Statistical Analysis Plan

Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy – (MASOLINO Study)

Protocol Number	:	MEIN/20/ZoAm-Hyp/001
Protocol Version	:	1.0
Protocol Date	:	23 April 2021
Plan Version	:	2.0
Plan Date	:	23 May 2022
Study Drug	:	Extemporaneous combination of Zofenopril (ZOF) 30 mg with Amlodipine (AML) 5 mg or Amlodipine (AML) 10 mg
Indication	:	Grade 1-2 Hypertension

Signature Page

The signatures below indicate that these individuals have reviewed this project-specific Statistical Analysis Plan and consent to this document as governing the tasks outlined within. The signatures below also indicate that the processes and quality standards set forth by this Statistical Analysis Plan are approved for use in this study.

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Document History

Version #	Issue Date	Author	Revisions
0.1	10Dec2021	Victoria Swaidan	First Draft
0.2	22Dec2021	Victoria Swaidan	• Abbreviations table updated • Details on data review meetings added to section 5.3 • Number of sites updated in section 5.8 • Sections 4.6, 6.2, 6.3, 6.5, 7.3, 8.2, 8.7, 9 updated for clarity
0.3	05Jan2022	Victoria Swaidan	Minor cosmetic/formatting updates
0.4	28Jan2022	Victoria Swaidan	• Updated definition of TEAE (section 8.2) to include AEs that occur in monotherapy period as well as combined therapy period. Updated list of corresponding tabulations accordingly. • Addition of e-cigarettes into section 6.3 and into corresponding TLF shells.
0.5	21Feb2022	Victoria Swaidan	• Added clarifying text to PP Population definition • Added additional information into section 8.1.4 for clarity • Minor updates to TLF shells
0.6	23Feb2022	Victoria Swaidan	• Added clarifying text to EFF Population definition
1.0	25Feb2022	Victoria Swaidan	Final/Approved Version
2.0	23May2022	Victoria Swaidan	• Added clarity to endpoints and analysis methods • Added clarifying text to Physical Examination section

Table of Contents

1 Abbreviations and Definitions

Abbreviations	Definitions
ACE-i	Angiotensin Converting Enzyme Inhibitor
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine Transaminase
AML	Amlodipine
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Class
BMI	Body Mass Index
BP	Blood Pressure
CCB	Calcium Channel Blocker
CI	Confidence Interval
eCRF	Electronic Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTMS	Clinical Trial Management System
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EFF	Efficacy Population
eGFR	Estimated Glomerular Filtration Rate
FAS	Full Analysis Set
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HR	Heart Rate
IB	Investigator's Brochure
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System

FAS	Full Analysis Set
LS	Least-Squares
LOCF	Last Observation Carried Forward
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MMRM	Mixed Model for Repeated Measures
N	Sample Size
NCS	Not Clinically Significant
PP	Per Protocol Population
PT	Preferred Term
RCT	Randomized Controlled Trial
RR	Respiratory Rate
SAE	Serious Adverse Event
SAF	Safety Population
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
SmPCs	Summary of Product Characteristics
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TESAE	Treatment-Emergent Serious Adverse Event
TLFs	Tables, Listings, and Figures
VR	Ventricular Rate
WHO-DD	World Health Organization Drug Dictionary
ZOF	Zofenopril

2 Introduction

2.1 Preface

Blood Pressure is a multi-regulated variable depending on many compensating pathways. Consequently, combinations of drugs, working through different mechanisms, are required to reduce BP in most people with hypertension. Thus, monotherapy is likely to be inadequate therapy in most patients. Indeed, almost all patients in RCTs have required combinations of drugs to control their BP[1].

Zofenopril (ZOF) has been widely investigated for the treatment of patients with hypertension and its BP lowering effect has been compared with either placebo or with all the classes of antihypertensive drugs currently recommended for the treatment of hypertension. Although there are data in literature showing an added antihypertensive effect of Amlodipine (AML) or Zofenopril to other antihypertensive treatment[2], there is scarce evidence at the moment on the antihypertensive effect of the extemporaneous combination of ZOF and AML versus each monotherapy. The trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

2.2 Purpose of the Analysis

These analyses will assess the anti-hypertensive efficacy and safety of the extemporaneous combination of ZOF 30 mg with AML 5 mg or AML 10 mg. Results will be included in the Clinical Study Report (CSR).

3 Study Objectives and Endpoints

3.1 Study Objectives

3.1.1 Primary Objectives

- **Objective 1.1**: To assess the anti-hypertensive efficacy of the extemporaneous combination of ZOF 30 mg with AML 5 mg or AML 10 mg in lowering the sitting diastolic BP between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with Zofenopril or Amlodipine (5 mg) monotherapies for at least 4 weeks.

3.1.2 Secondary Objectives

- **Objective 2.1**: To assess the antihypertensive efficacy of the extemporaneous combination of ZOF 30 mg in combination with AML 5 mg or AML 10 mg in lowering sitting systolic BP (SBP) between Visit 2 (Week 0) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF or AML 5 mg monotherapies for at least 4 weeks.

- **Objective 2.2**: To assess the antihypertensive efficacy of the extemporaneous combination of ZOF/AML 30/10 mg vs. ZOF/AML 30/5 mg, in lowering sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients with uncontrolled BP previously treated with ZOF or AML 5 mg monotherapies for at least 4 weeks.

- **Objective 2.3**: Monotherapy: to evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0). Combination therapy: to

evaluate the total number and percentage of patients who achieved the BP goal (sitting BP ≤130/80 mmHg) at Visit 3 (Week 4) and Visit 4 (week 8).

- **Objective 2.4**: To assess the compliance to the treatment (percentage of actual doses taken versus doses to be taken) at Visit 2 (Week 0), at Visit 3 (Week 4) and at Visit 4 (Week 8).

- **Objective 2.5**: To evaluate the safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) after 4 weeks of therapy and of the extemporaneous combinations (ZOF 30 mg and AML 5 mg or AML 10 mg) after 8 weeks of treatment.

3.1.3 Exploratory Objectives

- **Objective 3.1**: To assess change in mean sitting SBP and DBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

- **Objective 3.2**: To assess the antihypertensive efficacy at different time points in patients who (1) received ZOF or AML monotherapies before the run-in period, (2) received any other ACE-i or CCB monotherapies before the run-in period.

3.2 Endpoints

3.2.1 Primary Endpoints

- **Endpoint 1.1**: Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8).

3.2.2 Secondary Endpoints

- **Endpoint 2.1**: Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).

- **Endpoint 2.2**: Change in mean sitting DBP and SBP between Visit 3 (Week 4) and 4 (Week 8) in patients on combination of ZOF/AML 30/5 with uncontrolled BP at Visit 3 and up titrated to the extemporaneous combination of ZOF/AML 30/10 mg.

- **Endpoint 2.3**: Monotherapy: number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0). Combination therapy: number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 3 (Week 4) and Visit 4 (Week 8).

- **Endpoint 2.4**: Adherence to the treatments (percentage (%) of doses taken/ doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

- **Endpoint 2.5**: Safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) after 4 weeks of therapy and of the extemporaneous combination (ZOF 30 mg and AML 5 mg or AML 10 mg) after eight weeks of treatment.

3.2.3 Exploratory Endpoints

- **Endpoint 3.1**: Change in mean sitting SBP and DBP between Visit 1 (week -4) and Visit 2 (Week 0), visit 3 (Week 4) and Visit 4 (Week 8):
    - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.

- In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

- **Endpoint 3.2**: Change in mean sitting SBP and DBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4).
  - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
  - In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

- **Endpoint 3.3**:
  - Monotherapy: number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0):
    - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
    - In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).
  - Combination therapy: number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 3 (Week 4):
    - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
    - In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

- **Endpoint 3.4**:
  - Monotherapy: number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0):
    - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
    - In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).
  - Combination therapy: number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 3 (Week 4) and Visit 4 (Week 8):
    - In the group of patients who were on ZOF 30 mg and AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
    - In the group of patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

4 Study Methods

4.1 General Study Design and Plan

This is a phase IV, open-label, multicenter, multinational study with 2 study periods: a 4-week run-in period and an 8-week assessment period.

Approximately 290 patients are planned to be screened to ensure at least 216 patients complete the run-in period and start with the assessment period.

Patients with Grade 1-2 hypertensive patients (blood pressure [BP] ranging from ≥140/90 mmHg to ≤179/109 mmHg) on treatment with any angiotensin converting enzyme inhibitors (ACE-i) including Zofenopril 30 mg or with calcium channel blockers (CCBs) including Amlodipine 5 mg will be screened for eligibility (Visit 1).

Allowed CCBs: Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine. Patients treated with other dosages of Zofenopril (other than 30 mg) are not allowed to be screened.

After screening, on the same day, eligible patients, will enter into a 4-week run-in period, during which patients on other ACE-i will be assigned to monotherapy with ZOF 30 mg while patients on CCBs will be assigned to monotherapy with AML 5 mg for 4 weeks. Patients with on-going treatment zofenopril 30 mg and amlodipine 5mg will continue on the same treatment for 4 weeks.

After the run-in period (4 weeks ± 2 days), BP will be further assessed (Visit 2), if BP levels are over the defined controlled target goal (sitting SBP/DBP >130/80 mmHg), treatment is well tolerated and adherence to the treatments ranges from 80% to 120%, patients will enter the assessment period, where they will be assigned to the extemporaneous combination of ZOF 30 mg and AML 5 mg. At Visit 2 patients with SBP/DBP values classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study.

If patients, at Visit 2, after the run-in period, have a controlled BP (sitting SBP/DBP≤130/80 mmHg) or do not tolerate the treatment or have an adherence range below 80% or superior to 120%, they will be withdrawn from the study.

The patients will be assessed for further 8 weeks (assessment period).

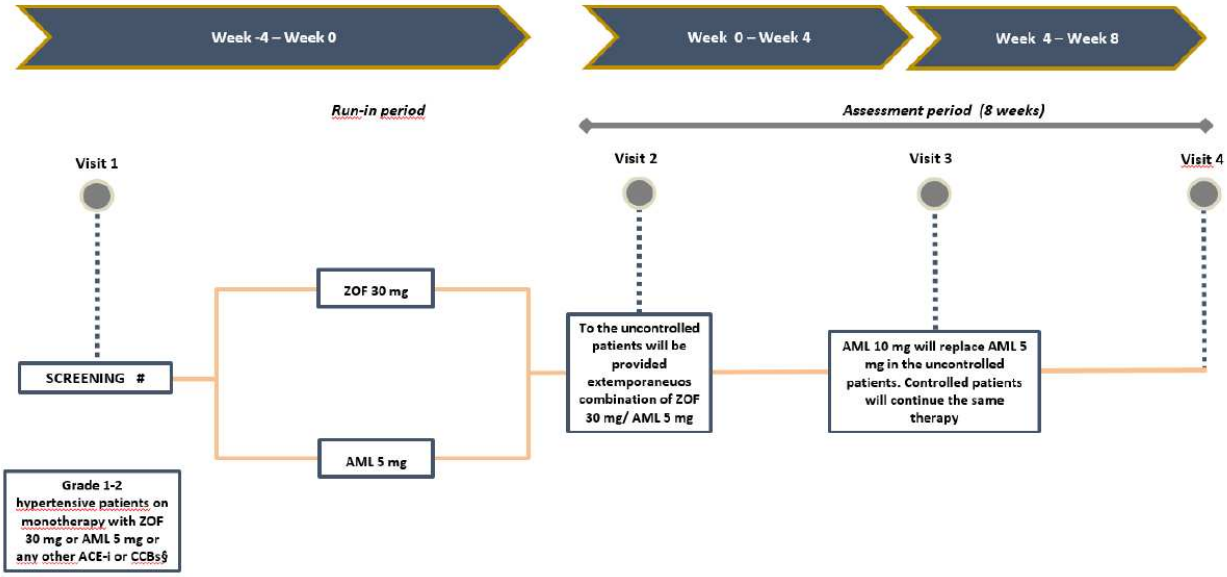
After 4 weeks ± 2 days from Visit 2, during the assessment period patients receiving the extemporaneous combination of ZOF 30 mg and AML 5 mg, will be further evaluated (Visit 3): controlled patients (sitting SBP/DBP ≤130/80 mmHg) will continue the same extemporaneous combination for additional 4 weeks ± 2 days, while uncontrolled patients (sitting SBP/DBP >130/80 mmHg) will be up-titrated from ZOF/AML 30/5 mg to ZOF/AML 30/10 mg for further 4 weeks ± 2 days.

At Visit 3 patients with SBP/DBP values classified as Grade 3 (SBP ≥ 180 or DBP ≥ 110 mmHg) hypertension will be withdrawn from the study.

If patients at Visit 3, do not tolerate the extemporaneous combination treatment or they have an adherence range below 80% or superior to 120%, they will be withdrawn from the study.
At the end of the assessment period (8 weeks ± 4 days) at Visit 4, the anti-hypertensive effect of the extemporaneous combination (ZOF/AML 30/5 mg and ZOF/AML 30/10 mg) will be evaluated.

Efforts will be made to achieve 1:1 ratio in the enrolment of patients receiving any ACE-i or allowed CCBs. At Visit 2, a minimum of 45% of uncontrolled patients receiving treatment with ZOF 30 mg or AML 5 mg are required to enter the assessment period, in order to maintain a balance between the 2 treatments during the assessment period.

4.2 Study Schematic



There is not a randomization procedure

§ Allowed CCBs at screening: Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine. Patients treated with Amlodipine 10 mg or Zofenopril other than 30 mg will not undergo screening procedures.

Grade 1-2 hypertensive patients: Blood pressure (BP) ranging from ≥ 140/90 mmHg to ≤ 179/109 mmHg

Uncontrolled patients with grade 1-2 hypertension: Sitting SBP/DBP > 130/80 mmHg. Patients with Grade 3 (SBP ≥ 180 or DBP ≥ 110 mHg) hypertension will be withdrawn from the study at Visit 2 and Visit 3.

