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LCZ696 sacubitril/valsartan

Clinical Trial Protocol CLCZ696BUS14 / NCT02970669

Multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study and 8-week open label extension to evaluate the effect of initiation of sacubitril/valsartan on objective measures of **wak**ing activity and sleep, as **h**ealth-related quality of life functions in subjects with **h**eart **f**ailure and reduced ejection fraction: (AWAKE-HF)

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List of abbreviations

AASM	American Academy of Sleep Medicine
ACC	Angioedema Adjudication Committee
ACEi	Angiotensin Converting Enzyme inhibitor
AE	Adverse Event
[redacted]	[redacted]
ARB	Angiotensin Receptor Blocker
b.i.d.	twice a day
BMI	Body Mass Index
CFR	US Code of Federal Regulations
CDS	Core Data Sheet (for marketing drugs)
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report/Record Form (paper or electronic)
CPAP	Continuous Positive Airway Pressure
CPO	Country Pharma Organization
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CTC	Common Terminology Criteria
CTRD	Clinical Trial Results Database
CV	Cardiovascular
DS&E	Drug Safety & Epidemiology
ECG	Electrocardiogram
EDC	Electronic Data Capture
eSource	Electronic Source
GCP	Good Clinical Practice
hCG	Human Chorionic Gonadotropin
HDPE	High Density Polyethylene
HF	Heart Failure
HFrEF	Heart failure with reduced ejection fraction
[redacted]	[redacted]
HR-QoL	Health Related Quality of Life
HST	Home Sleep Test
ICD	Implanted Cardioverter defibrillators
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
i.v.	intravenous
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	Intrauterine Device
IUS	Intrauterine System
KCCQ	Kansas City Cardiomyopathy Questionnaire

[redacted]

LFT	Liver function test
LVEF	Left Ventricular Ejection Fraction
MedDRA	Medical dictionary for regulatory activities
MWT	Minute Walk Test
NEP	Neutral Endopeptidase
NYHA	New York Heart Association
o.d.	once a day
OTC	Over the Counter
p.o.	Oral(ly)
PRO	Patient Reported Outcome
PSG	Polysomnography
RAAS	Renin Angiotensin Aldosterone System
SAE	Serious Adverse Event
SPPB	Short Physical Performance Battery
SUSAR	Suspected Unexpected Serious Adverse Reactions
STD	Study Treatment Discontinuation
USPI	United States Package Insert
[redacted]	[redacted]
WHO	World Health Organization
WoC	Withdrawal of Consent

[redacted]

Glossary of terms

Cohort	A specific group of patients/subjects fulfilling certain criteria
Control drug	Drugs(s) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the patient in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (eCRFs) into one application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Enrollment	Point/time of patient entry into the study at which informed consent must be obtained (e.g. prior to starting any of the procedures described in the protocol)
Epoch	A portion of the study which serves a specific purpose. Typical epochs are: screening/recruitment, wash-out, treatment, and follow-up
Investigational drug	The drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and is synonymous with “investigational new drug” or “investigational medicinal product.”
Medication pack number	A unique identifier on the label of each investigational drug package
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients/subjects with established disease and in those with newly-diagnosed disease.
Patient/subject ID	A unique number assigned to each patient upon signing the informed consent
Randomization number	A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment
Reduced Ejection Fraction	Left ventricular ejection fraction ≤ 40%

[redacted]

Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), placebo/comparator active drug run-ins or background therapy
Study Treatment Discontinuation (TD)	When the patient permanently stops taking study treatment prior to the defined study treatment completion date
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	Withdrawal of consent from the study is defined as when a patient does not want to participate in the study any longer, and does not want any further visits or assessments, and does not want any further study related contact, and does not allow analysis of already obtained biologic material

Amendment v02 rationale

The primary purpose of this amendment is to add statistical methodology to account for the possibility that the primary endpoint is not normally distributed. In the event that the primary endpoint is not normally distributed and the lognormal distribution is a better fit, a log transformation will be used in the analysis of the primary endpoint.

Changes to the protocol

- Protocol Summary – Data Analysis section updated based on amendment updates
- Section 9.4.2 Statistical model, hypothesis, and method of analysis: additional statistical methodology included
- Section 9.4.4 Sensitivity analyses: removed text for consistency with statistical methodology updates
- Section 9.8 Sample size calculation: added text consistent with statistical methodology updates

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

[redacted]

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein do NOT affect the trial specific model ICF.

Summary of previous amendments

Amendment v01 (26Jul2017)

Amendment rationale

[redacted] Additional clarification is added to inclusion criterion 3. These modifications are based on feedback received from investigators during site initiation visits. The trial objectives and related endpoints are simplified based on the reporting and analysis plan.

Changes to the protocol

- Table 2-1: Objectives and Related Endpoints – clarified endpoints for each objective based on reporting and analysis plan
- Inclusion criterion # 3: added definition of reduced ejection fraction
- [redacted]
- [redacted]

Changes to specific sections of the protocol are shown in the track changes version of the protocol using strike through red font for deletions and red underlined for insertions.

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC approval prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Protocol summary

Protocol number	CLCZ696BUS14
Full Title	Multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study and 8-week open label extension to evaluate the effect of initiation of sacubitril/valsartan on objective measures of waking activity and sleep, as health-related quality of life functions in subjects with heart failure and reduced ejection fraction (AWAKE-HF).
Brief title	Study on the effects of Sacubitril/Valsartan on physical activity and sleep in heart failure with reduced ejection fraction patients.
Sponsor and Clinical Phase	Novartis Pharmaceuticals: Phase IV
Investigation type	Interventional
Study type	Multicenter, randomized, double-blind, double dummy, parallel group, active-controlled
Purpose and rationale	The purpose of this study is to investigate the effects of initiation of sacubitril/valsartan vs enalapril treatment on objective measures of both waking activity and sleep in subjects with heart failure with reduced ejection fraction.
Primary Objective(s)	The primary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on physical activity during the waking hours as an objective measure of physical function. The primary endpoint is the change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of endpoint data collected each day during week -1) and the final randomized treatment phase measurement (mean of endpoint data collected each day during week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 min period collected during the most active 30 minutes of each day).
Secondary Objectives	The secondary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on subjects' sleep as an objective measure of physical function. <u>The secondary endpoints include:</u> • Change in mean activity (counts per minute) during sleep between baseline phase (mean of data collected during week -1) and the final randomized treatment phase measurement (mean of data collected during week 8), as measured by actigraphy (activity counts per minute during daily sleep period, wrist-worn accelerometer). • The change in mean activity during sleep between baseline phase (mean of data collected during the nights of week-1) and each randomized treatment and open label phase measurement , as measured by actigraphy (Week 1, 9, and 16) (activity counts per minute during daily sleep period, wrist-worn accelerometer). • The change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1) and each randomized treatment and open label phase measurement

[redacted]

	(Weeks 1, 9, and 16), as measured by wrist worn accelerometer collected actigraphy.
Study design	A multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study with open label extension using medical device-grade subject worn sensors to measure waking and sleeping physical activity in the ambulatory outpatient setting. The 18 week study duration will consist of a 2-week baseline observation phase (with subjects continuing their current heart failure drug therapy), followed by an 8 week blinded treatment phase during which subjects are randomized (1:1) to either initiation of sacubitril/valsartan treatment or enalapril comparator, and finally an 8 week open label extension phase during which all subjects are treated with sacubitril/valsartan. Each subject will undergo a 36 hour washout period [during which ACEi (Angiotensin converting enzyme inhibitor), or study drug will be withheld] before the start of the randomized, blinded treatment phase, and again before beginning the open label extension phase. The study will include 8 office visits and 5 tele-visits.
Population	The study population will consist of outpatient male and female subjects, between 18 - 80 years of age, with HFrEF NYHA class II or III. The goal is to have a total of approximately 136 subjects randomized, in approximately 25-30 centers in the United States. Subjects will have met all other inclusion and none of the exclusion criteria.
Key Inclusion criteria	Subjects eligible for inclusion in this study must fulfill all of the following criteria: • Written informed consent must be obtained before any assessment is performed. • Men and women between 18 and 80 years of age • Subjects diagnosed with NYHA class II or III heart failure and with reduced ejection (HFrEF). (Reduced ejection is defined as left ventricular EF ≤ 40%. LVEF ≤40% may be determined via any local measurement within the past 6 months prior to signing consent, using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF). • Subjects must be a candidate for treatment with sacubitril/valsartan as per United States Package Insert (USPI) • Subjects must be living in a traditional residence, apartment, or non-communal adult home where they can move about freely and frequently and are primarily responsible for scheduling their sleep and daily activities
Key Exclusion criteria	Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects. • Subjects with a history of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs. • Subjects with a history of angioedema drug related or otherwise

[redacted]

	• Subjects with symptomatic hypotension or systolic blood pressure <100 mmHg at screening or <95 mmHg at randomization
	• Subjects with any conditions in skin or upper extremities which would limit the ability to tolerate a wrist-worn actigraphy device on the non-dominant arm for 24 hours/day for the duration of the study.
	• Subjects who are nonambulatory or use mobility assistive devices such as motorized devices, wheelchairs, or walkers. The use of canes for stability while ambulating is acceptable.
	• Subjects with physical activity impairment primarily due to conditions other than heart failure such as:
	  • Exertional angina
	  • inflammatory or degenerative joint disease
	  • gout
	  • peripheral vascular disease
	  • neurologic disease affecting activity or mobility

Study treatment	All eligible subjects will be randomized to receive either sacubitril/valsartan or enalapril. Both sacubitril/valsartan and enalapril and their matching placebos will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulations governing handling of investigational treatments, and will be dispensed by the study physician. Sacubitril/valsartan and enalapril will be packaged separately to limit the number of pack types which will allow more flexibility in the drug supply process to cover all the different treatment possibilities (treatment arm and medication dose level), see Table 5-2 and Table 5-4.
Efficacy assessments	Will consist of measurements based on: • Actigraphy • [redacted]
Key safety assessments	Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.
[redacted]	• [redacted] • [redacted] • [redacted]
Data analysis	The primary endpoint is the change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1) and the final randomized treatment phase measurement (mean of endpoint data collected each day during week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 min period collected during the most active 30 minutes of each day). The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment and baseline activity as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported.

