy Treatment Period

In the run-in period, AEs were less frequent, with most being mild to moderate in severity. No Grade 4 events were reported, 2 deaths occurred (1 in each of the AZM 40 mg single-blind treatment group [run-in period] and AZM 80 mg single-blind treatment group [run-in period]), and 1 SAE of Grade 3 vertebrobasilar artery dissection (important medical event) occurred in AZM 80 mg single-blind treatment group (run-in period). None of deaths or SAEs were considered related to study drug. Adverse events resulting in treatment interruption/discontinuation occurred with a similarly low frequency across all treatment groups (from 4 [1.2%] subjects in the AML 5 mg single-blind treatment group [run-in period] to 11 [3.4%] subjects in the AZM 80 mg single-blind treatment group [run-in period]).

Double-blind Treatment Period

- In the AZM 40 mg non-responder group, the overall incidence of adverse events was similar with control group (monotherapy) and high-dose combination group (AZM/AML 40/10 mg) (21.3% and 20.5%, respectively), but lower in the low-dose combination group (AZM/AML 40/5 mg) (17.3%). AEs were predominantly Grade 1 to 2 in severity.

  Hypertriglyceridaemia was the most commonly reported adverse event across the treatment groups and it occurred in a higher percentage of subjects in the control group (monotherapy) than in both combination groups (AZM/AML 40/10 mg and AZM/AML 40/5 mg) (5.3%, 2.7% and 0% respectively).

The percentage of subjects with an adverse event that the investigator considered related to study drug was higher in the high-dose combination group (AZM/AML 40/10 mg) compared with low-dose combination group (AZM/AML 40/5 mg) and control group (monotherapy) (4.1%, 1.3% and 1.3%, respectively).

Six subjects experienced AEs leading to treatment interruption or discontinuation. One subject (AZM/AML 40/10 mg treatment group) experienced an SAE of Grade 3 uterine leiomyoma that was considered not related to study drug. No subject died in any treatment group during the double-blind treatment period.

- In the AZM 80 mg non-responder group, the overall incidence of adverse events was similar with high-dose combination group (AZM/AML 80/10 mg) and low-dose combination group (AZM/AML 80/5 mg) (10.4% and 11.6%, respectively), but higher in the control group (monotherapy) (20.0%). AEs were predominantly Grade 1 to 2 in severity.

  Hypertriglyceridaemia and hyperuricaemia were the most commonly reported adverse event across the treatment groups. Hypertriglyceridaemia occurred in a higher percentage of subjects in the low-dose combination group (AZM/AML 80/5 mg) than control group (monotherapy) and high-dose combination group (AZM/AML 80/10 mg) (4.3%, 0% and 0% respectively), and hyperuricaemia occurred in a higher percentage of subjects in high-dose combination group (AZM/AML 80/10 mg) than low-dose combination group (AZM/AML 80/5 mg) and control group (monotherapy) (3.0%, 0% and 0% respectively).

  The percentage of subjects with an adverse event that the investigator considered related to study drug was higher in the high-dose combination group (AZM/AML 80/10 mg) compared with low-dose combination group (AZM/AML 80/5 mg) and control group (monotherapy) (3.0%, 1.4% and 1.4%, respectively).

  Four subjects experienced AEs leading to treatment interruption or discontinuation. No SAEs were reported in any treatment group and no subject died in any treatment group during the double-blind treatment period.

- In the AML 5 mg non-responder group, the overall incidence of adverse events was similar with high-dose combination group (AZM/AML 80/5 mg) and low-dose combination group (AZM/AML 40/5 mg) (20.3% and 22.8%, respectively), but lower in the control group (monotherapy) (8.8%). AEs were predominantly Grade 1 to 2 in severity.

  Dizziness was the most commonly reported adverse event across the treatment groups and it occurred in a higher percentage of subjects in the high-dose combination group (AZM/AML 80/5 mg) than low-dose combination group (AZM/AML 40/5 mg) and control group (monotherapy) (3.8%, 1.3% and 1.3%, respectively).

  The percentage of subjects with an adverse event that the investigator considered related to study drug was higher in the high-dose combination group (AZM/AML 80/5 mg) compared with low-dose combination group (AZM/AML 40/5 mg) and control group (monotherapy) (5.1%, 3.8% and 1.3%, respectively).

  Seven subjects experienced AEs leading to treatment interruption or discontinuation. Two subjects (AZM/AML 80/5 mg treatment group and AZM/AML 40/5 mg treatment group) experienced SAEs of Grade 3 small cell lung cancer metastatic and Grade 2 acute myocardial infarction that were considered not related to study drug. No subject died in any treatment group during the double-blind treatment period.

- In the AZM 10 mg non-responder group, the overall incidence of adverse events was same with control group (monotherapy) and high-dose combination group (AZM/AML 80/10 mg) (12.7% and 12.7%, respectively), but higher in the low-dose combination group (AZM/AML 40/10 mg) (22.9%). AEs were predominantly Grade 1 to 2 in severity.

  There was no AE occurring in ≥3% of subjects in any treatment group.

  The percentage of subjects with an adverse event that the investigator considered related to study drug was higher in the high-dose combination group (AZM/AML 80/10 mg) and control group (monotherapy) (1.4% and 1.4%, respectively) compared with low-dose combination group (AZM/AML 40/10 mg) (0%).

  Six subjects had AEs leading to treatment interruption or discontinuation. Six subjects experienced SAEs of abscess limb, angina pectoris, and haemothorax in the AZM/AML 40/10 mg treatment group, cellulitis in the AZM/AML 80/10 mg treatment group, and diverticulitis intestinal haemorrhagic and pneumonia in the control group (monotherapy) and all SAE were considered not related to study drug. No subject died in any treatment group during the double-blind treatment period.

There were no clinically relevant differences noted among treatment groups with respect to vital signs, physical examination results, clinical laboratory or ECG results.

Conclusions:

Overall, AZM/AML as combination therapy represented a highly effective treatment option for subjects who are not meeting BP goals with AZM or AML as monotherapy.

Both the low- and high-dose options of AZM/AML combination therapy were safe and well tolerated in this study.