Controlled patients: SBP/DBP ≤ 130/80 mmHg

4.3 Schedule of Assessments

	VISIT 1 / WEEK -4	VISIT 2 / WEEK 0± 2 days	VISIT 3 / WEEK 4± 2 days	VISIT 4 / WEEK 8± 2 days
Informed consent submitted	✓			
IWRS[f] registration	✓	✓	✓	✓
Inclusion/exclusion criteria	✓			
Medical history	✓			
Prior medications	✓			
Demographic information	✓			
Concurrent diseases and medical conditions	✓	✓	✓	✓
Monotherapy of ZOF 30 mg or AML 5 mg dispensing[a]	✓			
Extemporaneous combination of ZOF/AML 30/5 mg dispensing		✓	✓[b]	
Extemporaneous combination of ZOF/AML 30/10 mg dispensing			✓[c]	
Study drug return/accounting (Compliance assessment)		✓	✓	✓
Concomitant medications	✓	✓	✓	✓
Urine Pregnancy test	✓	✓	✓	✓
Physical examination	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓
Laboratory tests[d]	✓			✓
Blood pressure assessment	✓	✓	✓	✓
ECG	✓			✓
AE/SAE assessment[e]	✓	✓	✓	✓
BP device provided to patients[h]	✓			
Patient diary provided to patients[g]	✓	✓	✓	
Patient diary to be returned by patient if used [g]			✓	✓
BP device returned to site[i]				✓

a. Patients on ZOF 30 mg or AML 5 mg will continue the same therapy for 4 weeks. Patients on any other ACE-i will be assigned to monotherapy with ZOF 30 mg and the patients on other CCBs (the allowed CCBs

are: felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) will be assigned to monotherapy with AML 5 mg
b. Only patients controlled at Visit 3 will receive ZOF/AML 30/5 mg
c. Only patients uncontrolled at Visit 3 will receive ZOF/AML 30/10 mg.
d. To ensure patient safety, the patients will be contacted over phone within 24 hours, in case of any abnormality and clinically relevant laboratory test according to the Investigator's judgement at any visit
e. The Investigator is expected to also record any AE which was ongoing at the last treatment dose and a follow-up phone call should be made after 2 weeks from the last study visit.
In case AE was ongoing, the Investigator is expected to follow-up until the outcome of the AE has been determined.
f. IWRS- Interactive Web Response System
g. The following procedure is applied only in case of COVID-19 restrictions.
h. Patients will be provided with an automatic blood pressure device to be used in case they are not able to go to the study centre due to Covid-19 pandemic situation.
i. The patient will return the device at the last visit at the site

4.4 Inclusion-Exclusion Criteria and General Study Population

4.4.1 Inclusion Criteria

A patient will be considered eligible for inclusion in the study only if all the following criteria are met:

1. Male or female Grade 1-2 hypertensive patients: with mean sitting SBP ≥140 mmHg and ≤179 mmHg and/or mean sitting DBP ≥ 90 mmHg and ≤109 mmHg at Screening, with ≥18 and ≤65 years of age, on monotherapy either with ZOF 30 mg or AML 5mg or any other ACE-I or CCBs (Felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nisoldipine) for at least 1 month before Visit 1 (Screening).
2. Patients who are able to understand and give written informed consent at Screening
3. Patients who are available for the entire trial period and willing to adhere to the protocol requirements
4. Ability to take oral medication and willing to adhere to the drug regimen
5. Female patients are eligible to participate if not pregnant, or not breastfeeding and must refrain from donating or storing eggs. For females of reproductive potential: use of highly effective contraception (e.g., method of birth control throughout the study period and for 4 weeks after study completion defined as a method which results in a failure rate of less than 1% per year) such as:
    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal)
    b. Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable)
    c. Intrauterine device (IUD)
    d. Intrauterine hormone-releasing system (IUS)
    e. Bilateral tubal occlusion
    f. Vasectomized partner (performed at least 2 months before screening) (if the partner is the sole sexual partner of the trial participant and that the vasectomized partner has received medical assessment of the surgical success)
6. A male patient must agree to use contraception during the whole study period and for at least 1 week after the last dose of study treatment and refrain from donating sperms during this period

4.4.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Known contraindications, presence of not recommended/contraindicated concomitant therapy allergies, or significant history of hypersensitivity to zofenopril, amlodipine, other ACE-inhibitors or dihydropyridines, or any related products (including excipients of the formulations as outlined in the Investigator's Brochure [IB]), or summary of product characteristics (SmPCs) or local package inserts for AML and ZOF
2. Patients with serious disorders (in the opinion of the Investigator) which may limit the ability to evaluate the efficacy or safety of the tested medications, including cerebrovascular, cardiovascular, renal, respiratory, hepatic, gastrointestinal, endocrine/ or metabolic, haematological, or oncological, neurological, and psychiatric diseases. The same applies for immunocompromised and/or neutropenic patients
3. Patients having a history of the following within the last 6 months: myocardial infarction, unstable angina pectoris, percutaneous coronary intervention, bypass surgery, valve replacement (transcatheter aortic valve implantation, mitraclip), cerebrovascular accident (stroke, heart failure, hypertensive encephalopathy, cerebrovascular accident (stroke), or transient ischemic attack. Patients with who have undergone other surgery that in the in the opinion of the Investigator may limit the ability to evaluate the efficacy or safety of the tested medications.
4. Patients with secondary hypertension of any aetiology such as renal diseases, pheochromocytoma, Cushing's syndrome hyperaldosteronism, renovascular disease, thyroid disorders
5. Patients with severe heart failure (New York Heart Association classification III-IV), a narrowing of the aortic or bicuspid valve, an obstruction of cardiac outflow (obstructive, hypertrophic cardiomyopathy) or symptomatic coronary disease
6. Patients with clinical evidence of renal disease as per the Investigator's judgement (including renovascular occlusive disease, nephrectomy and/or renal transplant, bilateral renal artery stenosis or unilateral renal artery stenosis in a solitary kidney, or severe renal impairment)
7. Patients with history of angioneurotic oedema
8. Patients with clinically relevant hepatic impairment
9. Patients with sick sinus syndrome, including sino-atrial block
10. Patients with second- or third-degree heart block (without a pacemaker)
11. Participation in any other interventional drug trial or exposure to other investigational agents within 30 days before Screening (Visit 1)
12. Inability to cooperate or any condition that, in the opinion of the Investigator, could increase the patient's risk of participating in the study or confound the outcome of the study
13. Patients with conditions that, in the opinion of the Investigator, would prevent a careful adherence to the protocol
14. Patients with severe hypotension
15. Patients who suffer from shock (including cardiogenic shock)
16. Patients treated with Amlodipine 10 mg and Zofenopril (other than 30 mg)

4.5 Randomization and Blinding

This is a non-randomized, unblinded study.

4.6 Sample Size

A total sample size of 216 patients is required to achieve 90% power at a 5% significance level

assuming a difference in mean DBP from baseline (Visit 2) to 8 weeks (Visit 4) of 4 mmHg and a standard deviation (SD) for this difference of 10 mmHg. The mean change in DBP for the null hypothesis is set equal to 2 mmHg. The alternative hypothesis is that the mean change in DBP is greater than 2 mmHg. To achieve this sample size, a total of 290 patients will be enrolled, allowing for a 25% withdrawal rate.

5 General Considerations

5.1 Timing of Analyses

No interim analysis is planned for this study. The final analysis will be performed after finalization and approval of this Statistical Analysis Plan (SAP) and after database lock.

5.2 Study Variables

5.2.1 Baseline

Patients are instructed to take the study treatment after all visit evaluations have been performed on scheduled visit days. Assessments performed at Visit 2 will be considered Baseline since the first dose combination therapy (ZOF/AML) occurs after the completion of Visit 2 assessments. For assessments performed at Visit 1 and not Visit 2 (e.g., laboratory and ECG assessments), the Visit 1 assessment will be considered Baseline.

5.2.2 First Dose

First dose is defined as the first administration of the extemporaneous combination of ZOF 30 mg and AML 5 mg that occurs on Visit 2 (Baseline). Monotherapies taken prior to Visit 2 should not be considered when defining first dose.

5.2.3 Study Day

Study Day of assessments or events is relative to first study drug dose date and is calculated as:

- (Date of assessment – date of first dose + 1) if date of assessment ≥ date of first dose.
- (Date of assessment – date of first dose) if date of assessment < date of first dose.

5.2.4 Visit Windows

It is expected that all visits should occur according to the protocol schedule. All visit data will be tabulated per the evaluation visit as recorded in the Electronic Case Report Form (eCRF), even if the assessment is outside of the visit window. Early termination visits will be presented in both summary tables and data listings, but unscheduled visits will be presented in the data listings only.

5.3 Analysis Populations

Agreement and authorization of patients included/excluded from each analysis population will be conducted prior to database lock of the study. A data review meeting will be conducted prior to database lock and confirm the patients in each analysis set population. Impact of Covid-19 pandemic on the missed data, missed visits or dropouts will be assessed during this meeting and appropriate decisions on population counts will be taken.

5.3.1 Full Analysis Set (FAS)

The Full Analysis Set (FAS) includes all study participants who sign informed consent.

5.3.2 Safety Population (SAF)

The Safety Population (SAF) is defined as all study participants in the Full Analysis Set who meet all screening criteria, are enrolled, and receive at least one dose of the assigned treatment during the run-in period. This population will be used for safety analyses.

5.3.3 Efficacy Population (EFF)

The Efficacy Population (EFF) is defined as all study participants in the Safety Population who complete the 4-week run-in period and meet continuation criteria at Visit 2 [uncontrolled BP (sitting SBP/DBP > 130/80 mmHg), tolerate treatment, and fall within 80-120% treatment adherence] and have at least one available post baseline primary efficacy assessment (from Visit 3 or 4). This population will be used for efficacy analyses.

5.3.4 Per Protocol Population (PP)

The Per Protocol Population (PP) is defined as all study participants in the Efficacy Population who were dosed according to the protocol (80% - 120% adherence reported for each dosing visit), complete the required study visits (Visits 1, 2, 3, 4), and do not experience any major protocol deviations that may impact the primary efficacy assessment through end of treatment.

Whether to include or exclude the patients from PP set will be finalized in the data review meeting prior to database lock.

5.4 Covariates and Subgroups

Exploratory endpoints 3.1, 3.2, and 3.4 will be analyzed on the following subgroups:

- Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued the same therapies.
- Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

Exploratory endpoint 3.4 will also be analyzed on the following subgroups, such that each subgroup above will be further stratified by the subgroups below:

- Hypertension grade (Grade 1 or 2) reported at Visit 1
  - Reported in the eCRF at Visit 1
- Presence of diabetes and/or hypercholesterolemia at Visit 1
  - Reported as ongoing Medical History event at Visit 1 using MedDRA terms below

Protocol Term	MedDRA Preferred Term
Diabetes	Diabetes mellitus
Hypercholesterolemia	Hypercholesterolemia

5.5 Reporting Conventions

The following conventions will be used across all study summaries and analyses, unless otherwise specified in the corresponding section.

- Summary statistics will consist of sample size (n), mean, standard deviation (SD), median, minimum (min), and maximum (max) values for continuous and some ordinal variables; and sample size (n), frequencies, and percentages (%) for categorical and some ordinal variables.
- Statistical tests and confidence intervals (CI) will be two-sided unless otherwise specified; statistical tests will use an alpha threshold of 0.05 and CIs will use 95% confidence unless otherwise specified.
- Mixed Models for Repeated Measures (MMRM) will be fit using the unstructured covariance matrices. In the event of lack of model convergence, other covariance structures may be used.
- P-values will be calculated to three decimal places. P-values less than 0.001 will be presented as "< 0.001."

Unless otherwise specified, descriptive summary tables will be structured with a column for each monotherapy group (ZOF 30 mg or AML 5 mg) or combined treatment group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and overall (All Patients) and will include the total population size for each group in the header. Conversely, inferential summary tables will use only the All Patients column, unless otherwise specified, to prevent overinflation of the type I error rate.

For descriptive summary tables, patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns within the summary tables, and not within the ZOF/AML 30/5 mg column.

Summary tables will also indicate the number of patients with complete data for each measurement, event, or outcome.

Data listings will be sorted by treatment group, patient, and visit (when applicable).

5.6 Missing Data

5.6.1 Imputation of Blood Pressure Data

Missing blood pressure values that occur after baseline will be imputed for the sensitivity analysis using Last Observation Carried Forward (LOCF). Any missing data for blood pressure at baseline will not be imputed. No other standard imputations of missing efficacy data will be applied.

5.6.2 Imputation of Adverse Event Start Dates

Partial start dates for Adverse Events (AEs) are imputed as detailed below in order to classify each AE as treatment-emergent, as defined in section 8.2.

Start date:

- If start date is completely missing, start date is set to date of first dose.
- If (1) year is present and month and day are missing or (2) year and day are present and month is missing:
    - If year = year of first dose, then set month and day to month and day of first dose.
    - If year < year of first dose, then set month and day to December 31st.
    - If year > year of first dose, then set month and day to January 1st.
- If month and year are present and day is missing:

- If year = year of first dose and
  - If month = month of first dose, then set day to day of first dose date.
  - If month < month of first dose, then set day to last day of month.
  - If month > month of first dose, then set day to 1st day of month.
- If year < year of first dose, then set day to last day of month.
- If year > year of first dose, then set day to 1st day of month.

5.6.3 Imputation of Prior/Concomitant Medication Start and Stop Dates

Partial start and end dates for medications are imputed as detailed below in order to classify each medication as either prior or concomitant, as defined in section 6.5.

Start date:

- If start date is completely missing, start date will be imputed with the informed consent date.
- If year is present and month and day are missing, set month and day to January 1.
- If year and day are present and month is missing, set month and day to January 1.
- If year and month are present and day is missing, set day to the 1st day of month.

Stop date:

- If end date is completely missing, end date will not be imputed and medication will be assumed to be ongoing.
- If year is present and month and day are missing, set month and day to December 31st.
- If year and day are present and month is missing, set month and day to December 31st.
- If year and month are present and day is missing, set day to the last day of month.

5.7 Interim Analyses and Data Monitoring

There will be no interim analyses for this study.

5.8 Multi-Center Studies

Approximately 31 study centers will be used to enroll patients into this study. All sites will be pooled and analyzed collectively, except for the sensitivity analysis for the primary efficacy endpoint which is described in section 7.2.2 of this SAP.

5.9 Multiple Testing

The current study has a single primary efficacy endpoint. The secondary efficacy endpoints are derived from the primary objective and will be used to support the conclusion of the primary efficacy endpoint, provided that the primary efficacy endpoint is met. Thus, adjustments for multiple testing in the secondary efficacy endpoints will not be applied.