[redacted]

	Before performing the above analysis, tests of normality of the variable and its log transformation (log (week 8 value) – log (baseline value)) will be performed. In the event the variable is not normally distributed (based on Shapiro-Wilk test p-value <0.05) but the lognormal distribution fits better, the above analysis will be performed using the log transformed data. Anti-log of the least squares mean difference of the treatment groups will be used to report the ratio of the treatment difference in the original scale. The secondary efficacy variables are the following: • Change in mean activity (counts per minute) during sleep between baseline phase and week 8 (Randomized treatment phase) • Change in mean activity during sleep between baseline phase and week 1 (Randomized treatment phase) • Change in mean activity during sleep between baseline phase and week 9 and 16 (Open label extension phase) • Change in mean activity counts during the most active 30 minutes of the subject's day between baseline phase and week 1(Randomized treatment phase) • Change in mean activity counts during the most active 30 minutes of the subject's day between baseline phase and week 9 and 16 (Open label extension phase) During the randomized treatment phase, mean change from baseline for each continuous variable will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable, and missing data will be imputed using the LOCF method. During the open label extension phase, change from baseline (mean of week -1) for each continuous variable will be analyzed at each time point using paired t-tests for the group randomized to sacubitril/valsartan. The analyses will be repeated using the week 8 measurement as baseline for the group randomized to Enalapril. Assuming a significance level of 0.05, a total sample size of 136 subjects would provide 90% power to detect a difference of 5000 in the change from baseline in mean activity counts collected during the most active 30 minutes between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 7400 (Maurer 2009) and a 20% drop-out rate and a 10% rate of subjects with non-evaluable data. Assuming a significance level of 0.05, a sample size of 136 subjects would provide 93% power to detect a 3.5 point difference in the change from baseline in mean activity value during the sleep (expressed as counts per minute) between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 4.9 and a 20% drop-out rate and a 10% rate of subjects with non-evaluable data (Peterson 2012)
Key words	Heart failure, HReEF, Physical Activity, Actigraphy, [redacted] wake

[redacted]

1 Introduction

1.1 Background

Fatigue is the cardinal symptom of heart failure (HF); the degree to which HF impacts patients' capacity for physical activity and restful sleep is the primary effector of health-related quality of life (HR-QoL) for these patients (Redeker 2005, Maurer 2009). Early real-world clinical experience with sacubitril/valsartan has been associated with anecdotal reports of clinically-meaningful improvements in HR-QoL for subjects with heart failure and reduced ejection fraction as early as shortly after initiation of sacubitril/valsartan therapy (during titration to target dose). Although assessment of HR-QoL in PARADIGM-HF by questionnaire demonstrated that treatment with sacubitril/valsartan slowed deterioration of HR-QoL in comparison to enalapril, the data did not show a statistically meaningful improvement in HR-QoL, nor was there any assessment of the short-term impact of treatment on HR-QoL (Jhund 2015). Moreover, assessment of changes in short-term HR-QoL in HF subjects is simply not feasible with current traditional questionnaire-based assessments due to the lack of validated questionnaires designed for a short-term recall period and limitations in sensitivity caused by the inherent variability associated with the subjective nature of these instruments.

To objectively assess the impact of initiation of sacubitril/valsartan treatment vs enalapril on early HR-QoL, we propose this clinical study using digital sensor technology to assess physical activity during awake and sleep, and short-term recall symptom assessment in outpatient ambulatory HF patients in their home environment.

Challenges in the assessment of HR-QoL

Various objective and subjective physical activity assessment methods have been developed. Subjective methods such as questionnaires, surveys and diaries are inexpensive tools that assess the level of physical activity in a subjects' everyday life outside of a clinic, but often rely on individual observations and are subject to patient recall (Wang 2011) and reporting bias (Sallis 2000). Interestingly, the benchmark instruments for physical assessment use subjective judgments to detect changes in what is actually a pattern of non-subjective events. For example, the Kansas City Cardiomyopathy Questionnaire (KCCQ) is a self-administered, 23-item questionnaire that quantifies physical limitations, symptoms, self-efficacy, social interference and quality of life. The physical limitation domain of this instrument was designed to detect clinically significant changes in capacity for physical activity, and was validated against the 6 Minute Walk Test (MWT) and physical limitation domains in other accepted questionnaire-base instruments (Guyatt 1985).

In comparison to subjective assessments, objective techniques like the 6 MWT are inherently more sensitive and reproducible; however, they traditionally do not provide any mechanism to assess subjects' physical limitation in the context of their everyday life. The artificial clinical setting in which traditional objective assessments take place limits the ability of these instruments to detect physical limitation as experienced in subjects' everyday life. Furthermore, objective techniques such as the 6 MWT or Short Physical Performance Battery (SPPB) (Vasunilashorn 2009) often impose a burden on the time and resources of clinics performing

[redacted]

them. The emergence of the use of wearable digital movement sensors such as accelerometers for measuring physical activity allows for the capture of data that is both objectively measured and captured in the context of subjects' everyday life.

Actigraphy: a new approach to assessment of physical activity

Accelerometers are digital sensors which can be worn on the wrist, thigh, trunk, or ankles and measure the accelerations of the device in motion along reference axes. Acceleration is proportional to external force and therefore can reflect intensity and frequency of human physical activity. The measurement of activity with a wearable accelerometer is known as actigraphy. Actigraphic assessment data from an accelerometer typically involves integration of acceleration data (collected in units of $ms^{-1}s^{-1}$) with respect to time (Chen 2005). Accelerometers typically sample acceleration at a rate of 32-100 Hz (cycles per second). Acceleration data is condensed and stored in the device in fixed 'epochs' of time.

Recently, actigraphy has been successfully used in prospective interventional studies to assess the impact of pharmacological treatment on the physical activity of subjects during both sleep and waking periods. A study of atopic dermatitis patients reported the use of actigraphy to evaluate treatment induced reduction of itch-related sleep disruption (Nemoto 2016). Notably in this study, the assessment of the impact of itch on sleep efficiency with actigraphy proved resistant to placebo effect which is typically observed when using traditional instruments to assess itch. Actigraphy was also successfully used to assess the impact of treatment with celecoxib on the daytime symptoms of patients with osteoarthritis (Trudeau 2015). Interestingly, questionnaire-based assessment of pain was subject to a high placebo response rate and did not meet statistical significance while actigraphic assessment of increase in subjects' activity levels demonstrated a significant treatment effect.

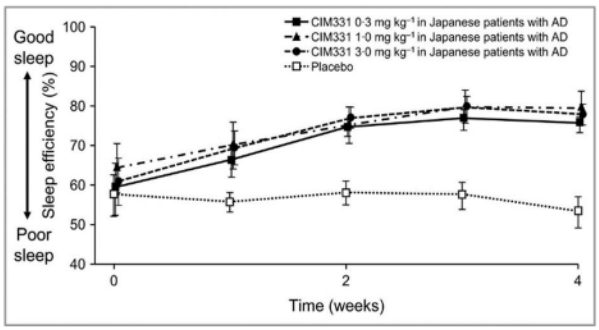


Figure 1 **Transitional change (mean ± SE) in actigraphically assessed sleep efficiency.**

[redacted]

The importance of physical activity in HF

The inability to perform exercise or physical activity without discomfort may be one of the first symptoms experienced by patients with HF and is a principal reason for seeking medical care. Heart failure is a major health problem, with an increasing incidence and a gloomy prognosis that is typically accompanied by an increasing limited capacity for physical activity and worsening overall HR-QoL (Wielenga 1997).

Physical inactivity alone is a serious problem and has been identified as the fourth leading risk factor for global mortality causing an estimated 3.2 million deaths worldwide (Caspersen 1985, Steele 2000).

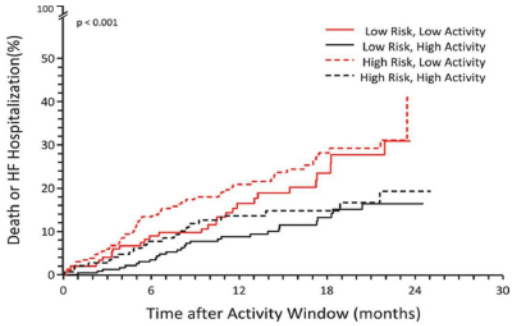


Figure 2 Kaplan–Meier estimates for the incidence of death or hospitalization. 834 patients stratified in 4 groups based on the combination of physical activity and the CHARM risk score. For both parameters, the median value (188 min/d and 4.8 points, respectively) is used to group patients in the low or high category. (Conraads 2014)

In multiple studies of HF patients, a reduction in physical activity as measured by actigraphy has been demonstrated to be strongly predictive of both mortality and hospitalization (Howell 2010). A study of actigraphy data collected from onboard accelerometers in implanted cardioverter defibrillators (ICDs) found physical activity to be a strong predictor of outcome in a large cohort of HF patients (Conraads 2014). In addition, a recent study of 60 New York Heart Association (NYHA) III HF patients identified the specific activity pattern features of skewness (a measure of the symmetry of the distribution curve) and kurtosis (a measure of the sharpness of the peak of the distribution curve) to be independently predictive of all-cause mortality (Melin 2016). On the other hand, an increase in capacity for physical activity has been shown to be beneficial for HF patients. Exercise induced improvement in capacity for activity results in a significant improvement in all parameters of quality of life including physical, psychological, social and environmental domains (Bocalini 2008).