6 Summary of Study Data

6.1 Patient Disposition

Patient disposition parameters including the number of patients screened, screen failures, enrolled, completed monotherapy period, completed combined treatment period, completed the study, discontinued the study, and reason for discontinuation will be summarized combined treatment group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and All Patients for the FAS population.

A by-patient data listing of study completion information, entry criteria violations, and the reason for study discontinuation will be presented for the FAS population.

6.2 Protocol Deviations

A list of protocol deviations (PD) will be prepared for the final statistical analysis and protocol deviations will be classified as major or minor by the sponsor in coordination with the study statistician based on their potential impact on the data quality and integrity. Critical deviations will be classified as Major for purposes of defining the PP population. Major protocol deviations will be specified prior to database lock and will include protocol deviations that may impact the primary efficacy endpoint.

All protocol deviations will be discussed and reviewed on a case-by-case basis before the DBL. All PDs authorized by Sponsor will be documented.

Individual PDs will be presented in a by-patient data listing for the FAS population who have at least one deviation. The number and percentage of patients with PDs will be summarized by deviation on the FAS population. Additional Major and Minor PDs may be identified during data review and will be reflected in the Table and Listing as appropriate.

All PDs will be recorded and classified in Clinical Trial Management System (CTMS).

6.3 Demographic and Baseline Variables

Demographic and baseline characteristics including study site, age, sex, race, ethnicity, height (cm), weight (kg), BMI (kg/m2), smoking status (including e-cigarette use), select medical history (hypertension grade 1 or 2, presence/absence of Diabetes, presence/absence of Hypercholesterolemia), and treatment at run-in will be summarized by combined treatment group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and All Patients for the SAF population.

A by-patient data listing of demographic and baseline characteristics will also be presented for the SAF population.

6.4 Medical History

Medical History will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later. Medical history will be presented in a by-patient data listing for the SAF population and will include the System Organ Class (SOC) and Preferred Term (PT) for each medical condition.

6.5 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHO-DD) version Sep 2021 or later. Concomitant procedures will be coded using MedDRA version 24.1 or later.

Prior medication is defined as any medication taken within 30 days prior to the start of the study which has a stop date prior to the date of first dose of monotherapy (ZOF 30 mg or AML 5 mg). Concomitant medication is defined as any medication with a start date on or before the date of *last* dose of study drug and is ongoing or has a stop date on or after date of *first* dose of monotherapy (ZOF 30 mg or AML 5 mg).

Prior and concomitant medications will be summarized separately by Anatomic Therapeutic Class (ATC) Level 1 and Preferred Term by combined treatment group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and All Patients for the SAF population. That is, all patients in the SAF population who took at least one prior/concomitant medication will be summarized together in the All Patients column of the corresponding summary tables. All patients who take ZOF/AML 30/10 mg will be summarized in the ZOF/AML 30/10 mg column, even for medications they took in the monotherapy period or while taking the ZOF/AML 30/5 mg regimen. Lastly, all patients who take ZOF/AML 30/5 mg for the duration of the combined therapy period will be summarized in the ZOF/AML 30/5 mg column, even for medications they took in the monotherapy period.

Patients taking the same medication multiple times will be counted once per medication. Prior and concomitant medications as well as concomitant procedures will be presented in by-patient data listings for the SAF population.

7 Efficacy Analyses

All efficacy analyses will be performed on the Efficacy population (EFF) unless otherwise specified. Monotherapy: visit 2 (week 0) efficacy analysis (number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2) will be performed on the Full Analysis Set (FAS population). Results will be presented as described in section 5.5. In addition to the inferential analyses discussed in the subsections below, descriptive analyses will be performed to summarize the observed and change from baseline values for mean sitting SBP and DBP for all study visits. All blood pressure parameters will also be presented in a by-patient data listing for the safety (SAF) population.

7.1 Efficacy Variable Derivations

7.1.1 Blood Pressure (BP) Goal (Controlled v Uncontrolled)

Multiple endpoints (2.3, 3.3, and 3.4) involve patients meeting the BP goal of sitting BP ≤ 130/80 mmHg at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

A patient will be considered to have met the BP goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg. If a patient meets one of these criteria but not the other, then they will not be considered to have met the BP goal. That is, a patient's BP is considered uncontrolled if their SBP > 130 mmHg OR their DBP > 80 mmHg.

7.2 Primary Efficacy Analyses (Endpoint 1.1)

7.2.1 Primary Analysis

Endpoint 1.1: Change in mean sitting DBP between Visit 2 (Week 0) and Visit 4 (Week 8).

Endpoint 1.1 will be analyzed using a paired t-test with a type I error rate of 0.05 to test the null hypothesis that the mean change in DBP is 0 mmHg against a two-sided alternative.

The observed values for sitting DBP will be summarized at Baseline (Visit 2) and Visit 4. The change from Baseline to Visit 4 values will be assessed using the paired t-test as described above and will present the mean, SD, min, max, critical t-value, degrees of freedom (df), 95% confidence internal (CI) and p-value. If resulting p-value ≤ 0.05, the null hypothesis will be rejected, and we will conclude that the mean sitting DBP at Visit 4 is significantly different from that at Baseline. Conversely, if p-value > 0.05, then we will

fail to reject the null hypothesis and we cannot conclude a significant difference between mean sitting DBP at Baseline and Visit 4.

7.2.2 Sensitivity Analyses

A sensitivity analysis for the primary endpoint (1.1) will be conducted by replicating the primary endpoint analysis under each of the following:

1. Per-protocol population (PP)
2. Imputation of missing data using last-observation-carried-forward (LOCF)
    - As described in section 5.6.1 of this SAP
3. Analysis stratified by study site
    - Approximately 31 sites will be used to enroll patients
    - Sensitivity analysis will be performed on each individual site
4. Analysis stratified by gender
    - Male
    - Female
5. Analysis stratified by age group
    - 18-45 years
    - 46-65 years

7.3 Secondary Efficacy Analyses

The secondary efficacy endpoints are derived from the primary objective and will be used to support the conclusion of the primary efficacy endpoint, provided that the primary efficacy endpoint is met.

All continuous efficacy variables will be summarized for all study visits using descriptive statistics for both actual values and change-from-baseline values. The Efficacy population will be used to analyse the secondary endpoints.

7.3.1 Mean Change (Endpoints 2.1 and 2.2)

Endpoint 2.1: Change in mean sitting SBP between Visit 2 (Week 0) and Visit 4 (Week 8).

Endpoint 2.1 will be analyzed using a paired t-test with a type I error rate of 0.05 to test the null hypothesis that the mean change in SBP is 0 mmHg from Visit 2 to Visit 4 against a two-sided alternative.

Endpoint 2.2: Change in mean sitting DBP and SBP between Visit 3 (Week 4) and Visit 4 (Week 8) in patients uncontrolled at Visit 3 and up titrated to the extemporaneous combination of ZOF/AML 30/10 mg.

Endpoint 2.2 will be analyzed using paired t-test for DBP and SBP with a type I error rate of 0.05 to test the null hypotheses of 0 mmHg mean change from Visit 3 to Visit 4 against a two-sided alternative.

7.3.2 Proportion of Patients (Endpoints 2.3 and 2.4)

Endpoint 2.3: Monotherapy: Number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 2 (Week 0). Combination therapy: number and proportion of patients achieving the BP goal (sitting BP≤130/80 mmHg) at Visit 3 (Week 4) and Visit 4 (Week 8).

Endpoint 2.4: Adherence to the treatments (% of doses taken/doses to be taken) at Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

Endpoints 2.3 and 2.4 will be analyzed using a 95% binomial confidence interval (CI) for each visit.

A patient who has taken at least 80% and no more than 120% of the required study medication since the last visit will be considered as compliant. Treatment adherence will be summarized incrementally rather than cumulatively so that changes in adherence over time can be accurately reflected. That is, a patient can be compliant between Visits 2 and 3, but non-compliant between Visits 3 and 4, or vice versa.

7.4 Exploratory Efficacy Analyses

Each of the exploratory efficacy analyses described in the subsections below will be performed on the following treatment subgroups:

Test Group: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued the same therapies.

Comparison Group: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).

7.4.1 Mean Change (Endpoints 3.1 and 3.2)

Endpoint 3.1: Change in mean sitting SBP and DBP between Visit 1 (Week -4) and Visit 2 (Week 0), Visit 3 (Week 4) and Visit 4 (Week 8).

Endpoint 3.2: Change in mean sitting SBP and DBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4).

Endpoints 3.1 and 3.2 will be analyzed using mixed models for repeated measured (MMRM) to assess the mean change in SBP and DBP. The models will be built as follows:

- Endpoint 3.1
  - *Response* = change from screening BP
  - *Covariates* = treatment subgroup, study visit, treatment subgroup-by-visit interaction, screening BP values
  - *Random effect* = patient
  - *Covariance matrix* = unstructured
    - In the event of lack of model convergence, other covariance structures may be used.
    - If all MMRM fail to converge, this endpoint will be analyzed as described in section 7.4.1.1 below.

- Endpoint 3.2
  - *Response* = change from baseline BP

- *Covariates* = treatment subgroup, study visit, treatment subgroup-by-visit interaction, baseline BP values
- *Random effect* = patient
- *Covariance matrix* = unstructured
  - In the event of lack of model convergence, other covariance structures may be used.
  - If all MMRM fail to converge, this endpoint will be analyzed as described in section 7.4.1.1 below.

Least-squares (LS) means, standard error (SE), and 95% CIs for mean change from screening/baseline for BP will be presented by visit and treatment subgroup. The LS-means difference, SE, 95% CI, and two-sided p-value for the difference between treatment subgroups in mean change from screening/baseline for sitting SBP and DBP will be presented where a p-value of ≤ 0.05 indicates a significant difference between groups.

7.4.1.1 Model Nonconvergence

If the above MMRMs fail to converge, endpoints 3.1 and 3.2 will be analyzed using independent sample t-tests to compare the mean change in BP in the test group to the comparison group (test/comparison groups defined in section 7.4).

7.4.2 Proportion of Patients (Endpoints 3.3 and 3.4)

Endpoint 3.3: Monotherapy: number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0). Combination therapy: number and proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 3 (Week 4).

Endpoint 3.4: Monotherapy: number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 2 (Week 0). Combination therapy: number and proportion of patients divided in subgroup by the hypertension grade, the presence of diabetes and/or of hypercholesterolemia achieving the BP goal (sitting BP ≤130/80 mmHg) at Visit 3 (Week 4) and Visit 4 (Week 8).

Endpoints 3.3 and 3.4 will be analyzed using a logistic MMRM to assess the proportion of patients achieving the BP goal (sitting BP ≤130/80 mmHg). The models will be built as follows:

- Endpoint 3.3
  - *Response* = achieving BP goal (sitting BP ≤130/80 mmHg)
  - *Covariates* = treatment subgroup, study visit, treatment subgroup-by-visit interaction, baseline BP values
  - *Random effect* = patient
  - *Covariance matrix* = unstructured
    - In the event of lack of model convergence, other covariance structures may be used.
    - If all logistic MMRM fail to converge, this endpoint will be analyzed as described in section 7.4.2.1 below.

- Endpoint 3.4 by hypertension grade
  - *Response* = achieving BP goal (sitting BP ≤130/80 mmHg)
  - *Covariates* = treatment subgroup, study visit, treatment subgroup-by-visit interaction, baseline BP values
  - *Random effect* = patient
  - *Covariance matrix* = unstructured
    - In the event of lack of model convergence, other covariance structures may be used.
    - If all logistic MMRM fail to converge, this endpoint will be analyzed as described in section 7.4.2.1 below.
  - *Stratification factor* = Baseline hypertension grade

- Endpoint 3.4 by presence of diabetes and/or of hypercholesterolemia
  - *Response* = achieving BP goal (sitting BP ≤130/80 mmHg)
  - *Covariates* = treatment subgroup, study visit, treatment subgroup-by-visit interaction, baseline BP values
  - *Random effect* = patient
  - *Covariance matrix* = unstructured
    - In the event of lack of model convergence, other covariance structures may be used.
    - If all logistic MMRM fail to converge, this endpoint will be analyzed as described in section 7.4.2.1 below.
  - *Stratification factor* = presence of diabetes and/or of hypercholesterolemia at baseline

The number (n), proportion (%), and 95% CI of the proportion of patients achieving controlled BP will be presented by visit and treatment subgroup. The odds ratio (OR), 95% CI of the OR, and two-sided p-value for the difference between treatment subgroups in proportion of patients achieving controlled BP will be presented where a p-value of ≤ 0.05 indicates a significant difference between groups.

7.4.2.1 Model Nonconvergence

If the above logistic MMRMs fail to converge, endpoints 3.3 and 3.4 will be analyzed using a 95% binomial confidence interval (CI) and Odds Ratio (OR) for each visit to assess the proportion of patients, by subgroup, who achieve the BP goal. Subgroups will include those described in section 7.4, as well as subgroups for hypertension grade and the presence of diabetes and/or hypercholesterolemia.

8 Safety Analyses (Endpoint 2.5)

Endpoint 2.5: Safety and tolerability of the monotherapies (ZOF 30 mg and AML 5 mg) after 4 weeks of therapy and of the extemporaneous combination (ZOF 30 mg and AML 5 mg or AML 10 mg) after eight weeks of treatment.

The variables for endpoint 2.5 are laboratory tests, physical examination, vital signs, 12-lead ECG, and incidence of AEs/SAEs, each of which are discussed in the subsections below.

Safety analyses will be performed on the SAF population. Results will be presented as described in section 5.5 unless otherwise specified.

8.1 Study Drug Accountability, Exposure, and Adherence

8.1.1 Study Medications

Study Medication	Dose	Frequency	Box Details
Zofenopril calcium (ZOF)	30 mg	Once daily	42 tablets (3 blisters of 14 tablets each)
Amlodipine (AML)	5 mg	Once daily	42 tablets (3 blisters of 14 tablets each)
Amlodipine (AML)	10 mg	Once daily	42 tablets (3 blisters of 14 tablets each)

8.1.2 Treatment Exposure by Visit

At Visit 1 (Week -4), patients on current treatment with AML 5 mg or approved CCBs (see section 4.2 for list of approved CCBs) are provided with 1 box of AML 5 mg for the 4-week run-in period. Patients on current treatment with ZOF 30 mg or other ACE-i are provided with 1 box of ZOF 30 mg for the 4-week run-in period.

At Visit 2 (Week 0), patients with uncontrolled BP (> 130/80 mmHg) will be provided with 1 box of ZOF 30 and 1 box of AML 5 mg while the following patients will be withdrawn from the study:

- Controlled BP (≤ 130/80 mmHg)
- Grade 3 Hypertension (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg)
- Does not tolerate the treatment
- Treatment adherence below 80% or above 120%

At Visit 3 (Week 4), patients with controlled BP (≤ 130/80 mmHg) will continue with ZOF 30 and AML 5 mg (receiving 1 box of each), patients with uncontrolled BP (> 130/80 mmHg) will be up-titrated to ZOF 30 and AML 10 mg (receiving 1 box of each), and the following patients will be withdrawn from the study:

- Grade 3 Hypertension (SBP ≥ 180 mmHg or DBP ≥ 110 mmHg)
- Does not tolerate the treatment
- Treatment adherence below 80% or above 120%

At Visit 4 (Week 8), the anti-hypertensive effect of the extemporaneous combination (ZOF/AML 30/5 mg and ZOF/AML 30/10 mg) will be evaluated.

8.1.3 Drug Accountability

The number of tablets dispensed and returned for each study medication at each visit is recorded in the eCRF and are expected to occur in the amounts detailed below.

Visit 1

- Dispensation:
  - 42 tablets of ZOF 30 mg, or
  - 42 tablets of AML 5 mg
- Return:
  - Not applicable

Visit 2

- Dispensation:
  - 42 tablets of ZOF 30 mg and 42 tablets of AML 5 mg
- Return:

- 14±2 tablets of ZOF 30 mg, or
- 14±2 tablets of AML 5mg

Visit 3

- Dispensation:
  - 42 tablets of ZOF 30 mg and 42 tablets of AML 5mg, or
  - 42 tablets of ZOF 30 mg and 42 tablets of AML 10 mg
- Return:
  - 14±2 tablets of ZOF 30 mg and 14±2 tablets of AML 5 mg

Visit 4

- Dispensation:
  - Not applicable
- Return:
  - 14±2 tablets of ZOF 30 mg and 14±2 tablets of AML 5mg, or
  - 14±2 tablets of ZOF 30 mg and 14±2 tablets of AML 10 mg

The average amount of study medication dispensed and returned will be summarized by medication type and study visit for the SAF Population. All study drug accountability and exposure details, including modified, missed, and interrupted doses, will also presented in by-patient data listings for the SAF population.

8.1.4 Treatment Adherence

Investigators should instruct the patient to take the study drug at the same time every day, in the morning. On the days of the patient's visits, the investigator should instruct the patient to not take the study drug at home.

Treatment adherence (eCRF and derived) will be summarized by medication type and study visit for the SAF Population. Adherence details will also be presented in a by-patient data listing for the SAF Population.

8.1.4.1 eCRF-Reported Adherence

Adherence to treatment will be measured through treatment compliance which is 100*(actual doses taken/planned dose) and will be reported in the eCRF at each visit. A patient who has taken at least 80% and no more than 120% of the required study medication intake since the last visit will be considered as compliant.

8.1.4.2 Derived Adherence

To ensure accuracy of adherence reported in the eCRF, adherence will also be derived directly for each patient at Visits 2, 3, and 4 as outlined below.

Treatment adherence = 100*(actual dose/planned dose)

Actual dose = tablets dispensed at previous visit – tablets returned at current visit.

- If a subject fails to return IP, then we assume that all IP was used and return amount will be imputed as 0 tablets. This errs on the side of safety, ensuring that subject data is included in the safety analyses and that AEs are classified as treatment-emergent if they occur after dispensation of IP.

Planned dose is 1 dose per day, for the number of days between:

- V1 to V2-1 (monotherapy period – approx. 28 days)
  - 1 dose = 1 tablet
- V2 to V3-1 (combined period 30/5 – approx. 28 days)
  - 1 dose = 1 tablet of each assigned therapy (2 tablets total per dose)
- V3 to V4-1 (combined period 30/5 or 30/10 – approx. 28 days)
  - 1 dose = 1 tablet of each assigned therapy (2 tablets total per dose)

For monotherapy period, adherence will be derived for each individual medication.

For combined therapy periods, adherence will be derived for each individual medication and then those individual adherence values will be averaged to get an overall adherence %.

Example 1:
If a patient has 28 days between V1 to V2-1, and takes 29 ZOF, then adherence is

- ZOF = 100*(29/28) = 103.57

Example 2:
If patient has 34 days between V3 to V4-1 and takes 34 ZOF but only 30 AML, then adherence is

- ZOF = 100*(34/34) = 100
- AML = 100*(30/34) = 88.24
- Total = (100+88.24) / 2 = 94.12

Example 3:
If patient has 14 days between V2 to V3-1 and takes 10 ZOF and 16 AML, then adherence is

- ZOF = 100*(10/14) = 71.43
- AML = 100*(16/14) = 114.29
- Total = (71.43+114.29) / 2 = 92.86

8.2 Adverse Events, Adverse Drug Reactions, and Deaths

Adverse Events (AEs) are any untoward medical occurrence in a clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Treatment Emergent AEs (TEAEs) are defined as AEs that occur only once treatment has started (after the first dose of monotherapy of ZOF or AML). Thus, all AEs that occur in both the monotherapy and combined therapy periods will be considered treatment-emergent.

Adverse Drug Reactions (ADRs) are defined as AEs that have a relationship of “certain,” “probable,” “possible,” or “unassessable.”

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or later.

The following tabulations will be produced for the monotherapy period and the combination therapy periods for the SAF population:

- Monotherapy Period (Day of Visit 1 through day before Day of Visit 2)
  - All treatment-emergent AEs (TEAEs)

    - Severe TEAEs
    - Adverse Drug Reactions (ADRs)
    - TEAEs leading to study discontinuation
    - Serious TEAEs (TESAEs)
    - Serious ADRs
    - TESAEs with outcome of death
- Combination Therapy Period (Day of Visit 2 through Day of Visit 4)
    - All treatment-emergent AEs (TEAEs)
    - Severe TEAEs
    - Adverse Drug Reactions (ADRs)
    - TEAEs leading to study discontinuation
    - Serious TEAEs (TESAEs)
    - Serious ADRs
    - TESAEs with outcome of death

Key guidelines for counting incidence proportions of AEs/TEAEs/ADRs (collectively referred to as AEs for the remainder of this section) are as follows:

- When a patient has the same AE reported multiple times during an analysis period based on MedDRA terminology (SOC or PT), the patient will only be counted once within a level of MedDRA in an AE incidence table.
- When assessing investigator reported relationship to study drug of the AEs, if an AE reported multiple times changes in causal relationship during an analysis period for a patient, the event with highest relatedness will be presented. Related AEs (i.e., ADRs) will include those reported as “certain,” “probable,” “possible,” or “unassessable” by the investigator.
- When summarizing severity of the AEs (mild, moderate, severe), if there are multiple AEs of the same preferred term but different severity during an analysis period for a patient, the AE with the maximum severity will be reported. If the AE term (SOC and PT) is reported more than once, one of them with missing severity, and at least another with non-missing severity, the maximum severity will be chosen from the non-missing severity and the missing severity can be ignored. If all are of missing severity, then the AE severity will be summarized with an additional “Missing” category. In summary of severe AEs, missing severity will be included in severe category following the conservative approach.

All AE tabulations for the monotherapy period will present the incidences separately for the monotherapy groups (ZOF 30 mg or AML 5 mg) and All Patients for the SAF population. That is, all patients who experienced at least one AE in the monotherapy period will be summarized together in the All Patients column of the corresponding summary tables. All patients who take ZOF 30 mg will be summarized in the ZOF 30 mg column and all patients who take AML 5 mg will be summarized in the AML 5 mg column.

All AE tabulations for the combined therapy period will present the incidences separately for the combined treatment groups (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and All Patients for the SAF population. That is, all patients who experienced at least one AE in the combined therapy period will be summarized together in the All Patients column of the corresponding summary tables. All patients who take ZOF/AML 30/10 mg will be summarized in the ZOF/AML 30/10 mg column, even for AEs that occurred while taking the ZOF/AML 30/5 regimen. Lastly, all patients who take ZOF/AML 30/5 mg for the duration of the combined therapy period will be summarized in the ZOF/AML 5 mg column.

In summaries by SOC and PT (for both monotherapy and combined therapy periods), AEs will be sorted by descending frequency for SOC and PT in the All Patients column. All AEs will also be presented in by-patient data listings for Adverse Events for the SAF population.

8.3 Clinical Laboratory Evaluations

For laboratory safety continuous variables, values recorded as "<X" or "≤X" or ">Y" or "≥Y" will be imputed by "X" and "Y" respectively for descriptive statistics. This will be documented in a footnote in all output where such a replacement was performed. Continuous clinical laboratory observed values and change from Baseline (Visit 1) to Visit 4 will be summarized by combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and overall for the SAF population.

Each laboratory result will be classified as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS) at each visit. Shift tables from Baseline (Visit 1) to Visit 4 will be provided for each laboratory parameter, summarized by combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and overall for the SAF population. If a patient has a missing lab parameter value at Visit 1 or Visit 4, that patient will be excluded from the shift analysis for that lab parameter but will be included in the corresponding by-patient data listing.

All laboratory parameters will also be presented in by-patient data listings for the SAF population.

Test	Visit	Laboratory Parameters to be Analyzed
Haematology	Screening (Visit 1) and Visit 4	Red blood cell White blood cell Haemoglobin Haematocrit Platelets Neutrophils Lymphocytes Monocytes Eosinophils Basophils Neutrophils absolute Lymphocytes absolute Monocytes absolute Eosinophils absolute Basophils absolute
Serum Chemistry	Screening (Visit 1) and Visit 4	ALT Albumin Alkaline phosphatase AST Direct bilirubin Total bilirubin Total protein Creatinine Blood urea nitrogen Creatine kinase GGT Triglycerides Cholesterol High- and low-density lipoprotein Chloride eGFR Blood glucose Potassium Uric acid

8.4 Vital Signs

Vital signs are collected at each study visit and include the following parameters: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Heart Rate (HR), and Temperature (temp). Vital sign parameters will be analyzed for the SAF population as follows:

Monotherapy analysis: observed values and change from Screening (Visit 1) to Baseline (Visit 2) will be summarized for each monotherapy group (ZOF 30 mg and AML 5 mg) and for All Patients.

Combined therapy analysis: observed values and change from Baseline (Visit 2) to scheduled post-baseline visits (Visits 3 and 4) will be summarized for each combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and for All Patients.

All vital sign parameters will also be presented in a by-patient data listing for the SAF population.

8.5 Physical Examination

Physical examination results for each body system will be classified as Normal or Abnormal (CS or NCS) at each visit and will be analyzed as follows:

Monotherapy analysis: shift from Screening (Visit 1) to Baseline (Visit 2) will be summarized (count and percentage) for each monotherapy group (ZOF 30 mg and AML 5 mg) and for All Patients.

Combined therapy analysis: shift from Baseline (Visit 2) to scheduled post-baseline visits (Visits 3 and 4) will be summarized (count and percentage) for each combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and for All Patients.

All physical examination details will also be presented in a by-patient data listing for the SAF population.

8.6 Electrocardiogram (ECG)

Electrocardiograms (ECGs) are performed in triplicate at Screening (Visit 1) and Visit 4 and include the following parameters: Ventricular Rate (VR), PR Interval, RR Interval, QRS Interval, QT Interval, QTcF, QTcB, Rhythm, and Interpretation.

8.6.1 ECG Variable Derivations

For continuous ECG parameters, the mean of all 3 measurements will be presented in the summary tables. For categorical ECG parameters, the most frequently occurring response across all 3 measurements will be presented in the summary tables. If the Interpretation results in a unique response at each of the 3 measurements, then the most severe (Abnormal, Clinically Significant) will be presented in the summary tables.

8.6.2 ECG Variable Analyses

Continuous ECG observed values and change from Baseline (Visit 1) to Visit 4, as well as the number and % of patients in each Rhythm category (Sinusal or Other), will be summarized by combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and overall for the SAF population.

ECG Interpretations will be classified as Normal, Abnormal Not Clinically Significant (NCS), or Abnormal Clinically Significant (CS) at each visit. Shift tables from Baseline (Visit 1) to Visit 4 will be provided the EDC Interpretations, summarized by combined therapy group (ZOF/AML 30/5 mg or ZOF/AML 30/10 mg) and overall for the SAF population. If a patient has a missing ECG Interpretation at Visit 1 or Visit 4, that patient will be excluded from the shift analysis but will be included in the corresponding by-patient data listing.

All ECG parameters, including individual results from all 3 measurements at each visit, as well as the final result used in the summary tables, will be presented in a by-patient data listing for the SAF population.

8.7 Pregnancies

A urine pregnancy test will be performed in all females of childbearing potential at each study visit. Any pregnancy resulting in an abnormal outcome will be reported as an SAE in the eCRF. All pregnancy test details, including reason not performed, will be presented in a by-patient data listing for the SAF population.

9 Technical Details

All analyses described in this SAP will be generated using SAS version 9.4 or higher, unless otherwise specified and includes the following packages: Base SAS, SAS/STAT, SAS/GRAPH, SAS/Secure 168-bit, SAS/Secure Windows, SAS Enterprise Guide, SAS/ACCESS Interface to PC Files, SAS Workspace Server for Local Access, and High Performance Suite.

10 Summary of Changes to the Protocol

10.1 Analysis Populations

The Full Analysis Set (FAS) population was added to the SAP for its use to generate tables and listings related to enrollment and disposition.

The definition of the Efficacy Population (EFF) was slightly modified to include the enrollment continuation requirements at Visit 2 (uncontrolled BP, tolerate treatment, and 80-120% treatment adherence).

10.2 Exploratory Efficacy Analyses

Although not explicitly stated in the protocol, exploratory efficacy endpoint 3.2 [Change in mean sitting SBP and DBP for uncontrolled patients at Visit 3 (Week 4), between Visit 2 (Week 0) and Visit 3 (Week 4)] will be performed on the treatment subgroups described in section 7.4.