Actigraphy to assess impact of HF management on physical activity

To date, only one study has used actigraphy to assess treatment effects in HF patients. A study of the effect of isosorbide mononitrate on the activity levels of HF patients with preserved ejection fraction used actigraphy to assess effects on subjects' movement levels over 6 weeks (Redfield 2015). While there was no significant between-group difference in 6 MWT, or QoL questionnaire results (KCCQ, Minnesota living with heart failure), actigraphy data revealed a dose-dependent trend toward lower activity levels and a statistically significant decrease in active time per day in subjects in the highest dose treatment arm. Although the reduction of activity levels in the treatment group was unexpected, this study further demonstrated the sensitivity of objective assessments in comparison to traditional questionnaire-based approaches. It is noteworthy that there were significant technical limitations in the device used in this study that may have contributed to the seemingly paradoxical results. The activity sensor used in this study compiled and stored data in 15 minute epochs; while this has no impact on the measurement of overall activity, grouping activity data into epochs this length reduced the

[redacted]

resolution of the activity data, and limits opportunities for the assessment of activity patterns. Other actigraphy studies of patients with chronic illness have demonstrated that more symptomatic patients have generally both a reduction in activity when active and are less still when resting, compared to healthier patients (Maurer 2009). If HF patients spend most of their time at rest, treatment related increases in physical activity when active may be offset by a concomitant reduction in movement when at rest. As a result, this can appear as a simple decrease in overall activity if accelerometry data is compiled and averaged over large periods of time (when long measurement epochs are used).

Sleep and HF

Sleep is the companion HR-QOL function to physical activity, and is equally important as it fills the portion of the day not available for physical activity. Multiple studies of sleep dysfunction in heart failure patients have demonstrated an inextricable association between sleep function, mortality, and sleep-disordered breathing (Penzel 2015). Other studies also suggest that sleep apnea may lead to the progression of cardiac dysfunction in HF patients (Berman 1991). The adverse effect on cardiac function probably arises from repetitive apneas causing excessive stimulation of the sympathetic nervous system, arterial oxyhemoglobin desaturation and increases in systemic blood pressure (Bradley 1996). The incidence of sleep-disordered breathing, specifically central sleep apnea, is higher in the congestive heart failure (CHF) population where it has been demonstrated to be an independent predictor of mortality (Kasai 2012, Lanfranchi 1999). There is also evidence of a complex association between ventricular arrhythmias and sleep-disordered breathing (Sin 1999) and data that suggests the observed increase in mortality is the result of increased incidence of sudden death (Yumino 2009, Kasai 2012). In addition, the discontinuity of sleep by frequent arousals may also lead to the development of excessive daytime sleepiness and fatigue in CHF patients with sleep apneas (Hanly 1995). In HF patients, poor sleep quality and continuity was correlated with reduced daytime activity, self-reported physical function, and mental health (Redeker 2005).

1.2 Purpose

The purpose of this study is to investigate the effects of initiation of sacubitril/valsartan vs enalapril treatment on objective measures of both waking activity and sleep in subjects with heart failure with reduced ejection fraction.

2 Study objectives and endpoints

Measurements will be done at weeks -1, 1, 8, 9, and 16. Week 8 is considered the primary time point (end of double blind period).

[redacted]

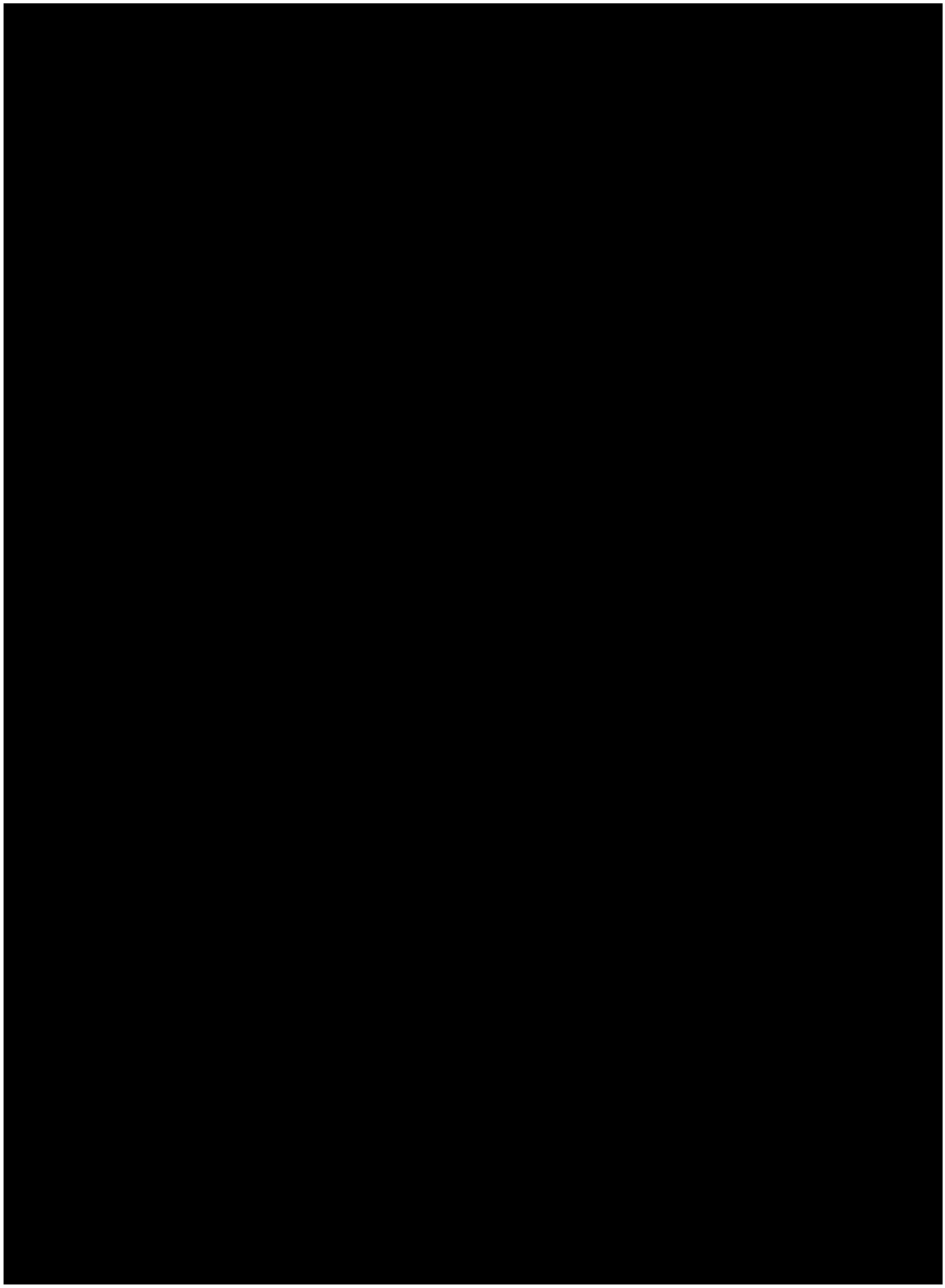
2.1 Objectives and related endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s) • The primary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on physical activity during the waking hours as an objective measure of physical function.	**Endpoint(s) for primary objective(s)** • The primary endpoint is the change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1) and the final randomized treatment phase measurement (mean of endpoint data collected each day during week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 min period collected during the most active 30 minutes of each day).
Secondary Objective(s) • The secondary objective is to evaluate the effect of initiation of sacubitril/valsartan treatment versus enalapril on subjects' sleep as an objective measure of physical function.	**Endpoint(s) for secondary objective(s)** **<u>The secondary endpoints include:</u>** • Change in mean activity (counts per minute) during sleep between baseline phase (mean of data collected during week -1) and the final randomized treatment phase measurement (mean of data collected during week 8), as measured by actigraphy (activity counts per minute during daily sleep period, wrist-worn accelerometer). • The change in mean activity during sleep between baseline phase (mean of data collected during the nights of week -1) and each randomized treatment and open label phase measurement, as measured by actigraphy (Week 1, 9, and 16) (activity counts per minute during daily sleep period, wrist-worn accelerometer). • The change in mean activity counts collected during the most active 30 minutes of the subject's day between

[redacted]

Objective(s)	Endpoint(s)
	baseline phase (mean of data collected each day during week -1) and each randomized treatment and open label phase measurement (Week 1, 9, and 16), as measured by wrist worn accelerometer collected actigraphy.
[redacted]	



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3 Investigational plan

3.1 Study design

This study is a multicenter, randomized, double-blind, double dummy, parallel group, active-controlled 8-week study with open label extension using medical device-grade subject worn sensors to measure waking and sleeping physical activity in the ambulatory outpatient setting. The 18 week study duration will consist of a 2-week baseline observation phase (with subjects continuing their current heart failure drug therapy), followed by an 8 week blinded treatment phase during which subjects are randomized (1:1) to either initiation of sacubitril/valsartan treatment or enalapril comparator, and finally an 8 week open label extension phase during which all subjects are treated with sacubitril/valsartan. Each subject will undergo a 36 hour washout period [during which ACEi (Angiotensin converting enzyme inhibitor), or study drug will be withheld] before the start of the randomized, blinded treatment phase, and again before beginning the open label extension phase. The study will include 8 office visits and 5 tele-visits.

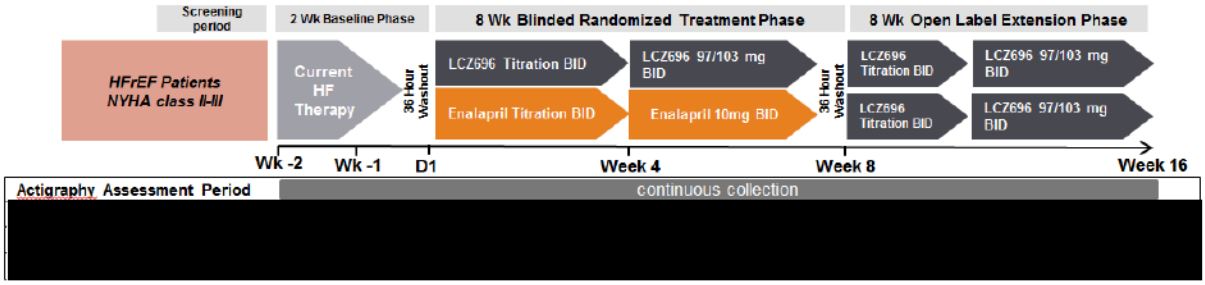
Subjects will wear a wrist-worn actigraphy device continuously for the 18 week duration of the study, from the time of enrollment (the start of the 2 week baseline phase) to the end of the open-label extension phase (end of treatment week 16). During this 18 week interval, the devices will be exchanged five times during five study visits, to guard against data loss and ensure adequate battery life. Data will be collected continuously during the trial and although only data collected during assessment periods will contribute to prospectively defined endpoints, other data may be assessed in future analysis of patterns observed during the study. Additionally, continuous wear reduces opportunities for lapses in compliance while adding very minimal assessment burden for subjects.

Each assessment period is seven contiguous days. This will allow for continuous actigraphy recording over the seven day period, [redacted]

[redacted]

[redacted]

Figure 3-1 Study design



[redacted]

3.2 Rationale for study design

The design of the study facilitates the assessment of change in sequential daily physical activity, [redacted] HF symptoms and health-related quality of life; between baseline to select time point assessment periods after randomized, blinded assignment to treatment with sacubitril/valsartan versus the active comparator enalapril. Assessment of the primary endpoint at 8 weeks captures the early impact of initiation of sacubitril/valsartan versus enalapril, which is the focus of the study.

Waking activity will be the primary endpoint, and sleep activity (a measure of sleep disturbance) is the secondary endpoint. Actigraphy, which has been well characterized for the measurement of both daytime and sleep physical activity variables, will be used to inform the primary and secondary endpoints.

[redacted]

Prior to randomization, there will be a 2 week phase where device familiarization and baseline assessment will be completed. The initial baseline week will provide an opportunity for the subjects to become familiar and acclimated to the testing devices and assessment routines, prior to entering the baseline phase of the study. Data from the second week of this phase, the 'baseline phase' (Week -1) will be considered as the baseline value for comparison to subsequent periods. Data collected outside of the defined measurement periods will be excluded from analysis for the defined study endpoints.

The 36-hour wash-out interval after randomization and before entering the open-label extension is required per the FDA approved USPI label because there is a potential for increased risk for angioedema in subjects who receive both an ACE inhibitor and the combination of sacubitril/valsartan.

The randomized comparison phase of 8 weeks provides the direct assessment of the initial and early changes associated with sacubitril/valsartan treatment to treatment with the active comparator enalapril.

[redacted]

The open label phase of 8 weeks provides the opportunity for every subject to receive sacubitril /valsartan. This results in one group of subjects that will receive sacubitril/valsartan for a total of 16 weeks, providing information on the endpoints after this duration of continuous therapy. It also provides the opportunity to evaluate changes after initiating sacubitril/valsartan in a group of subjects who all had been previously receiving enalapril treatment for 8 weeks.

The subject population will be described in more detail in the Section 4 below.

[redacted]

3.4 Rationale for choice of comparator

Treatment with ACEi has been well established as the standard of care for renin–angiotensin–aldosterone system (RAAS) blockade and is recommended by treatment guidelines as a 1A recommendation for all subjects with CHF and reduced left ventricular ejection fraction (LVEF), unless ACEi-intolerant. Additionally, ACEi may reduce aortic stiffness by opposing vasoconstrictive, hypertrophic, and profibrotic effects of angiotensin II on the vessel wall.

[redacted]

3.5 Purpose and timing of interim analyses/design adaptations

Not applicable.

3.6 Risks and benefits

The risk to subjects in this trial will be minimized by compliance with the eligibility criteria and study procedures, close clinical monitoring, and the provision of rescue options.

Experience in the PARADIGM-HF trial; both in the run-in phase as well as the double-blind randomization phase indicated that the major risks associated with the treatment of sacubitril/valsartan are renal dysfunction, hyperkalemia, and hypotension. Results from the TITRATION study indicated that subjects whom are ACEi or ARB naïve are at an increased risk of experiencing these adverse events.

In this study, the risk of experiencing renal dysfunction, hyperkalemia, and hypotension are mitigated in this study by appropriate up-titration of the drug at weeks 2, 4, 8, 10, and 12. The risks are further mitigated by appropriate inclusion and exclusion criteria. Subjects are excluded if they have a potassium > 5.2 mmol/l at screening.

Sacubitril/valsartan may also cause angioedema. The risk of developing angioedema is increased if subjects take both an ACEi and sacubitril/valsartan. To decrease this risk, all subjects will undergo a 36 hour wash out period before entering the randomized phase epoch and before continuing into the open-label treatment epoch to minimize the interaction between an ACEi and sacubitril/valsartan in potentiating the development of angioedema.

All subjects will be allowed to continue receiving the rest of their background cardiovascular (CV) medications throughout the study. Subjects will be randomized to study treatment only after the investigator has confirmed the subject is on stable treatment with guideline-directed therapy for heart failure with reduced ejection fraction (HFrEF), other than ACEis and ARBs, which will ensure that subjects are receiving appropriate treatment for their heart failure.

In the PARADIGM-HF study, sacubitril/valsartan reduced the risk of cardiovascular (CV) death, HF hospitalization and due to these significant results, sacubitril/valsartan is now indicated to reduce these risks in subjects with chronic heart failure (NYHA class II-IV) and reduced ejection fraction.

4 Population

The study population will consist of outpatient male and female subjects, between 18 - 80 years of age, with HFrEF NYHA class II or III. The goal is to have a total of approximately 136 subjects randomized, in approximately 25-30 centers in the United States. Subjects must met all inclusion and none of the exclusion criteria.

4.1 Inclusion criteria

Subjects eligible for inclusion in this study must fulfill all of the following criteria:

[redacted]

1. Written informed consent must be obtained before any assessment is performed.
2. Men and women between 18 and 80 years of age
3. Subjects diagnosed with NYHA class II or III heart failure and with reduced ejection (HFrEF) (Reduced ejection is defined as left ventricular EF ≤ 40%. LVEF ≤40% may be determined via any local measurement within the past 6 months prior to signing consent, using echocardiography, multi gated acquisition scan (MUGA), CT scanning, MRI or ventricular angiography provided no subsequent study documenting an EF of >40%. If the EF measurement is expressed as a value range, the average of the range endpoint values should be used as the EF).
4. Subjects must be a candidate for treatment with sacubitril/valsartan as per USPI
5. Subjects must be living in a traditional residence, apartment, or non-communal adult home where they can move about freely and frequently and are primarily responsible for scheduling their sleep and daily activities

4.2 Exclusion criteria

Subjects fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

1. Subjects with a history of hypersensitivity to any of the study drugs, including history of hypersensitivity to drugs of similar chemical classes, or allergy to ACEIs, ARBs, or NEP inhibitors as well as known or suspected contraindications to the study drugs.
2. Subjects with a history of angioedema drug related or otherwise
3. Subjects with symptomatic hypotension or systolic blood pressure <100 mmHg at screening or <95 mmHg at randomization.
4. Subjects with any conditions in skin or upper extremities which would limit the ability to tolerate a wrist-worn actigraphy device on the nondominant arm for 24 hours/day for the duration of the study.
5. Subjects unwilling or unable to wear and operate the study measurement devices for the phases required.
6. Subjects who are currently hospitalized, or were discharged from the hospital within 4 weeks prior to enrollment.
7. Subjects who are already taking sacubitril/valsartan
8. Subjects who are nonambulatory or use mobility assistive devices such as motorized devices, wheelchairs, or walkers. The use of canes for stability while ambulating is acceptable.
9. Subjects with physical activity impairment primarily due to conditions other than heart failure such as:
    - Exertional angina
    - inflammatory or degenerative joint disease
    - gout
    - peripheral vascular disease

[redacted]

- neurologic diseases affecting activity or mobility

10. Subjects with nontypical circadian behavioral patterns (for example: shift workers actively rotating shifts, subjects with non-24-hour sleep wake disorder as result of blindness)
11. Subjects with tremor, rigor or mobility limitations affecting the nondominant arm (e.g. due to Parkinson's disease, joint contractures, paralysis, injury etc.)
12. Subjects with chronic obstructive pulmonary disease (COPD) who require supplemental oxygen.
13. Subjects using a continuous positive airway pressure (CPAP) devices or similar technology for treatment of sleep disorders
14. Subjects unwilling or unable to refrain from the use of prescription and/or over the counter (OTC) sleep aids for the duration of the study
15. Subjects with body mass index (BMI) > 35
16. Subjects with chronic persistent atrial fibrillation.
17. Subjects with diabetes who are taking aliskiren.
18. Subjects receiving nesiritide
19. Subjects taking bile acid sequestering agents such as cholestyramine or colestipol (to avoid interference with study drug absorption).
20. Subjects who are enrolled or participating as a subject in any other clinical trial involving any investigational agent or investigational device within 30 days before screening.
21. Subjects with a potassium > 5.2 mEq/L at screening.
22. Subject with a history of malignancy of any organ system who have a life expectancy of less than 1 year.
23. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test.
24. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception during dosing and for 7 days after stopping of study medication. Highly effective contraception methods include:
    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    c. Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
    d. Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS) or other forms of hormonal contraception that have comparable efficacy (failure rate $<1\%$), for example hormone vaginal ring or transdermal hormone contraception.

[redacted]

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking investigational drug.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

5 Treatment

5.1 Study treatment

5.1.1 Investigational and control drugs

All eligible subjects will be randomized to receive either sacubitril/valsartan or enalapril. The following study treatment will be provided:

Table 5-1 Investigational and comparator treatment during the double-blind epoch

Treatment Arm	Number of Subjects	Minimum dose	Maximum dose	Frequency	Formulation	Administration Route
sacubitril/valsartan*	68	24/26 mg	97/103 mg	BID	Tablet	Oral
sacubitril/valsartan matching placebo						Oral
enalapril	68	2.5 mg	10 mg	BID	Tablet	Oral
enalapril matching placebo						Oral

*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

Table 5-2 Treatment dose levels during the double-blind epoch

Dose Level	Sacubitril/valsartan*	Enalapril
1	24/26 mg or matching placebo BID	2.5 mg or matching placebo BID
2	49/51 mg or matching placebo BID	5 mg or matching placebo BID
3	97/103 mg or matching placebo BID	10 mg or matching placebo BID

[redacted]

Dose Level	Sacubitril/valsartan*	Enalapril
*Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.		