11 Listing of Tables, Listings, and Figures

Please reference document “MEIN-20-ZoAm-Hyp-001 TLF Shells v2.0 16May2022.pdf” for the complete list of all tables, listings, and figures (TLFs) as well as corresponding mock shells. Minor changes made to the layout or formatting of the TLFs after SAP finalization will not necessitate a modification to the SAP.

12 References

1. Mensah GA, Bakris G. Treatment and control of high blood pressure in adults. Cardiol Clin. 2010;28:609–22

2. Borghi C, Omboni S, Reggiardo G, et al. Efficacy of zofenopril in combination with amlodipine in patients with acute myocardial infarction: a pooled individual patient data analysis of four randomized, double-blind, controlled, prospective studies. Curr Med Res Opin. 2018;34(10):1869-1874.

Mock TLF Shells

Interventional clinical trial to assess efficacy and safety of the extemporaneous combination of zofenopril calcium and amlodipine in grade 1-2 hypertensive patients versus each monotherapy – (MASOLINO Study)

Protocol Number	:	MEIN/20/ZoAm-Hyp/001
Protocol Version	:	1.0
Protocol Date	:	23 April 2021
Plan Version	:	2.0
Plan Date	:	23 May 2022
Study Drug	:	Extemporaneous combination of Zofenopril (ZOF) 30 mg with Amlodipine (AML) 5 mg or Amlodipine (AML) 10 mg
Indication	:	Grade 1-2 Hypertension

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2 Mock TLF Shells

Tables

2.1.1 Demographic Data

Table 14.1.1
Patient Enrollment and Disposition
(Full Analysis Set)

Disposition [1,2,3]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Total Number of Patients				
Screened	n			xx
Screen Failures	n (%)			xx (xx.x)
Enrolled	n	xx	xx	xx
Completed Monotherapy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed Combined Therapy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Completed the Study	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Discontinued the Study	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Reason for Study Discontinuation				
Excluded at Visit 2	n (%)	xx (xx.x)		xx (xx.x)
Excluded at Visit 3	n (%)	xx (xx.x)		xx (xx.x)
Meets Exclusion Criteria	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Adverse Event	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Non-Compliance	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Withdrawal of Consent	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Failure to Report to Study Visits	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lost to Follow-up	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Investigator Decision	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Lack of Efficacy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Pregnancy	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Protocol Deviation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Study Terminated by Sponsor	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Abnormal Renal Function or Liver Enzyme	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
COVID-19	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] Percentages for Screen Failures is based on the number Screened. Percentages for all subsequent percentages are based on the number Enrolled.
[2] Excluded at Visit 2 = Patients with controlled BP, patients who do not tolerate the treatment, or patients < 80% or > 120% treatment adherence.
[3] Excluded at Visit 3 = Patients who do not tolerate the extemporaneous combination of treatment, or patients < 80% or > 120% treatment adherence.

Source: Listing 16.2.1
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column.

Table 14.1.2
Analysis Populations and Exclusions
(Full Analysis Set)

Analysis Populations [7]	Statistic	All Patients (N=xx)
Included in Safety (SAF) [1,4]	n (%)	xx (xx.x)
Excluded from Safety (SAF)	n (%)	xx (xx.x)
Did Not Meet all Screening Criteria	n (%)	xx (xx.x)
Did Not Receive At Least One Dose During Run-In	n (%)	xx (xx.x)
Included in Efficacy (EFF) [2,5]	n (%)	xx (xx.x)
Excluded from Efficacy (EFF)	n (%)	xx (xx.x)
Did Not Complete Run-In Period	n (%)	xx (xx.x)
Did Not Meet Continuation Criteria at Visit 2	n (%)	xx (xx.x)
Did Not Complete Visit 3 or 4	n (%)	xx (xx.x)
Included in Per Protocol (PP) [3,6]	n (%)	xx (xx.x)
Excluded from Per Protocol (PP)	n (%)	xx (xx.x)
Not Dosed According to Protocol	n (%)	xx (xx.x)
Did Not Complete Required Study Visits	n (%)	xx (xx.x)
Major Protocol Deviation That May Impact the Primary Efficacy Assessment	n (%)	xx (xx.x)

[1] Percentage based on number of All Patients.
[2] Percentage based on number of subjects included in SAF.
[3] Percentage based on number of subjects included in EFF.
[4] Safety Population (SAF): All study participants who sign informed consent, meet all screening criteria, are enrolled, and receive at least one dose of the assigned treatment during the run-in period.
[5] Efficacy Population (EFF): All study participants in the Safety Population who complete the 4-week run-in period and meet continuation criteria at Visit 2 [uncontrolled BP (sitting SBP/DBP > 130/80 mmHg), tolerate treatment, and fall within 80-120% treatment adherence] and have at least one available post baseline primary efficacy assessment (from Visit 3 or 4).
[6] Per Protocol Population (PP): All study participants in the Efficacy Population who were dosed according to the protocol (80% - 120% adherence reported for each dosing visit), complete the required study visits (Visits 1, 2, 3, 4), and do not experience any major protocol deviations that may impact the primary efficacy assessment through end of treatment.
[7] If subjects are excluded for more than one reason, they will only be counted for the first listed reason.
Source: Listing 16.2.3
Program Name: XXXX.SAS Date: DDMMMYYYY

Table 14.1.3
Summary of Demographic and Baseline Characteristics
(Safety Population)

Parameter	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Age (Years)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Sex				
Male	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Female	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Unknown/Undifferentiated	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ethnicity				
Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Hispanic or Latino	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Ashkenazi Jew	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Sephardic Jew	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Reported/Unknown	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Race				
American Indian or Alaska Native	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Asian	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Black	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Native Hawaiian or Other Pacific Islander	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
White	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Not Applicable	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Height (cm)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Weight (kg)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

BMI (kg/m2)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Smoking Status				
Never Tobacco Smoker	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Former Tobacco Smoker	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Daily	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Occasional	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Current Tobacco Smoker	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Daily	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Occasional	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Undisclosed	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
e-Cigarettes	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Medical History	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypertension Grade 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypertension Grade 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Diabetes mellitus	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Hypercholesterolemia				
Treatment at Run-In	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Zofenopril 30 mg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Amlodipine 5 mg	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other ACE-i	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other CCB				
Study Site	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
201	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
202	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
….. (repeat for all sites)				

Source: Listings 16.2.4.1, 16.2.4.2
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column.

- In the medical history section, the first two rows (hypertension grade) will come from raw EDC data RUNDIS.RHYPEGRD and the second two rows (diabetes and hypercholesterolemia) will come from raw EDC data MH as per usual.

Table 14.1.4
Summary of Protocol Deviations
(Full Analysis Set)

Disposition [1,2]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Subjects with at least one PD	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Critical PD	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Major PD	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Major PD that may impact the primary efficacy assessment	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Subjects with at least one Minor PD	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
PD Category 2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Etc.	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] PD: Protocol Deviation.
[2] Critical deviations will be classified as Major for purposes of defining the PP Population but are displayed here as Critical.
Source: Listing 16.2.2
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column.

2.1.2 Efficacy

Table 14.2.1.1
Summary and Change from Baseline for Mean Sitting Diastolic Blood Pressure (DBP) by Visit
(Efficacy Population)

Visit [1]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Screening (Visit 1)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Baseline (Visit 2)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Visit 3	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Visit 3 CFB	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Visit 4	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx
Visit 4 CFB	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Min, Max	xx, xx	xx, xx	xx, xx

[1] CFB = Change from Baseline.
Source: Listing 16.2.6
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column. Same for tables in the list below.
- Repeat for the following tables:
    - 14.2.1.2 – Summary of Change from Baseline for Mean Sitting Systolic Blood Pressure (SBP) by Visit – Efficacy Population
    - 14.2.1.3 – Summary of Change from Baseline for Mean Sitting Diastolic Blood Pressure (DBP) by Visit – Per Protocol Population
    - 14.2.1.4 – Summary of Change from Baseline for Mean Sitting Systolic Blood Pressure (SBP) by Visit – Per Protocol Population

Table 14.2.2.1
Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4
(Efficacy Population)

Visit [1]	Statistic [2,3]	All Patients (N=xx)
Baseline (Visit 2)	n	xx
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
Visit 4	n	xx
	Mean (SD)	xx.x (xx.xx)
	Median	xx.x
	Min, Max	xx, xx
Visit 4 CFB	n	xx
	Mean (SD)	xx.x (xx.xx)
	Min, Max	xx, xx
	t-value (df)	x.xx (x)
	95% CI	(xx.x, xx.x)
	p-value	x.xxx

[1] CFB = Change from Baseline.
[2] SD = Standard Deviation. CI = Confidence Interval. df = degrees of freedom.
[3] Visit 4 CFB results are generated using paired t-test with alpha = 0.05 to evaluate if the mean change in diastolic blood pressure (DBP) from Baseline (Visit 2) to Visit 4 is significantly different from 0.
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Repeat for the following tables:
  - 14.2.2.2 – Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 – Per Protocol Population
    - Change column header from “EFF” to “PP”
  - 14.2.2.3 – Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 Using LOCF – Efficacy Population
    - Add footnote to statistic column “[4] Missing blood pressure (BP) values that occur after Baseline (Visit 2) are imputed using Last Observation Carried Forward (LOCF).”
  - 14.2.2.4 – Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 by Study Site – Efficacy Population
    - Use of SAS #byar/#byval will produce this table separately for each study site within the same output file.
  - 14.2.3.1 – Summary of Change in Mean Sitting Systolic Blood Pressure (SBP) from Visit 2 to Visit 4 – Efficacy Population

Table 14.2.2.5
Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 by Gender
(Efficacy Population)

		All Patients (N=xx)	
Visit [1]	Statistic [2,3]	Male	Female
Baseline (Visit 2)	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Visit 4	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Visit 4 CFB	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Min, Max	xx, xx	xx, xx
	t-value (df)	x.xx (x)	x.xx (x)
	95% CI	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx

[1] CFB = Change from Baseline.
[2] SD = Standard Deviation. CI = Confidence Interval. df = degrees of freedom.
[3] Visit 4 CFB results are generated using paired t-test with alpha = 0.05 to evaluate if the mean change in systolic (SBP; endpoint 2.1) or diastolic blood pressure (DBP; endpoint 1.1) from Baseline (Visit 2) to Visit 4 is significantly different from 0.
Source: Listings 16.2.4.1, 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Repeat for the following tables:
  - 14.2.2.6 – Summary of Change in Mean Sitting Diastolic Blood Pressure (DBP) from Visit 2 to Visit 4 by Age Group – Efficacy Population
    - Change column headers from “Male” and “Female” to “18-45 Years” and “46-65 Years”, respectively

Table 14.2.3.2
Summary of Change in Mean Sitting Systolic (SBP) and Diastolic Blood Pressure (DBP) from Visit 3 to Visit 4 for Patients Uncontrolled and Up-Titrated at Visit 3 (Efficacy Population)

		All Patients (N=xx)	
Visit [1,2]	Statistic [3,4]	SBP	DBP
Visit 3	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Visit 4	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx, xx	xx, xx
Visit 4 CFV3	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Min, Max	xx, xx	xx, xx
	t-value (df)	x.xx (x)	x.xx (x)
	95% CI	(xx.x, xx.x)	(xx.x, xx.x)
	p-value	x.xxx	x.xxx

[1] CFV3 = Change from Visit 3.
[2] Patients uncontrolled at Visit 3 are those who have SBP/DBP > 130/80 mmHg. These patients are up-titrated from ZOF/AML 30/5 mg to ZOF/AML 30/10 mg.
[3] SD = Standard Deviation. CI = Confidence Interval. df = degrees of freedom.
[4] Visit 4 CFV3 results are generated using paired t-test with alpha = 0.05 to evaluate if the mean change in systolic (SBP) or diastolic blood pressure (DBP) from Visit 3 to Visit 4 is significantly different from 0 for patients who were uncontrolled at Visit 3 and up-titrated (endpoint 2.2).
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Table 14.2.3.3
Proportion of Patients Achieving Sitting BP Goal (≤ 130/80 mmHg) at Visits 2, 3, and 4
(Full Analysis Set and Efficacy Population)

Therapy Type	Visit	Statistic [1,2,3]	All Patients (N=xx)
Monotherapy	Visit 2	n/N (Proportion %)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)
Combined Therapy	Visit 3	n/N (Proportion %)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)
	Visit 4	n/N (Proportion %)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)

Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
[1] A patient is considered to have met the Blood Pressure (BP) goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg.
[2] n = number of patients who have achieved sitting BP goal at that visit. N = number of patients with data at that visit, regardless of BP goal status.
[3] CI = Confidence Interval.
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Table 14.2.3.4
Proportion of Patients with 80% - 120% Adherence to Treatment at Visits 2, 3, and 4
(Full Analysis Set and Efficacy Population)

			All Patients (N=xx)	
Therapy Type	Visit	Statistic [1,2]	eCRF-Reported Adherence	Derived Adherence
Monotherapy	Visit 2	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)	(xx.x, xx.x)
Combined Therapy	Visit 3	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)	(xx.x, xx.x)
	Visit 4	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
		95% CI	(xx.x, xx.x)	(xx.x, xx.x)

Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
[1] n = number of patients who met 80% - 120% adherence to treatment at that visit. N = number of patients with data at that visit, regardless of treatment adherence status.
[2] CI = Confidence Interval.
Source: Listing 16.2.5.1
Program Name: XXXX.SAS

Date: DDMMMYYYY

Table 14.2.4.1
Difference in Mean Change for Sitting Systolic (SBP) and Diastolic Blood Pressure (DBP) From Visit 1 to Visits 2, 3, and 4
(Full Analysis Set and Efficacy Population)

				SBP		DBP	
Therapy Type	Visit [1]	Statistic Type [2,3]	Statistic	ZOF/AML [4] (N=xx)	ACE-i/CCB [5] (N=xx)	ZOF/AML [4] (N=xx)	ACE-i/CCB [5] (N=xx)
Monotherapy	Visit 2 CFS	MMRM	n	xx	xx	xx	xx
			LSM (SE)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	LSM Difference (SE)	xx		xx	
			95% CI	xx.x (xx.xxx)		xx.x (xx.xxx)	
			p-value	x.xxx		x.xxx	
Combined Therapy	Visit 3 CFB	MMRM	n	xx	xx	xx	xx
			LSM (SE)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	LSM Difference (SE)	xx		xx	
			95% CI	xx.x (xx.xxx)		xx.x (xx.xxx)	
			p-value	x.xxx		x.xxx	
	Visit 4 CFB	MMRM	n	xx	xx	xx	xx
			LSM (SE)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	LSM Difference (SE)	xx		xx	
			95% CI	xx.x (xx.xxx)		xx.x (xx.xxx)	
			p-value	x.xxx		x.xxx	

Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
[1] CFS = Change from Screening (Visit 1). CFB = Change from Baseline (Visit 2).
[2] MMRM = Mixed Model Repeated Measures.
[3] A separate model is used for the monotherapy and combined therapy analyses. The models use an unstructured covariance matrix; change from screening (monotherapy) or baseline (combined therapy) for SBP/DBP as the response variable; visit, treatment subgroup, visit*treatment subgroup interaction, and screening (monotherapy) or baseline (combined therapy) SBP/DBP as covariates; and a random effect for patient.
[4] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies.
[5] ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-i or CCBs at Visit 1 (Week -4).
Source: Listing 16.2.6
Program Name: XXXX.SAS
Date: DDMMMYYYY

Programming Note:

- If a different covariance structure is used in case of model nonconvergence, footnote 3 should be updated accordingly.