Both sacubitril/valsartan and enalapril and their matching placebos will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulations governing handling of investigational treatments, and will be dispensed by the study physician.

Sacubitril/valsartan and enalapril will be packaged separately to limit the number of pack types which will allow more flexibility in the drug supply process to cover all the different treatment possibilities (treatment arm and medication dose level), see Table 5-2 and Table 5-4.

Packaging type is described below:

- sacubitril/valsartan and its matching placebo will be provided in high-density polyethylene (HDPE) bottles.
- enalapril 2.5 mg and its matching placebo will be provided in HDPE bottles.
- enalapril 5 mg and 10 mg and its matching placebos will be provided in blister packs.

Each participating site will be provided with an investigational drug supply containing Dose Levels 1, 2, 3 and their matching placebos. Bottles and blister packs will be numbered and assigned via an interactive response technology (IRT). Treatment for the day of randomization and all visits forward will be assigned via IRT.

All subjects will begin the study on Dose Level 1. At each subsequent study visit during the double-blind epoch, the study physician will sequentially up-titrate the study drug dose (based on clinical tolerance and the USPI) to achieve the desired dose of Dose Level 3 (97/103 mg sacubitril/valsartan BID or 10 mg enalapril BID).

Subjects not tolerating escalation from Dose Level 1 to Dose Level 2 (or Dose Level 2 to Dose Level 3) can be titrated down to the next lower Dose Level (including active medication and matching placebos), if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

This study is designed as a double-blind, double-dummy trial to ensure blinding during the entire course of the study. To maintain the blinding, subjects will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily.

Table 5-3 Investigational treatment during the open label epoch

Treatment	Number of subjects	Minimum dose*	Maximum dose	Frequency	Formulation	Route
Open-label (sacubitril/ valsartan)	136	24/26 mg	97/103 mg	BID	Tablet	Oral
*sacubitril/valsartan 24/26 mg BID (Dose Level 1) will be given to subjects who completed the double-blind treatment epoch on Dose Level 1 and is also available if down-titration is required.						

[redacted]

Table 5-4 Treatment Dose Levels during the open-label epoch

Dose Level*	Sacubitril/valsartan
1	24/26 mg BID
2	49/51 mg BID
3	97/103 mg BID
*sacubitril/valsartan 24/26 mg BID (Dose Level 1) will be given to subjects who completed the double-blind treatment epoch on Dose Level 1 and is also available if down-titration is required.	

Open-label sacubitril/valsartan will be packaged and labeled by the sponsor in accordance with the US Code of Federal Regulation governing handling of investigational treatments, and will be dispensed by the study physician. Open-label treatment will be provided for 8 weeks.

All subjects entering the open label-treatment epoch will be given sacubitril/valsartan 49/51 mg BID (Dose Level 2) unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these subjects will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID dose (Dose Level 1). At each subsequent study visit during the open-label epoch, the study physician will sequentially up-titrate the study drug dose (based on clinical tolerance and the USPI) to achieve the targeted desired dose of 97/103 mg sacubitril/valsartan BID (Dose Level 3).

During the open label phase, patients not tolerating the escalation from Dose Level 1 to Dose Level 2 (or Dose Level 2 to Dose Level 3) can be titrated down to the next lower Dose Level, if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

5.1.2 Additional treatment

The protocol requires subjects to continue their current heart failure drug therapy, during the 2-week baseline phase.

5.2 Treatment arms

Subjects will be assigned at Day 1 to one of the following two treatment arms in a 1:1 ratio:

- sacubitril/valsartan; or,
- enalapril

Subjects will be assigned at Week 8 to open label extension phase during which all subjects will receive:

- sacubitril/valsartan

[redacted]

5.3 Treatment assignment and randomization

At visit 3 all eligible subjects/subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study drug to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subject and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Drug Supply Management using a validated system that automates the random assignment of medication numbers to packs containing the investigational drug(s).

The randomization scheme for subjects will be reviewed and approved by a member of Biometrics USCDMA.

5.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments, data analysts and the Clinical Trial Team (CTT) will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study with the exception of the IRT provider generating the randomization code. (2) The identity of the treatments will be concealed by the use of investigational treatments that are identical in packaging, labeling, and schedule of administration, appearance, taste and odor.

A double-dummy design is used because the identity of the study drug cannot be disguised, as the drug products are visibly different. To maintain the blinding, subjects will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily.

Unblinding will only occur in the case of subject emergencies (see Section 5.6) and at the conclusion of the study.

5.5 Treating the patient

Sponsor qualified medical personnel will be readily available to advise on trial related medical questions or problems.

5.5.1 Subject Numbering

Each subject is uniquely identified in the study by a combination of his/her center number and subject number. The center number is assigned by Novartis to the investigative site. Upon signing the informed consent form, the subject is assigned a subject number by the investigator. At each site, the first subject is assigned subject number 1, and subsequent subjects are assigned

[redacted]

consecutive numbers (e.g. the second subject is assigned subject number 2, the third subject is assigned subject number 3). The investigator or his/her staff will contact the IRT and provide the requested identifying information for the subject to register them into the IRT. Only the assigned subject number must be entered in the field labeled "Subject ID" on the EDC data entry screen (e.g. enter '1', '2', etc.). Once assigned to a subject, the subject number will not be reused. If the subject fails to be randomized for any reason, the IRT must be notified within 2 days that the subject was not randomized.

5.5.2 Dispensing the study drug

Each study site will be supplied with study drug in packaging of identical appearance.

Novartis will supply each study site with the randomized and open-label treatment in clinical trial packaging. The study drug packaging has a 2-part label. A unique randomization number is printed on each part of this label which corresponds to one of the "n" treatment arms and a [specific visit or dose/dose level]. Investigator staff will identify the study drug package(s) to dispense to the subject by contacting the IRT and obtaining the medication number(s). Immediately before dispensing the package to the patient, investigator staff will detach the outer part of the label from the packaging and affix it to the source document (Drug Label Form) for that subject's unique subject number.

5.5.3 Handling of study and additional treatment

No additional treatment is provided as part of the study

5.5.3.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO Quality Assurance. Medication labels will include storage conditions but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.3.2 Handling of additional treatment

Not applicable.

[redacted]

5.5.4 Instructions for prescribing and taking study treatment

Novartis will supply the investigators with all medications sufficient for the course of the study. Subjects will be provided with medication packs containing study drug corresponding to their assigned treatment arm and dose level, sufficient to last until the next scheduled visit. Study medication should be taken with a glass of water with or without food. If the patient misses taking any study drug dose, he/she should take it as soon as possible, unless it is within 4 hours for the following scheduled dose. In this case, the patient should skip the missed dose and return back to his/her regular study drug administration schedule.

In order to adequately blind the study, patients will be required to take their assigned active treatment tablet along with placebo matching the opposite treatment twice daily. Subjects will be instructed to take a total of two tablets by mouth twice a day for the duration of the double-blind treatment epoch, as follows:

- One tablet from the sacubitril/valsartan – sacubitril/valsartan matching placebo pack, and;
- One tablet from the enalapril - enalapril matching placebo pack

Table 5-5 summarizes the study drug that will be taken during the double-blind treatment epoch by visit and Table 5-6 summarizes the study drug that will be taken during the open-label treatment epoch.

[redacted]

Forced-titration will proceed according to the following table:

Table 5-5 Study drug dispensed during double-blind treatment epoch

Visit	Dose Level	Sacubitril/valsartan**	Enalapril	Route	Timing
Rando/Visit 3	1[a,b]	24/26 mg or matching placebo BID	2.5 mg or matching placebo BID	Oral	AM & PM
Week 2/Visit 5	2[c]/3[d]	49/51 mg / 97/103 mg or matching placebo BID	5 mg or matching placebo BID	Oral	AM & PM
Week 4/Visit 6	2[c]/3[d]	49/51 mg / 97/103 mg or matching placebo BID	10 mg or matching placebo BID	Oral	AM & PM

**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.

a. Initial starting dose (Level 1) Eligible patients will be randomized via IRT to either sacubitril/valsartan or enalapril, Dose Level 1.

b. Available after Rando/Visit 3 to end of double-blind treatment epoch only if Dose Levels 2 and 3 are not tolerated despite modification of other non-disease-modifying HF medications and re-challenge.

c. Only if Dose Level 3 is not tolerated despite modification of other non-disease-modifying HF medications and re-challenge.

d. This target Dose Level must be maintained for as long a duration as possible. If down-titration is necessary due to side effects, the patient should be re-challenged as soon as medically possible per the investigator's judgment.

- At Randomization on Day 1 (Visit 3, enrolled subjects will be randomized via IRT to either sacubitril/valsartan or enalapril. All subjects will start at Dose Level 1 (2.5 mg enalapril or 24/26 mg sacubitril/valsartan, BID).
- At Week 1 (Visit 4), subjects will have a telephone visit.
- At Week 2 (Visit 5), subjects will be force-titrated to the next dose, Dose Level 2 (5 mg enalapril or 49/51 mg sacubitril/valsartan, BID) or Dose Level 3 (10 mg enalapril or 97/103 mg sacubitril/valsartan, BID) and remain on this dose through the evening dose prior to Week 4 (Visit 6).
- At Week 4 (Visit 6), subjects will be force-titrated to the next dose, Dose Level 2 (5 mg enalapril or 49/51 mg sacubitril/valsartan, BID) or Dose Level 3 (10 mg enalapril or 97/103 mg sacubitril/valsartan, BID) and remain on this dose through the evening dose prior to Week 8 (Visit 8).
- At Week 6 (Visit 7), subjects will have a telephone visit.
- All subjects that complete the 8 week double-blind treatment epoch will proceed into the 8-week open-label epoch on sacubitril/valsartan.
- At Week 8 (Visit 8), Drug accountability will be performed and all double-bind treatment medication will be returned to the site.