Table 14.2.4.2
Difference in Mean Change for Sitting Systolic (SBP) and Diastolic Blood Pressure (DBP) from Visit 2 to Visit 3 for Patients with Uncontrolled BP at Visit 3
(Efficacy Population)

			SBP		DBP	
Visit [1]	Statistic Type [2,3]	Statistic	ZOF/AML [4] (N=xx)	ACE-i/CCB [5] (N=xx)	ZOF/AML [4] (N=xx)	ACE-i/CCB [5] (N=xx)
Visit 3 CFB	MMRM	n	xx	xx	xx	xx
		LSM (SE)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)	xx.x (xx.xxx)
		95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
	v. ACE-i/CCB	LSM Difference (SE)	xx		xx	
		95% CI	xx.x (xx.xxx)		xx.x (xx.xxx)	
		p-value	x.xxx		x.xxx	

1] CFB = Change from Baseline (Visit 2).
[2] MMRM = Mixed Model Repeated Measures.
[3] Model uses an unstructured covariance matrix; change from baseline for SBP/DBP as the response variable; visit, treatment subgroup, visit*treatment subgroup interaction, and baseline SBP/DBP as covariates; and a random effect for patient.
[4] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies.
[5] ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-I or CCBs at Visit 1 (Week -4).
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- If a different covariance structure is used in case of model nonconvergence, footnote 3 should be updated accordingly.

Table 14.2.4.3
Proportion of Patients Achieving Sitting BP Goal (≤ 130/80 mmHg) at Visits 2, 3, and 4 by Treatment Subgroup
(Full Analysis Set and Efficacy Population)

Therapy Type	Visit	Statistic Type [1,2]	Statistic [3,4]	ZOF/AML [5] (N=xx)	ACE-i/CCB [6] (N=xx)
Monotherapy	Visit 2	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	Odds Ratio	x.xx	
			95% CI	(x.xx, x.xx)	
			p-value	x.xxx	
Combined Therapy	Visit 3	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	Odds Ratio	x.xx	
			95% CI	(x.xx, x.xx)	
			p-value	x.xxx	
	Visit 4	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	Odds Ratio	x.xx	
			95% CI	(x.xx, x.xx)	
			p-value	x.xxx	

Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
[1] Logistic MMRM = Logistic Mixed Model Repeated Measures.
[2] A separate model is used for the monotherapy and combined therapy analyses. Models use an unstructured covariance matrix; achieving sitting BP goal as the response variable; visit, treatment subgroup, visit*treatment subgroup interaction, and screening (monotherapy) or baseline (combined therapy) SBP/DBP as covariates; and a random effect for patient.
[3] A patient is considered to have met the Blood Pressure (BP) goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg.
[4] n = number of patients who have achieved sitting BP goal at that visit. N = number of patients with data at that visit, regardless of BP goal status.
[5] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies.
[6] ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-I or CCBs at Visit 1 (Week -4).
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- If a different covariance structure is used in case of model nonconvergence, footnote 2 should be updated accordingly.

Table 14.2.4.4.1
Proportion of Patients Achieving Sitting BP Goal (≤ 130/80 mmHg) at Visits 2, 3, and 4 by Hypertension Grade and Treatment Subgroup
(Full Analysis Set and Efficacy Population)

				Hypertension Grade 1 (N=xx)		Hypertension Grade 2 (N=xx)	
Therapy Type	Visit	Statistic Type [1,2]	Statistic [3,4]	ZOF/AML [5] (N=xx)	ACE-i/CCB [6] (N=xx)	ZOF/AML [5] (N=xx)	ACE-i/CCB [6] (N=xx)
Monotherapy	Visit 2	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
			Odds Ratio	x.xx		x.xx	
		v. ACE-i/CCB	95% CI	(x.xx, x.xx)		(x.xx, x.xx)	
			p-value	x.xxx		x.xxx	
Combined Therapy	Visit 3	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
			Odds Ratio	x.xx		x.xx	
		v. ACE-i/CCB	95% CI	(x.xx, x.xx)		(x.xx, x.xx)	
			p-value	x.xxx		x.xxx	
	Visit 4	Logistic MMRM	n/N (Proportion %)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)	xx/xx (xx.x)
			95% CI	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)	(xx.x, xx.x)
		v. ACE-i/CCB	Odds Ratio	x.xx		x.xx	
			95% CI	(x.xx, x.xx)		(x.xx, x.xx)	
			p-value	x.xxx		x.xxx	

Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
[1] Logistic MMRM = Logistic Mixed Model Repeated Measures.
[2] A separate model is used for the monotherapy and combined therapy analyses. Models use an unstructured covariance matrix; achieving sitting BP goal as the response variable; visit, treatment subgroup, visit*treatment subgroup interaction, and screening (monotherapy) or baseline (combined therapy) SBP/DBP as covariates; and a random effect for patient. Analysis will be stratified by Hypertension grade reported at Baseline.
[3] A patient is considered to have met the Blood Pressure (BP) goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg.
[4] n is the number of patients who have achieved sitting BP goal at that visit. N is the number of patients with data at that visit, regardless of BP goal status.
[5] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies.
[6] ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-I or CCBs at Visit 1 (Week -4).
Source: Listing 16.2.6
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- If a different covariance structure is used in case of model nonconvergence, footnote 2 should be updated accordingly. Same applies to the table listed below.
- Repeat for the following tables:
    - 14.2.4.4.2 – Proportion of Patients Achieving Sitting BP Goal (≤ 130/80 mmHg) at Visits 2, 3, and 4 by Presence of Diabetes and/or Hypercholesterolemia and Treatment Subgroup – Full Analysis Set and Efficacy Population
        - In the column headers, "Hypertension Grade 1" and "Hypertension Grade 2" will change to "Diabetes/Hypercholesterolemia Present" and "Diabetes/Hypercholesterolemia Absent", respectively.
        - Footnotes will be as follows:
            - Note: The Monotherapy analysis (Visit 2) is performed on the Full Analysis Set. The Combined Therapy analysis (Visits 3 and 4) are performed on the Efficacy Population.
            - [1] Logistic MMRM = Logistic Mixed Model Repeated Measures.
            - [2] A separate model is used for the monotherapy and combined therapy analyses. Models use an unstructured covariance matrix; achieving sitting BP goal as the response variable; visit, treatment subgroup, visit*treatment subgroup interaction, and screening (monotherapy) or baseline (combined therapy) SBP/DBP as covariates; and a random effect for patient. Analysis will be stratified by presence of Diabetes and/or Hypercholesterolemia reported at Baseline.
            - [3] A patient is considered to have met the Blood Pressure (BP) goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg.
            - [4] n is the number of patients who have achieved sitting BP goal at that visit. N is the number of patients with data at that visit, regardless of BP goal status.
            - [5] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies.
            - [6] ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-I or CCBs at Visit 1 (Week -4).

2.1.3 Safety

Table 14.3.1.1.1
Overall Summary of Treatment Emergent Adverse Events – Monotherapy Period
(Safety Population)

Adverse Events [1,2,3,4]	Statistic	ZOF 30 mg (N=xx)	AML 5 mg (N=xx)	All Patients (N=xx)
Total Number of TEAEs	n	xx	xx	xx
Total Number of TESAEs	n	xx	xx	xx
Total Number of ADRs	n	xx	xx	xx
Number of Patients with:				
At Least One TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Severe TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One ADR	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One TEAE Leading to Study Discontinuation	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One TESAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One Serious ADR	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
At Least One TESAE with Outcome of Death	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

[1] AE: Adverse Event. Defined as any untoward medical occurrence in a clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
[2] TEAE: Treatment Emergent Adverse Event. Defined as AEs that occur after the first dose of monotherapy of ZOF or AML.
[3] TESAE: Treatment Emergent Serious Adverse Event.
[4] ADR: Adverse Drug Reaction. Defined as AEs that have a relationship of "certain," "probable," "possible," or "unassessable."
Source: Listings 16.2.7.1, 16.2.7.2, 16.2.7.3
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- For the combined therapy period table presented in the list below: Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column.
- Repeat for the following tables:
    - 14.3.1.1.2 – Overall Summary of Treatment Emergent Adverse Events – Combined Therapy Period – Safety Population
        - In the column headers, "ZOF 30 mg" and "AML 5mg" will change to "ZOF/AML 30/5 mg" and "ZOF/AML 30/10 mg", respectively.

Table 14.3.1.2.1
Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Monotherapy Period
(Safety Population)

Adverse Events [1,2,3,4]	Statistic	ZOF 30 mg (N=xx)	AML 5 mg (N=xx)	All Patients (N=xx)
Total Number of TEAEs	n	xx	xx	xx
Number of Patients with at Least One TEAE	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
System Organ Class #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.				
System Organ Class #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.				

[1] AE: Adverse Event. Defined as any untoward medical occurrence in a clinical trial patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
[2] TEAE: Treatment Emergent Adverse Event. Defined as AEs that occur after the first dose of monotherapy of ZOF or AML.
[3] Patients will be counted once per System Organ Class/Preferred Term (SOC/PT).
[4] MedDRA Dictionary version XX.X was used to code adverse events.
Source: Listings 16.2.7.1, 16.2.7.2, 16.2.7.3
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- For the combined therapy period tables presented in the list below: Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Patients that do not belong to the ZOF/AML 30/5 mg or ZOF/AML 30/10 mg group will be included only in the All Patients column.
- Repeat for the following tables:
  - 14.3.1.2.2 – Summary of Treatment Emergent Adverse Events by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population
    - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
  - 14.3.1.3.1 – Summary of Treatment Emergent Severe Adverse Events by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
    - Rows 1 and 2 will change from TEAE(s) to Severe TEAE(s).
  - 14.3.1.3.2 – Summary of Treatment Emergent Severe Adverse Events by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population

- Rows 1 and 2 will change from TEAE(s) to Severe TEAE(s).
- In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.

- 14.3.1.4.1 – Summary of Adverse Drug Reactions by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to ADR(s).
  - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
  - Footnote [2] will change to [ADR: Adverse Drug Reaction. Defined as AEs that have a relationship of “certain,” “probable,” “possible,” or “unassessable.”]
- 14.3.1.4.2 – Summary of Adverse Drug Reactions by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to ADR(s).
  - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
  - Footnote [2] will change to [ADR: Adverse Drug Reaction. Defined as AEs that have a relationship of “certain,” “probable,” “possible,” or “unassessable.”]
- 14.3.1.5.1 – Summary of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to TEAE(s) Leading to Study Discontinuation.
- 14.3.1.5.2 – Summary of Treatment Emergent Adverse Events Leading to Study Discontinuation by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to TEAE(s) Leading to Study Discontinuation.
  - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
- 14.3.2.1.1 – Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to TESAE(s).
  - Footnote [2] will change to “TESAE: Treatment Emergent Serious Adverse Event.”
- 14.3.2.1.2 – Summary of Treatment Emergent Serious Adverse Events by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to TESAE(s).
  - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
  - Footnote [2] will change to “TESAE: Treatment Emergent Serious Adverse Event.”
- 14.3.2.2.1 – Summary of Serious Adverse Drug Reactions by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to Serious ADR(s).
  - Footnote [2] will change to [Serious ADR: Serious Adverse Drug Reaction. Defined as SAEs that have a relationship of “certain,” “probable,” “possible,” or “unassessable.”]
- 14.3.2.2.2 – Summary of Serious Adverse Drug Reactions by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to Serious ADR(s).
  - In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
  - Footnote [2] will change to [Serious ADR: Serious Adverse Drug Reaction. Defined as SAEs that have a relationship of “certain,” “probable,” “possible,” or “unassessable.”]
- 14.3.2.3.1 – Summary of Treatment Emergent Serious Adverse Events with Outcome of Death by System Organ Class and Preferred Term – Monotherapy Period – Safety Population
  - Rows 1 and 2 will change from TEAE(s) to TESAE(s) with Outcome of Death.
  - Footnote [2] will change to “TESAE: Treatment-Emergent Serious Adverse Event.”
- 14.3.2.3.2 – Summary of Treatment Emergent Serious Adverse Events with Outcome of Death by System Organ Class and Preferred Term – Combined Therapy Period – Safety Population

- Rows 1 and 2 will change from TEAE(s) to TESAE(s) with Outcome of Death.
- In the column headers, “ZOF 30 mg” and “AML 5mg” will change to “ZOF/AML 30/5 mg [4]” and “ZOF/AML 30/10 mg [4]”, respectively.
- Footnote [2] will change to “TESAE: Treatment-Emergent Serious Adverse Event.”