[redacted]

- Open-label sacubitril/valsartan will be dispensed at Week 8 (Visit 8) with subject's instructions **NOT** to start their open label-treatment until after completing a 36-hour wash out. All patients will have the wash out in order to maintain the blinding of the core study.

All dose levels will be available throughout the study. Dose adjustments to lower dose levels may be made at any time at both scheduled and unscheduled visits only if indicated for blood pressure control/tolerability reasons.

All study treatment assigned by the IRT will be recorded/databased in the IRT.

All dosages prescribed and dispensed to the subject and all dose changes during the study must be recorded in the IRT and on the Dosage Administration Record eCRF.

Study medication should be taken twice daily with a glass of water with or without food.

If the subject misses taking any study drug dose, he/she should take it as soon as possible and within 4 hours of the scheduled dose time. If the patient is unable to take the missed dose within 4 hours of the scheduled dose time, he/she should skip the missed dose and return back to his/her regular study drug administration schedule.

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and the validity of the study. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed.

Table 5-6 Study drug dispensed during open-label treatment epoch

Visit	Dose Level	Sacubitril/ valsartan**	Route	Timing
Week 8/Visit 8	1	24/26 mg	Oral	AM & PM
Weeks 10-16	2	49/51 mg	Oral	AM & PM
	3	97/103 mg	Oral	AM & PM
**Investigational product labeling for sacubitril/valsartan dose levels is based on the total contribution of both components of sacubitril/valsartan and reads, 50 mg, 100 mg and 200 mg. This is equivalent to the sacubitril/valsartan dose levels 24/26 mg, 49/51 mg and 97/103 mg, respectively.				

- All subjects entering the open-label treatment epoch will start open-label treatment on sacubitril/valsartan 49/51 mg BID (Dose Level 2) unless they completed the double-blind treatment epoch on Dose Level 1. Instead, these subjects will enter the open-label epoch on sacubitril/valsartan 24/26 mg BID dose (Dose Level 1).
- Study treatment will be force-titrated every 2 weeks to reach the target dose of sacubitril /valsartan 97/103 mg BID (Dose Level 3).

[redacted]

Schedule and dose adjustments will only be allowed if, in the investigator's judgement, the adjustment/elimination of concomitant medications is not possible or does not alleviate the side effects of concern. See Section 5.5.5.

5.5.5 Permitted dose adjustments and interruptions of study treatment

Every attempt should be made to maintain subjects on the target study drug dose level for as long as possible throughout the study. If, however, in the opinion of the investigator, a subject is unable to tolerate the protocol-specified target dose, the investigator should consider whether dose adjustments of concomitant medications may rectify the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, the investigator may down-titrate the dose of the study drug to the previous dose level. If needed, the study drug may be stopped completely, if this occurs, the subject should return to the clinic as soon as possible, after discontinuation of study drug, for an end of study visit. Subjects may restart their current dose of study drug following an interruption of treatment, based on investigator judgment.

Study drug dose level adjustments should be mainly based on overall safety and tolerability with special focus on:

- Hyperkalemia
- Symptomatic hypotension
- Clinically significant decrease in eGFR/increase in serum creatinine (defined as a serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR).

These changes must be recorded on the Dosage Administration Record CRF.

Adjustment of study drug dose level

Table 5-7 Safety and tolerability guidance for dose adjustments

Parameter	Criteria
Potassium level	K > 5.3 mEq/L
Kidney function	• eGFR reduction ≥ 35% compared to baseline; OR, serum creatinine of ≥0.5mg/dl with at least a 25% decrease in eGFR
Blood pressure	• No symptomatic hypotension or SBP < 90 mmHg
Adverse events (AEs) or conditions	• No postural symptoms or any conditions that preclude continuation according to the investigator's judgment

[redacted]

Every attempt should be made to maintain subjects on target study drug Dose Level 3 for as long as possible throughout the study. If, however, in the opinion of the investigator, a patient is unable to tolerate the protocol-specified target dose, the investigator will manage the patient's treatment according to the below guidelines:

Steps:

1. **Adjust Concomitant Medications**
   - Dose adjustments/elimination of concomitant medications may remedy the situation before reducing the dose of study treatment. If adjustment of the concomitant medications is not possible or does not alleviate the side effects of concern, THEN;

2. **Adjust Study Treatment Dose Level**
   - Down-titrate study treatment to the previous dose level. The subject may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks.
   - A re-challenge to titrate back up to the target dose level should be attempted at 2 weeks, or when subject is deemed stable. THEN:

3. **Further Adjust Study Treatment Dose Level**
   - If tolerability issues are not alleviated despite down-titration by one dose level, the investigator may down-titrate further to the next lower study treatment dose level. The subject may continue receiving the lower dose level for a recommended period of 1 to a maximum of 4 weeks. See Step 5.
   - Again, once stable, the subject should be re-challenged with up-titration to the next higher dose level in an attempt to gradually bring the subject back to the target study treatment dose level (Dose Level 3).
   - The investigator may choose the next dose level for down- or up-titration according to his or her clinical judgment.

4. **Stopping Study Treatment**

   If needed, the study treatment may be stopped completely, however, every effort must be made to complete an end of study visit and obtain follow up health status information for any subject that withdraws from the study. See Section 5.6.2

5. **Study drug restart after temporary treatment interruption**
   - Once the investigator considers the subject's condition appropriate for receiving the study drug, the investigator should re-start the subject on study treatment at the most appropriate and allowable dose level per his/her medical judgment.
   - If tolerated, the subject should be titrated up to the next dose level every 1 to 4 weeks, as per the investigator's judgment.

- In some instances, Dose Level 1 or 2 could be maintained if the investigator considers that the subject's condition would not allow any further up-titration to the target dose of study medication (Dose Level 3). In this case, it would be acceptable to maintain the subject at Dose Level 1 or 2, whichever is the higher and tolerated dose level by the subject, but reasons for not getting to Dose Level 3 need to be captured in the eCRF.
- Should the subject not tolerate the re-start study drug dose level, he/she may be down-titrated again (if appropriate) or discontinued from study treatment.

Subjects re-started on the study drug will retain their original randomization and study identification numbers.

The IRT must be contacted to register any changes in the subject's study treatment dose level, including in cases of temporary and permanent withdrawal or re-start of the study drug, and to obtain the medication numbers of the study drug supplies required for the new study treatment dose level. All dose changes and interruptions must also be recorded on the Dosage Administration Record eCRF.

Study visits should occur as close as possible to the pre-defined visit and time schedule described in Table 6-1. The timeframe between the regular visits should be maintained as scheduled, irrespective of the number of unscheduled visits that may be performed in between, or dose interruptions that may occur.

In case of pregnancy discovered during the study, the patient should be instructed to stop taking the study drug immediately. (See Sections 6.5.6 and Section 7.4)

5.5.6 Rescue medication for worsening heart failure

At any time during the 8 week randomized, double-blind treatment epoch, investigators have the option to withdraw subjects from study treatment if they develop signs and symptoms of worsening heart failure for which the investigator would like to administer appropriate therapy.

- Appropriate adjustments, intensifications, or additions to concomitant medications should be considered before deciding to withdraw the subject from study treatment.
- **Subjects CANNOT receive ACE is and/or ARBs during the study. These medications can ONLY be administered if the investigator believes that the subject needs to be withdrawn from study treatment so that they may be treated with these therapies due to signs and symptoms of worsening heart failure.**
- **A 36 hour wash-out period is required if the investigator chooses to withdraw the subject from double-blind treatment and switch to sacubitril/valsartan or ACEi due to symptoms of worsening heart failure.**
- Use of rescue medication must be recorded on the appropriate Concomitant Medications eCRF.

Investigators will use clinical judgement to determine if subject's condition requires closer monitoring. Unscheduled visits are permitted as needed.

[redacted]

5.5.7 Concomitant medication

The investigator must instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded in the Concomitant Medications or Surgical and Medical Procedures eCRF as appropriate.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started.

ACEi and ARBs:

The concomitant use of open-label ACEI or ARB is strictly prohibited while the subject is receiving study medication. If the investigator believes that addition of an ACEI or ARB is necessary, then study drug must be discontinued. Study medication should be stopped 36 hours prior to addition of open-label ACEI.

Other heart failure and cardiovascular medication

If a subject's condition warrants any change in concomitant heart failure or cardiovascular medications, changes may be made at the investigator's discretion. Oral diuretics may be used and may be adjusted throughout the study duration at the discretion of the investigator.

Medications and substances known to raise potassium levels

Potassium sparing diuretics, potassium supplements, aldosterone antagonists, and any other medications known to raise potassium levels should be used with caution while the subject is receiving study medication due to the increased possibility of occurrence of hyperkalemia. Salt substitutes containing potassium chloride are also to be avoided when possible. Potassium levels should be monitored regularly especially in those who are receiving these medications.

Concomitant administration of renin inhibitors, such as aliskiren, is prohibited in patients with diabetes mellitus.

Phosphodiesterase-5 (PDE-5) inhibitors

PDE-5 inhibitors should be used with caution while the subject is receiving study medication due to the increased possibility of occurrence of hypotension.

Nesiritide and intravenous nitrates

The concomitant admission of sacubitril/valsartan with nesiritide or intravenous nitrates has not been studied. Given biological interaction between sacubitril and BNP, concomitant use of nesiritide (recombinant BNP) is prohibited. Intravenous nitrates are also prohibited.

5.5.8 Prohibited medication

Use of the treatments displayed in the table below and Appendix 9 is NOT allowed after the baseline phase. Please note the list of prohibited medication is not exhaustive. If you have any questions, the medical monitor should be contacted.