Table 14.3.4.1.1
Summary and Change from Baseline (Visit 1) to Visit 4 for Haematology Parameters
(Safety Population)

Parameter (Unit)	Visit [1]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
xxxxxxx (xxx)	Baseline (Visit 1)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4 CFB	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
Repeat for All Parameters		Min, Max	xx, xx	xx, xx	xx, xx

[1] CFB = Change from Baseline. Visit 1 values will serve as Baseline since laboratory parameters are not assessed at Visit 2.
Source: Listing 16.2.8.1
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column. Same for table in the list below.
- Repeat for the following tables:
    - 14.3.4.1.2 – Summary and Change from Baseline (Visit 1) to Visit 4 for Serum Chemistry Parameters – Safety Population
        - Footnote for Source will change to “Source: Listing 16.2.8.2”
        - Source will change to Listing 16.2.8.2

Table 14.3.4.2.1
Shift from Baseline (Visit 1) to Visit 4 for Haematology Parameters
(Safety Population)

				Baseline (Visit 1) Value		
Parameter (Unit)	Combined Therapy Group	Visit 4 Value	Statistic	Normal	Abnormal, NCS	Abnormal, CS
xxxxxxx (xxx)	ZOF/AML 30/5 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ZOF/AML 30/10 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	All Patients (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Repeat for All		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Parameters		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.8.1
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients sections, not within the ZOF/AML 30/5 mg section. Same for table in the list below.
- Repeat for the following tables:
    - 14.3.4.2.2 – Shift from Baseline (Visit 1) to Visit 4 for Serum Chemistry Parameters – Safety Population
        - Source will change to Listing 16.2.8.2

Table 14.3.5
Summary of Study Drug Accountability, Exposure, and Adherence
(Safety Population)

Visit	Parameter [1,2,3]	Statistic	ZOF 30 mg	AML 5 mg	AML 10 mg
Visit 1 (Week -4)	IP Dispensed (tablets)	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
Visit 2 (Week 0)	IP Dispensed (tablets)	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	IP Returned (tablets)	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Adherence (%) Derived	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Adherence (%) CRF				
	< 80%	n/N (%)	xx/xx (xx.x)	xx/xx (xx.x)	
	≥ 80% and ≤ 120%	n/N (%)	xx/xx (xx.x)	xx/xx (xx.x)	
	> 120%	n/N (%)	xx/xx (xx.x)	xx/xx (xx.x)	
Visit 3 (Week 4)	IP Dispensed (tablets)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	IP Returned (tablets)	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	

	Adherence (%) Derived				
	Individual IP	n	xx	xx	
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	
		Median	xx.x	xx.x	
		Min, Max	xx, xx	xx, xx	
	Combined IP (ZOF/AML)	n		xx	
		Mean (SD)		xx.x (xx.xx)	
		Median		xx.x	
		Min, Max		xx, xx	
	Adherence (%) CRF				
	< 80%	n/N (%)		xx/xx (xx.x)	
	≥ 80% and ≤ 120%	n/N (%)		xx/xx (xx.x)	
	> 120%	n/N (%)		xx/xx (xx.x)	
Visit 4 (Week 8)	IP Returned (tablets)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Adherence (%) Derived				
	Individual IP	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Combined IP (ZOF/AML)	n		xx	xx
		Mean (SD)		xx.x (xx.xx)	xx.x (xx.xx)
		Median		xx.x	xx.x
		Min, Max		xx, xx	xx, xx
	Adherence (%) CRF				
	< 80%	n/N (%)		xx/xx (xx.x)	xx/xx (xx.x)
	≥ 80% and ≤ 120%	n/N (%)		xx/xx (xx.x)	xx/xx (xx.x)
	> 120%	n/N (%)		xx/xx (xx.x)	xx/xx (xx.x)

[1] Adherence is reported in the CRF and derived directly for each patient using the following formula: Adherence (%)=100*(actual doses taken/planned dose).
[2] A patient who has taken at least 80% and no more than 120% of the required study medication intake since the last visit will be considered as compliant.
[3] Values for Adherence CRF and Adherence Derived for Combined IP (ZOF/AML) are presented at Visits 3 and 4 under the corresponding AML columns (AML 5 mg at Visit 3, AML 5 mg at Visit 4 for patients on the ZOF/AML 30/5 mg regimen, and AML 10 mg at Visit 4 for patients up-titrated to the ZOF/AML 30/10 mg regimen).
Source: Listings 16.2.5.1, 16.2.5.2, 16.2.5.3
Program Name: XXXX.SAS Date: DDMMMYYYY

Table 14.3.6.1
Summary and Change from Screening (Visit 1) to Baseline (Visit 2) for Vital Sign Parameters – Monotherapy Period
(Safety Population)

Parameter (Unit)	Visit [1]	Statistic	ZOF 30 mg (N=xx)	AML 5 mg (N=xx)	All Patients (N=xx)
xxxxxxx (xxx)	Screening (Visit 1)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Baseline (Visit 2)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Baseline (Visit 2)	n	xx	xx	xx
	CFS	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Repeat for All Vital Sign		Median	xx.x	xx.x	xx.x
Parameters		Min, Max	xx, xx	xx, xx	xx, xx

[1] CFS = Change from Screening (Visit 1).
Source: Listing 16.2.9
Program Name: XXXX.SAS

Date: DDMMMYYYY

Table 14.3.6.2
Summary and Change from Baseline (Visit 2) to Visit 4 for Vital Sign Parameters – Combined Therapy Period
(Safety Population)

Parameter (Unit)	Visit [1]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
xxxxxxx (xxx)	Baseline (Visit 2)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 3	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 3 CFB	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4 CFB	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Repeat for All Vital Sign Parameters		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx

[1] CFB = Change from Baseline (Visit 2).
Source: Listing 16.2.9
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column.

Table 14.3.7.1
Shift from Screening (Visit 1) to Baseline (Visit 2) for Physical Examination – Monotherapy Period
(Safety Population)

Body System	Monotherapy Group	Baseline (Visit 2) Value	Statistic	Screening (Visit 1) Value		
				Normal	Abnormal, NCS	Abnormal, CS
xxxxxxx	ZOF 30 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	AML 5 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	All Patients (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Repeat for All		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Body Systems		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.10
Program Name: XXXX.SAS

Date: DDMMMYYYY

Table 14.3.7.2
Shift from Baseline (Visit 2) to Visit 4 for Physical Examination – Combined Therapy Period
(Safety Population)

Body System	Combined Therapy Group	Visit	Visit Value	Statistic	Baseline (Visit 2) Value		
					Normal	Abnormal, NCS	Abnormal, CS
xxxxxxx	ZOF/AML 30/5 mg (N=xxx)	Visit 3	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Visit 4	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ZOF/AML 30/10 mg (N=xxx)	Visit 3	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Visit 4	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	All Patients (N=xxx)	Visit 3	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Visit 4	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Repeat for All Body Systems			Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
			Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.10
Program Name: XXXX.SAS
Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients sections, not within the ZOF/AML 30/5 mg section.

Table 14.3.8.1
Summary and Change from Baseline (Visit 1) to Visit 4 for Electrocardiogram (ECG) Parameters
(Safety Population)

Parameter (Unit)	Visit [1]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Rhythm	Baseline (Visit 1)				
Sinusal		n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Other		n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	Visit 4				
		n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
xxxxxxx (xxx)	Baseline (Visit 1)	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x	xx.x
		Min, Max	xx, xx	xx, xx	xx, xx
	Visit 4 CFB	n	xx	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
Repeat for All		Median	xx.x	xx.x	xx.x
Parameters		Min, Max	xx, xx	xx, xx	xx, xx

[1] CFB: Change from Baseline. Visit 1 values will serve as Baseline since ECG parameters are not assessed at Visit 2.
Source: Listing 16.2.11
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column.

Table 14.3.8.2
Shift from Baseline (Visit 1) to Visit 4 for ECG Interpretation
(Safety Population)

Parameter	Combined Therapy Group	Visit 4 Value	Statistic	Baseline (Visit 1) Value		
				Normal	Abnormal, NCS	Abnormal, CS
Interpretation	ZOF/AML 30/5 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	ZOF/AML 30/10 mg (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
	All Patients (N=xxx)	Normal	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, NCS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
		Abnormal, CS	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)

Source: Listing 16.2.11
Program Name: XXXX.SAS
Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients sections, not within the ZOF/AML 30/5 mg section.

Table 14.3.9.1
Summary of Prior Medications by ATC Class Level 1 and Preferred Term
(Safety Population)

Medication Name [1,2,3]	Statistic	ZOF/AML 30/5 mg (N=xx)	ZOF/AML 30/10 mg (N=xx)	All Patients (N=xx)
Number of Patients with at Least One Prior Medication	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
ATC Class Level 1 #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.				
ATC Class Level 1 #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #1	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #2	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
Preferred Term #3	n (%)	xx (xx.x)	xx (xx.x)	xx (xx.x)
etc.				

[1] Patients will be counted once per ATC Class/Preferred Term.
[2] WHO Drug Dictionary version Sep 2020 was used to code medication names.
[3] Prior medication is defined as any medication taken within 30 days prior to the start of the study which has a stop date prior to the date of first dose of monotherapy (ZOF 30 mg or AML 5 mg).
Source: Listing 16.2.12.1
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Patients will be classified as either ZOF/AML 30/5 mg or ZOF/AML 30/10 mg such that no patients are counted in both groups. That is, even though patients in the ZOF/AML 30/10 mg group are also exposed to the ZOF/AML 30/5 mg treatment, they will only be included in the ZOF/AML 30/10 mg and All Patients columns, not within the ZOF/AML 30/5 mg column.
- Repeat for 14.3.9.2 – Summary of Concomitant Medications by ATC Class Level 1 and Preferred Term – Safety Population
  - First row text will change from "…Prior Medication" to "…Concomitant Medication"
  - Footnote [3] will change to "Concomitant medication is defined as any medication with a start date on or before the date of *last* dose of study drug and is ongoing or has a stop date on or after date of *first* dose of monotherapy (ZOF 30 mg or AML 5 mg).

Listings

Listing 16.2.1
Patient Enrollment and Disposition
(Full Analysis Set)

Patient ID	Analysis Population [1]	Disposition	Completed Monotherapy/ Completed Combined Therapy	Date of Last Monotherapy/ Date of Last Combined Therapy	Date of Study Completion or Discontinuation	Reason for Study Discontinuation or Screen Failure
xxxxxx	SAF, EFF, PP	Screen Failure, Completed, Discontinued	Yes, No/ Yes, No	DDMMMYYYY/ DDMMMYYYY	DDMMMYYYY	xxxxxxxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.2
Protocol Deviations
(Full Analysis Set)

Patient ID	Analysis Population [1]	Date of Deviation	Deviation Grade [2]	Deviation Category	Deviation Description
xxxxxx	SAF, EFF, PP	DDMMMYYYY	Critical, Major, Minor	xxxxxxxx	xxxxxxxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Critical deviations will be classified as Major for purposes of defining the PP Population but are displayed here as Critical.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.3
Patients Excluded from Analysis Populations
(Full Analysis Set)

Patient ID	Safety Population [1]	Efficacy Population [2]	Per Protocol Population [3]	Reason for Exclusion
xxxxxx	Yes, No	Yes, No	Yes, No	Did Not Meet all Screening Criteria/Did Not Enroll Did Not Receive At Least One Dose During Run-In Did Not Complete Run-In Period Did Not Complete V2 BP Assessment Not Dosed According to Protocol Did Not Complete Required Study Visits Major Protocol Deviation That May Impact the Primary Efficacy Assessment

[1] Safety Population (SAF): All study participants who sign informed consent, meet all screening criteria, are enrolled, and receive at least one dose of the assigned treatment during the run-in period.
[2] Efficacy Population (EFF): All study participants in the Safety Population who complete the 4-week run-in period and the Visit 2 blood pressure assessment.
[3] Per Protocol Population (PP): All study participants in the Efficacy Population who were dosed according to the protocol, complete the required study visits, and do not experience any major protocol deviations that may impact the primary efficacy assessment through end of treatment.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Listing 16.2.4.1
Demographic Characteristics
(Safety Population)

Patient ID	Analysis Population [1]	Age (Years)	Sex	Ethnicity	Race	Height (cm)	Weight (kg)	BMI (kg/m2)
xxxxxx	SAF, EFF, PP	xx	Male, Female, Unknown/ Undifferentiated	Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown	American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other (Specify)	xxx.xx	xxx.xx	xx.xx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.4.2
Baseline Characteristics
(Safety Population)

Patient ID	Analysis Population [1]	Smoking Status	Smoking Frequency	e-Cigarette Details	Medical History	Treatment at Run-In	Study Site
xxxxxx	SAF, EFF, PP	Never Tobacco Smoker, Former Tobacco Smoker, Current Tobacco Smoker, Undisclosed	Daily, Occasional	xxxxx	Hypertension Grade 1, Hypertension Grade 2, Diabetes mellitus, Hypercholesterolemia	Zofenopril 30 mg, Amlodipine 5 mg, Other ACE-i, Other CCB	201, 202, etc.

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.
- Smoking Frequency should only be populated when Smoking Status is “Former Tobacco Smoker” or “Current Tobacco Smoker.”
- E-Cigarette details should only be populated if the checkbox for e-cigarette use is checked in the EDC (raw.dm.smkesig).