[redacted]

Table 5-8 Prohibited medication (Please also see Appendix 9)

Medication	Prohibition period	Action taken
ACEIs Inhibitors: benazepril, enalapril, Lisinopril, captopril, Ramipril, Fosinopril, Moexipril Quinapril, Trandolapril	Duration of study	Discontinue study treatment
Aliskiren (only subjects with concurrent diabetes)	Duration of study	Discontinue study treatment
Bile acid sequestering agents (such as cholestyramine or colestipol)	Duration of study	Switch to alternate agent to avoid interference with study drug absorption. If use of alternate agent is not appropriate, do not randomize or discontinue study drug treatment.
Nesiritide and intravenous nitrates	Duration of study	Do not randomize. If hospitalized, either interrupt or discontinue study treatment. Nesiritide and intravenous nitrates have not been studied. Oral, topical and sublingual nitrates are permissible.
Prescription and non-prescription medications taken for insomnia or to induce sleep *(See Appendix 9 for details and examples)*	Duration of study	Discontinue study treatment

5.5.9 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the patient safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a patient, he/she must provide the requested patient identifying information and confirm the necessity to break the treatment code for the patient. The investigator will then receive details of the investigational drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the Study Team that the code has been broken.

[redacted]

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- study drug name (if available)
- patient number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

5.6 Study completion and discontinuation

5.6.1 Study completion and post-study treatment

A subject will be considered to have completed the study when the subject has completed the last visit planned in the protocol (Visit 13). At the end of study visit, subjects will be asked to return all remaining study drug. The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.6.2 Discontinuation of study treatment

Subjects may voluntarily discontinue the study drug for any reason at any time.

Study drug must be discontinued under the following circumstances:

- Withdrawal of consent
- Pregnancy
- Use of prohibited concomitant medication
- Any protocol deviation that constitutes a risk to the subject
- Investigator believes that continuation of study drug may be detrimental to the subject's well-being
- Study medication may be discontinued at the investigator's discretion if any of the following occur:
- Any severe suspected drug related AE
- Suspected occurrence of angioedema. A subject with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator to determine if it constitutes a reason for discontinuation of study medication.

Depending on the serum potassium, blood pressure, or eGFR, subjects may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued; or, if appropriate, have potentially contributing agents adjusted. Refer to appendices for treatment guidelines for hyperkalemia, hypotension or renal dysfunction, respectively.

In the case of study drug discontinuation, every effort must be made to complete an end of study visit and obtain follow up health status information for any subjects that withdraw from the

[redacted]

study. If the subject refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the subject expressly refuses such contacts.

The investigator must notify the sponsor of any study drug discontinuation and record it on the Dosage Administration Record eCRF.

If discontinuation of study treatment occurs, the subject should NOT be considered withdrawn from the study. The subject should return to the clinic as soon as possible, after discontinuation of study drug, for an end of study visit. All assessments from the final visit (Visit 13) in the visit schedule of assessments (Table 6-1) must be completed and recorded in the eCRF. The Study Completion eCRF will also need to be completed. The investigator must determine the primary reason for the subject's premature discontinuation of study treatment and record this information in the eCRF.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

The investigator must also contact the sponsor to register the subject's discontinuation from study treatment.

5.6.3 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent from the study is defined as when a subject:

- Does not want to participate in the study anymore
  and
- Does not want any further visits or assessments
  and
- Does not want any further study related contacts
  and
- Does not allow analysis of already obtained biologic material

In this situation, the investigator must make every effort (e.g. telephone, e-mail, letter) to determine the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the patient's study withdrawal should be made as detailed in the assessment table below.

[redacted]

5.6.4 Loss to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject cannot be considered as lost to follow-up until the time point of his/her scheduled end of study visit has passed.

5.6.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit risk assessment of participating in the study, practical reasons, or for regulatory or medical reasons (including slow enrolment). Should this be necessary, the subject must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

6 Visit schedule and assessments

All assessments are listed in Table 6-1. Assessments that are to be reported in the clinical database are marked with an 'X'. Assessments that will only be reported in the source documentation are marked with an 'S'. Subjects should be seen for all visits on the designated day or as close to it as possible, with an allowed visit window of ± 3 days for visits 1, 3, 5, 6, 8, 10, 11, and 13.. Study staff should call subjects for all tele-visits on the designated day or as close to it as possible, with an allowed visit window of ± 3 day for visits 2, 4, 7, 9 and 12.

Eligible subjects may start study treatment once it is confirmed that they meet all inclusion criteria and none of the exclusion criteria.

Subjects may be contacted for safety evaluations for 30 days after the last dose. Documentation of attempts to contact the subject should be recorded in the source documentation. Unscheduled visits for safety/medication evaluation/unscheduled assessments are permitted at any time during the study.

[redacted]

Table 6-1 Assessment schedule

Phase	Screening/Baseline		Randomized Treatment						Open Label Extension					Unscheduled◊
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13/EOS	
Days	- Day 14	- Day 7 to - Day 1	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56	Day 63	Day 70	Day 84	Day 98	Day 112	UNSCHED
Time of Visit	Week -2	Week -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	UNSCHED
Visit type	Office	Tele-visit	Office (randomization)	Tele-visit	Office	Office	Tele-visit	Office	Tele-visit	Office	Office	Tele-visit	Office	Office
Inclusion/ Exclusion	X		X											
Informed consent**	X													
Demographics	X													
Medical History	X													
HF Sign and symptoms/NYHA Classification (HF Sign and symptoms)	X		X		X	X		X		X	X		X	X
Complete Physical examination	S							S					S	S
Limited Cardiovascular Physical Examination			S								S			S
Height[1]	X													
Weight[2]	X		X		X	X		X		X	X		X	X
Vital Signs	X		X		X	X		X		X	X		X	X
Dispense study medication			X		X	X		X		X	X			
Blind titration					X	X								

[redacted]

Phase	Screening/Baseline		Randomized Treatment						Open Label Extension					Unscheduled◊
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13/EOS	
Days	- Day 14	- Day 7 to - Day 1	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56	Day 63	Day 70	Day 84	Day 98	Day 112	UNSCHED
Time of Visit	Week -2	Week -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	UNSCHED
Visit type	Office	Tele-visit	Office (randomization)	Tele-visit	Office	Office	Tele-visit	Office	Tele-visit	Office	Office	Tele-visit	Office	Office
Titration					X	X		X		X	X			
Laboratory Evaluations (per protocol)[3]	X		X		X			X		X			X	X
Urine pregnancy (site)[4]	X													
Serum pregnancy			X			X		X			X		X	
Open label titration for control arm								X (control only)						
[redacted]														
Randomization			X											
Sensor use training[6]	S													
ActiWatch Exchange & Data Upload			X			X		X			X		X	
[redacted]														

[redacted]

Phase	Screening/Baseline		Randomized Treatment						Open Label Extension					Unscheduled◊
Visit Number	1	2	3	4	5	6	7	8	9	10	11	12	13/EOS	
Days	- Day 14	- Day 7 to - Day 1	Day 1	Day 7	Day 14	Day 28	Day 42	Day 56	Day 63	Day 70	Day 84	Day 98	Day 112	UNSCHED
Time of Visit	Week -2	Week -1	Day 1	Week 1	Week 2	Week 4	Week 6	Week 8	Week 9	Week 10	Week 12	Week 14	Week 16	UNSCHED
Visit type	Office	Tele-visit	Office (randomization)	Tele-visit	Office	Office	Tele-visit	Office	Tele-visit	Office	Office	Tele-visit	Office	Office
Adverse Events/Serious Adverse Events[8]	X	X[8]	X	X[8]	X	X	X[8]	X	X[8]	X	X	X[8]	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dosage Administration Record			X		X	X		X		X	X		X	X
Drug Accountability					S	S		S		S	S		S	S
IRT Call	X		X		X	X		X		X	X		X	X
Study Completion/ Early Termination													X	
Angioedema Assessments	X		X		X	X		X		X	X		X	X

**IC must be obtained prior to all study specific screening procedures during or as close to the start of the screening phase as possible
◊ = Unscheduled visit assessments marked with (X) are optional procedures that may be performed at the investigators discretion, or if the patient withdraws early from treatment or study.
X = assessment to be recorded on clinical data base
S = assessment to be documented in source data

1. Height should be measured in centimeters if possible
2. Weight should be captured in every office visit to the nearest 0.1 kg, without shoes and in indoor clothing
3. Laboratory evaluations include Chemistry, Hematology, and Urinalysis
4. Urine pregnancy test must be performed on site at visit 1
5. [redacted]
6. Actiwatch to be provided at baseline visit.
7. [redacted]
8. At visit 2, 4, 7, 9, and 12 if a subject reports an angioedema-like event, the subject should be requested to come in for an unscheduled visit for safety assessment.

[redacted]

[redacted]

[redacted]

6.1 Information to be collected on screening failures

All subjects who have signed informed consent but not entered into the next epoch will have the study completion page for the screening epoch, demographics, inclusion/exclusion, and serious adverse event (SAE) data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

6.2 Patient demographics/other baseline characteristics

Subject demographic and baseline characteristic data to be collected on all subjects include: year of birth, age, sex, race, ethnicity, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded. HF medications and other CV medications will be recorded in eCRFs such that they can be separated from other medications. Likewise, detailed HF history and other relevant CV medical history will be recorded on eCRFs separately from other medical history.

Investigators will have the discretion to record abnormal test findings on the Medical History eCRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

6.3 Treatment exposure and compliance

Compliance will be assessed by the investigator and/or study personnel at each visit using pill counts and information provided by the care giver. This information should be captured in the source document at each visit.

Subject compliance should be at least 80% during the titration and maintenance treatment phase. The investigator and/or study personnel will counsel the subject if compliance is below 80%. Study drug accountability will also be determined by the site monitor while performing routine site visits and at the completion of the study.

Duration of the study titration and maintenance study drug exposure will be calculated based upon the start and stop dates recorded in the eCRF.

6.4 Efficacy

6.4.1 Efficacy assessment

The efficacy end points are:

Primary:

The change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1) and the final randomized treatment phase (mean of data collected each day during week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 min period collected during the most active 30 minutes of each day).

Secondary:

[redacted]

The change in mean activity during sleep between baseline phase (mean of data collected during week -1) and the final randomized treatment phase (mean of data collected during week 8), as measured by actigraphy (activity counts per minute during daily sleep period, wrist-worn accelerometer).