Listing 16.2.5.1
Study Drug Accountability and Adherence
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Dispensed/ Returned	Date/Time of Dispensation/Return	Medication Type	CTM Code	IP Amount	Uncontrolled Sitting BP [3]	Tx Well Tolerated [4]	Adherence (%) Derived/ Adherence (%) CRF [5]
xxxxxx	SAF, EFF, PP	Visit 1	Dispensed	DDMMMYYYY/HH:MM	ZOF 30 mg or AML 5mg	xxxxxxx	xx tablets			
		Visit 2	Dispensed	DDMMMYYYY/HH:MM	ZOF 30 mg AML 5 mg	xxxxxxx xxxxxxx	xx tablets xx tablets	Yes, No	Yes, No	xx.x/ < 80%, ≥ 80% and ≤ 120%, > 120%
			Returned	DDMMMYYYY/HH:MM	ZOF 30 mg or AML 5mg	xxxxxxx	xx tablets			
		Visit 3	Dispensed	DDMMMYYYY/HH:MM	ZOF 30 mg AML x mg	xxxxxxx xxxxxxx	xx tablets xx tablets	Yes, No	Yes, No	xx.x/ < 80%, ≥ 80% and ≤ 120%, > 120%
			Returned	DDMMMYYYY/HH:MM	ZOF 30 mg AML 5 mg	xxxxxxx xxxxxxx	xx tablets xx tablets			
		Visit 4	Returned	DDMMMYYYY/HH:MM	ZOF 30 mg AML x mg	xxxxxxx xxxxxxx	xx tablets xx tablets			xx.x/ < 80%, ≥ 80% and ≤ 120%, > 120%

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
[3] Uncontrolled sitting BP = SBP/DBP > 130/80mmHg.
[4] Tx = Treatment.
[5] Adherence is reported in the CRF and derived directly for each patient using the following formula: Adherence (%)=100*(actual doses taken/planned dose).
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Listing 16.2.5.2
Study Drug Exposure
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Therapy Type	Medication Type	Start Date/Time	End Date/Time
xxxxxx	SAF, EFF, PP	Visit 1	Monotherapy	ZOF 30 mg or AML 5 mg	DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM or DDMMMYYYY/HH:MM
		Visit 2	Combination	ZOF 30 mg AML 5 mg	DDMMMYYYY/HH:MM DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM DDMMMYYYY/HH:MM
		Visit 3	Combination	ZOF 30 mg AML x mg	DDMMMYYYY/HH:MM DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM DDMMMYYYY/HH:MM

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS

Date: DDMMMYYYY

Listing 16.2.5.3
Modified, Missing, and Interrupted Doses
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Type	Dose Modification	Dose Missed/ Interrupted	Missed/ Interrupted by	Interruption Start Date/Time Restart Date/Time	Reason for Dose Modified, Missing, Interrupted	AE #
xxxxxx	SAF, EFF, PP	Visit 2 Visit 3 Visit 4	Modification Missed Dose Interruption	Dose Increased, Dose Reduced, Drug Withdrawal, Unknown	ZOF 30 mg, AML 5 mg, AML 10 mg, ZOF/AML 30/5 mg, ZOF/AML 30/10 mg	Investigator, Patient	DDMMMYYYY/HH:MM DDMMMYYYY/HH:MM	Adverse Event, Other, Specify	xx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8. Visit reflects when the missing/interrupted dose was reported, not necessarily when the dose was missed/interrupted.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Listing 16.2.6
Mean Sitting Systolic and Diastolic Blood Pressure Details
(Efficacy Population)

Patient ID	Analysis Population [1]	Treatment Subgroup [2]	Visit [3]	Date/Time of Assessment	Parameter (Unit)	Result [4]	Normality and Clinical Significance	Met BP Goal [5]	Up-Titrated at Visit 3 [6]
xxxxxx	SAF, EFF, PP	ZOF/AML, ACE-i/CCB	Visit 1, Visit 2, Visit 3, Visit 4	DDMMMYYYY/HH:MM	SBP (mmHg), DBP (mmHg)	xx.x, xx.x*	Normal, Abnormal NCS, Abnormal CS	Yes, No	Yes, No

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] ZOF/AML subgroup: Patients who were on ZOF 30 mg or AML 5 mg at Visit 1 (Week -4) and continued on same therapies. ACE-i/CCB subgroup: Patients who switched to ZOF 30 mg or AML 5 mg from any other ACE-I or CCBs at Visit 1 (Week -4).
[3] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
[4] Results imputed using Last Observation Carried Forward (LOCF) are noted with *.
[5] A patient is considered to have met the Blood Pressure (BP) goal (controlled BP) if their SBP ≤ 130 mmHg AND their DBP ≤ 80 mmHg.
[6] Patients uncontrolled at Visit 3 are those who have SBP/DBP > 130/80 mmHg. These patients are up-titrated from ZOF/AML 30/5 mg to ZOF/AML 30/10 mg.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.7.1
Adverse Events
(Safety Population)

Patient ID	Analysis Population [1]	System Organ Class/ Preferred Term [2]	AE #	CM #	Start Date	End Date/ Ongoing	Serious	SAE Criteria	Treatment Emergent [3]	Therapy Period [4]
xxxxxx	SAF, EFF, PP	xxxxxxx/ xxxxxxxx	xxx	xxx	DDMMMYYYY	DDMMMYYYY, Ongoing	Yes, No	xxxxx	Yes, No	M, C

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] MedDRA Dictionary version XX.X was used to code adverse events.
[3] Treatment-Emergent Adverse Event. Defined as AEs that occur after the first dose of monotherapy of ZOF or AML.
[4] M: Monotherapy Period. C: Combined Therapy Period.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.7.2
Adverse Event Details
(Safety Population)

Patient ID	Analysis Population [1]	System Organ Class/ Preferred Term [2]	AE #	Severity	Relationship	Outcome	Action Taken	Led to Study Discontinuation
xxxxxx	SAF, EFF, PP	xxxxxxx/ xxxxxxxx	xxx	Mild, Moderate, Severe	Not Related, Unlikely, Possible, Probable, Certain, Un-assessable	Resolved, Resolving, Not Resolved, Resolved with Sequelae, Fatal, Unknown	Withdrawn, Dose Reduced, Increased, Not Changed, Unknown, Not Applicable	Yes, No

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] MedDRA Dictionary version XX.X was used to code adverse events.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.7.3
Deaths
(Safety Population)

Patient ID	Analysis Population [1]	Date/Time of First Dose	Date/Time of Last Dose	Date of Death	System Organ Class/ Preferred Term [2]	AE #
xxxxxx	SAF, EFF, PP	DDMMMYYYY/HH:MM	DDMMMYYYY/HH:MM	DDMMMYYYY	xxxxxxx/ xxxxxxxx	xxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] MedDRA Dictionary version XX.X was used to code adverse events.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.8.1
Haematology Parameters
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Date/Time of Assessment	Parameter (Unit)	Result	Normality	Clinically Significant
xxxxxx	SAF, EFF, PP	Visit 1, Visit 4	DDMMMYYYY/HH:MM	xxxxxxxx (xxx)	xx.x	Normal, Abnormal	Yes, No

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.
- Repeat for 16.2.8.2 – Serum Chemistry Parameters – Safety Population

Listing 16.2.8.3
Pregnancy Test
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Date of Assessment	Result	Reason Not Done
xxxxxx	SAF, EFF, PP	Visit 1, Visit 2, Visit 3, Visit 4	DDMMMYYYY	Not Done, Positive, Negative	Subject is surgically sterile, Subject is post-menopausal, Other (specify)

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.9
Vital Signs
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Date/Time of Assessment	Parameter (Unit)	Result	Normality	Clinically Significant	Position	Arm
xxxxxx	SAF, EFF, PP	Visit 1, Visit 2, Visit 3, Visit 4	DDMMMYYYY/HH:MM	xxxxxxxx (xxx)	xx.x	Normal, Abnormal	Yes, No	Sitting, Standing	Left, Right

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS

Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.
- Last 2 columns will only be populated for blood pressure parameters.

Listing 16.2.10
Physical Examination
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	Date/Time of Assessment	Body System	Result	Clinically Significant	Specify Abnormality
xxxxxx	SAF, EFF, PP	Visit 1, Visit 2, Visit 3, Visit 4	DDMMMYYYY/HH:MM	xxxxxxxx	Normal, Abnormal	Yes, No	xxxxxxxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 2 is Week 0. Visit 3 is Week 4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.
- Height (cm), weight (kg), and BMI (kg/m2) are all presented in 16.2.4.1 and thus are not presented here.

Listing 16.2.11
Electrocardiogram (ECG) Parameters
(Safety Population)

Patient ID	Analysis Population [1]	Visit [2]	ECG Number	Date/Time of Assessment	Parameter (Unit)	Result	Describe CS Interpretation
xxxxxx	SAF, EFF, PP	Visit 1, Visit 4	1, 2, 3	DDMMMYYYY/HH:MM	xxxxxxxx (xxx), Rhythm, Interpretation	xx.x, Sinusal or Other (Specify), Normal, Abnormal NCS, or Abnormal CS	xxxxxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] Visit 1 is Week -4. Visit 4 is Week 8.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.
- Interpretation and Rhythm will be included as a separate parameter for each ECG number.

Listing 16.2.12.1
Prior and Concomitant Medications
(Safety Population)

Patient ID	Analysis Population [1]	ATC Class Level 1/ Preferred Term [2]	CM #	Start Date / End Date or Ongoing	Indication	Dose (Unit)	Form	Frequency	Route	Prior Med [3,4]	Treatment Given For
xxxxxx	SAF, EFF, PP	xxxxxxx/ xxxxxxxx	xxx	DDMMMYYYY/ DDMMMYYYY or Ongoing	xxx	xxx (xxx)	xxx	xxx	xxx	Yes, No	MH #, AE #, Prophylactically, Other (Specify)

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] WHO Drug Dictionary version YYYYMMM was used to code medication names.
[3] Prior medication is defined as any medication taken within 30 days prior to the start of the study which has a stop date prior to the date of first dose of monotherapy.
[4] Concomitant medication is defined as any medication with a start date on or before the date of *last* dose of study drug and is ongoing or has a stop date on or after date of *first* dose of monotherapy.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.12.2
Non-Drug Treatments/Procedures
(Safety Population)

Patient ID	Analysis Population [1]	System Organ Class/ Preferred Term [2]	PR #	Procedure Date	Indication	Treatment Given For
xxxxxx	SAF, EFF, PP	xxxxxxx/ xxxxxxxx	xxx	DDMMMYYYY	xxx	MH #, AE #, Prophylactically, Other (Specify)

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] MedDRA Dictionary version XX.X was used to code non-drug treatments/procedures.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.13
Medical History
(Safety Population)

Patient ID	Analysis Population [1]	System Organ Class/ Preferred Term [2]	MH #	Start Date	Current Treatment	CM #
xxxxxx	SAF, EFF, PP	xxxxxxx/ xxxxxxxx	xxx	DDMMMYYYY	Yes, No	xxx

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
[2] MedDRA Dictionary version XX.X was used to code medical history events.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

Listing 16.2.14
Blood Pressure Device and Diary Details
(Safety Population)

Patient ID	Analysis Population [1]	Date of BP Device Dispense	Date of BP Device Return	Date of Diary Dispense	Date of Diary Return
xxxxxx	SAF, EFF, PP	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY	DDMMMYYYY

[1] SAF: Safety Population. EFF: Efficacy Population. PP: Per Protocol Population.
Source: SDTM.XXXX or ADaM.XXXX
Program Name: XXXX.SAS Date: DDMMMYYYY

Programming Note:

- Analysis Population column should list *all* populations to which the patient belongs.

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Signer Events	Signature	Timestamp
Giorgio Reggiardo giorgioreggiardo@cvbf.net Security Level: Email, Account Authentication (Required)	DocuSigned by: Giorgio Reggiardo Nome firmatario: Giorgio Reggiardo Motivo per la firma: Approvo il documento Ora firma: 24 maggio 2022 | 9:57:07 PM PDT 55ABF8D8F49E465284E330F8AB1E18C8 Signature Adoption: Pre-selected Style Signed by link sent to giorgioreggiardo@cvbf.net Signature ID: 55ABF8D8-F49E-4652-84E3-30F8AB1E18C8 Using IP Address: 93.32.76.148 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Approvo il documento	Sent: 5/24/2022 8:38:07 AM Viewed: 5/24/2022 9:56:22 PM Signed: 5/24/2022 9:57:13 PM
Electronic Record and Signature Disclosure: Accepted: 5/24/2022 9:56:22 PM ID: b8ba5121-ed9e-4f6d-ad89-fdd48ee3aaa3		
Hanna Lytvynenko hlytvynenko@biorasi.com Security Level: Email, Account Authentication (Required)	Hanna Lytvynenko Signature Adoption: Pre-selected Style Signed by link sent to hlytvynenko@biorasi.com Signature ID: 3BBBAE2E-DC07-497E-965F-70C9C798DB1D Using IP Address: 176.113.166.5 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/24/2022 8:38:05 AM Viewed: 5/25/2022 2:34:25 AM Signed: 5/25/2022 2:34:52 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		

Signer Events	Signature	Timestamp
John Reber jreber@biorasi.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to jreber@biorasi.com Signature ID: CC5A8051-CACD-4A8C-AFD6-A96A3092CB46 Using IP Address: 66.228.227.97 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/24/2022 8:38:05 AM Viewed: 5/24/2022 8:41:36 AM Signed: 5/24/2022 8:41:46 AM
Electronic Record and Signature Disclosure: Accepted: 2/14/2021 9:23:55 AM ID: 7ebbb550-6705-417a-af0e-7c752602df9c		
Julia Solovyeva jsolovyeva@biorasi.com Project Manager II Biorasi Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to jsolovyeva@biorasi.com Signature ID: E17D0303-84C0-43B8-93BD-F491C8A6193A Using IP Address: 80.250.209.54 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/24/2022 8:38:06 AM Viewed: 5/24/2022 8:42:28 AM Signed: 5/24/2022 8:42:46 AM
Electronic Record and Signature Disclosure: Not Offered via DocuSign		
Paolo Fabrizzi pfabrizzi@menarini.it Paolo Fabrizzi Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signed by link sent to pfabrizzi@menarini.it Signature ID: 9D1DC95A-F30F-4AA9-B407-09F91A9C3C83 Using IP Address: 151.11.86.7 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document	Sent: 5/24/2022 8:38:06 AM Viewed: 5/24/2022 10:31:46 AM Signed: 5/24/2022 10:32:02 AM
Electronic Record and Signature Disclosure: Accepted: 8/13/2021 10:05:10 AM ID: 23af8ef9-0ece-4677-92ca-1fb5d97b1ff9		

Signer Events	Signature	Timestamp
Victoria Swaidan vswaidan@biorasi.com Biorasi Security Level: Email, Account Authentication (Required)	Victoria Swaidan Signature Adoption: Pre-selected Style Signed by link sent to vswaidan@biorasi.com Signature ID: F18BA1C2-BF7C-48A4-B775-BE54652AC840 Using IP Address: 98.55.173.86 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I am the author of this document	Sent: 5/24/2022 8:38:05 AM Viewed: 5/24/2022 8:38:25 AM Signed: 5/24/2022 8:38:38 AM
Electronic Record and Signature Disclosure: Accepted: 6/24/2020 9:03:50 AM ID: 42b1d68e-a4bb-4cee-b689-c158e740ba19		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/24/2022 8:38:07 AM
Certified Delivered	Security Checked	5/24/2022 8:38:25 AM
Signing Complete	Security Checked	5/24/2022 8:38:38 AM
Completed	Security Checked	5/25/2022 2:34:52 AM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

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