Other secondary endpoints:

The change in mean activity during sleep between baseline (mean of nights collected during week -1) and each randomized treatment and open label phase, as measured by actigraphy (week 1, 9 and 16) (activity counts per minute during daily sleep period, wrist-worn accelerometer).

The change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1)and each randomized treatment and open label phase (week 1, 9 and 16), as measured by wrist worn accelerometer collected actigraphy.

6.4.2 Appropriateness of efficacy assessments

Actigraphy is an appropriate and effective method for the objective measurement of physical activity in a subject's everyday life (both waking and sleeping). The sensor employed in this study, the Philips Actiwatch Spectrum, is an FDA cleared class II medical device indicated for this purpose. Assessment of both physical activity and sleep metrics using this method with this and similar devices (accelerometers) has been previously reported by other investigators. This method has been used effectively in the HF population to assess: the effect of symptom treatment on daytime activity levels (Redfield 2015), the impact of anergia on sleep and daytime activity (Maurer 2009), the effect of sleep on QoL (Redeker 2005), and physical activity patterns associated with long term survival (Melin 2016).

[redacted]

While polysomnography (PSG) is the standard assessment tool for sleep disordered breathing, [redacted] The Portable Monitoring Task Force of the American Academy of Sleep Medicine (AASM) recommends the use of portable monitors as an alternative to PSG for the assessment of sleep disordered breathing in patients with high pretest probability of moderate to severe sleep apnea (Collop 2007).

[redacted]

6.5 Safety

Safety assessments will consist of monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

6.5.1 Physical examination

A complete physical exam will be performed at visit number 1, 8, and 13. It will include the examination of general appearance, skin, neck, eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and vascular and neurological examinations. If indicated based on medical history, and/or symptoms, rectal, external genitalia, breast and pelvic exams will be performed.

Limited cardiovascular physical examination will be performed at visit 3 and 11, and will include the examination of vital signs (systolic and diastolic blood pressure, pulse and respiration rate), heart and lung sounds, jugular venous distension, and extremities.

Signs and symptoms of heart failure will be reviewed by the investigator at all office visits during the study. The signs and symptoms evaluation may include, but are not limited to, paroxysmal nocturnal dyspnea, fatigue, edema, dyspnea at rest, dyspnea upon effort, orthopnea, rales, jugular venous distention, presence of a third heart sound. NYHA classification will be assessed and scored at each visit.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that were present prior to the subject providing written informed consent for the study must be included in the Relevant Medical History/Current Medical Conditions eCRF. Significant findings made after the subject provides written informed consent for the study which meet the definition of an adverse event must be recorded on the Adverse Event eCRF.

6.5.2 Vital signs

Vital signs will be assessed at every office visit. This will include blood pressure and pulse measurements. BP will be measured using a standard sphygmomanometer with an appropriate sized cuff and the non-dominant arm in the sitting position after 5 minutes of rest. Every effort should be made to use the same arm for the subject for all vital signs assessments and where possible, the same person doing the assessment.

6.5.3 Height and weight

Height in centimeters if possible, body weight to the nearest 0.1 kg without shoes will be measured at visit 1. Body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured at every office visit.

6.5.4 Angioedema

Angioedema is a type of abrupt swelling that occurs under the skin and/or mucous membranes and is often localized to the head, neck, throat, and/or tongue, but may occur elsewhere, including the genitalia and intestines. Severe cases may be associated with airway compromise. Although, the mechanism is not fully understood, bradykinin has been implicated as the putative mediator. Therefore, medications that raise the levels of endogenous bradykinin by inhibiting the enzymes responsible for its breakdown, such as ACE, aminopeptidase P, and NEP, may result in this potentially dangerous side effect. All suspected cases of angioedema, regardless of suspected causality, must be reported. The Adjudication Questionnaire for Angioedema-like Event and Adverse Event eCRFs must be completed and the Novartis Medical Monitor must be notified.

If the angioedema event meets SAE criteria, the investigator must ensure that an SAE form is completed and submitted to Novartis Drug Safety and Epidemiology. In addition, all angioedema events will be adjudicated as described in Section 8.5.

6.5.5 Laboratory evaluations

A central laboratory will be used for all laboratory evaluations with the exception of the urine pregnancy test (hCG) performed at visit 1 (screening) at the site, required to determine eligibility and analysis of all collected specimens from screening through the final visit. Details on the collections, shipment of samples and reporting of results by the central laboratory will be provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

When laboratory values exceed the boundaries of a notable laboratory abnormality, additional laboratory evaluations should be performed, as judged appropriate by the investigator. If the laboratory abnormality induces clinical signs or symptoms, or requires therapeutic intervention, then the diagnosis or medical condition must be entered on the AEs screen of the subject's eCRF. If the laboratory abnormality is the primary reason for an unforeseen hospitalization or otherwise fulfills the seriousness category of an AE, then the procedure for rapid notification of SAEs must be followed. Likewise, if the laboratory abnormality leads to discontinuation from the study drug (temporarily or permanently), the subject must be followed until the abnormality resolves or until it is judged to be permanent. This investigation may include

[redacted]

continued monitoring by repeat laboratory testing or by performing additional laboratory tests as deemed necessary by the investigator or the Novartis medical monitor.

6.5.5.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured at all visits: 1, 3, 5, 8, 10, and 13 (central lab).

6.5.5.2 Clinical chemistry

Blood urea nitrogen (BUN), glucose, creatinine, total bilirubin, AST (SGOT), ALT (SGPT), alkaline phosphatase, sodium, potassium, chloride, calcium, hemoglobin A1C, total protein, albumin, uric acid, and lipid profile will be measured at all visits 1, 3, 5, 8, 10, and 13 (central lab).

6.5.5.3 Urinalysis

Dipstick-test determination of specific gravity, pH, blood, total protein, bilirubin, ketones, and leukocytes will be measured at Visits 1, 3, 5, 8, 10, and 13 (central lab). If dipstick is positive, a qualitative microscopic determination, including white blood cells high power field (WBCs/HPF) and red blood cells high power field (RBCs/HPF) will be performed.

6.5.6 Pregnancy and assessments of fertility

All female subjects of childbearing potential will have a urine pregnancy test (hCG) performed at Visit 1 (site) In addition, these subjects will have a serum pregnancy test performed at visits 3, 6, 8, 11 and 13 (central lab). If any of these tests are positive, the subject must be discontinued from the study.

6.5.7 Appropriateness of safety measurements

The majority of safety assessments selected for this study are standard for this indication/subject population. They include the monitoring and recording of all adverse events and serious adverse events, evaluation of hematology, blood chemistry and urine, regular measurements of vital signs and the performance of physical examinations.

6.6 Other assessments

[redacted]

6.6.4 Sensor Measurements

There are two wearable sensor systems that will be used for measurement:

Actiwatch

- Wrist worn activity and light monitor using the Philips Actiwatch (waterproof) (Philips Respironics, Boston MA): This device is a 510k registered class 2 medical device indicated to: "collect and score data for sleep parameters and assess activity in any instance where quantifiable analysis of physical motion is desired".
  - This device will be worn on the non-dominant wrist of the subject, day and night for the entire study duration from the time of enrollment (start of the 2 week baseline phase) to the end of the open-label extension phase (treatment week 16).This device uses an accelerometer to monitor the occurrence and degree of sensor motion which is captured in 'counts' (0.000175 G-force per activity count). Data from the accelerometer will be sampled at a frequency of 32 Hz and stored in 30 second data epochs. Data from the sensor will be uploaded from the Actiwatch to Philips data collection system during assessment periods, which will be scored by Philips and will be blinded to treatment. For the purpose of endpoint determination, onset of sleep will be defined by 10 consecutive motionless (< 40 counts/min) 1-minute intervals and waking will be determined by 10 consecutive intervals of activity (< 40 counts/min). Sleep onset and awakening times will be confirmed by a Philips technician, over-read and verified to align with typical sleep wake times and ambient light sensor data.

- Actiwatch data captured during the baseline phase is crucial. If a subject is not compliant (not wearing the Actiwatch more than 3 days or less than half of the 2 week baseline phase), they will be asked to repeat the 2 week baseline phase. After randomization, subjects who refuse to wear the device will be discontinued; subjects who have an unintentional lapse of compliance will be asked to immediately resume wearing the device.
- During visit 1, subjects will be trained on the Philips Actiwatch. The Actiwatch will be exchanged and data uploaded by the site at visit 3, 6, 8, 11 and 13.

Actiwatch data:

- Total activity counts from most active 30 minutes of day
- Total activity counts from most active contiguous 30 minutes of day
- Total activity counts from most active 6 minutes of day
- Total activity counts from most active contiguous 6 minutes of day
- Mean activity counts per minute during sleep interval
- Mean activity per day: This is the average activity value during all activity periods above 200 cts/min in a 24-hr day. It is a comprehensive assessment of activity.
- Sleep Efficiency: (Scored Total Sleep Time divided by (Sleep Interval Duration minus Total Invalid Time (Sleep/Wake)) of the given Rest Interval) multiplied by 100.
- Wake After Sleep Onset (WASO): The total number of epochs between the Start Time and the End Time of the given Sleep Interval scored as WAKE by Actiware software (or manually set as WAKE during over read) multiplied by the Epoch Length in minutes (so the Wake After Sleep Onset is in minutes).

[redacted]

6.6.5 Resource utilization

Not Applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

In addition, all reports of intentional misuse and abuse of the product are also considered an adverse event irrespective if a clinical event has occurred.

The occurrence of adverse events must be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for laboratory and other test abnormalities are included in Appendix 1.

Adverse events must be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them, accompanied by the following information:

[redacted]

the [severity grade] *(select as appropriate)*

If severity grade is selected, add the following

- mild: usually transient in nature and generally not interfering with normal activities
- moderate: sufficiently discomforting to interfere with normal activities
- severe: prevents normal activities

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- no action taken (e.g. further observation only)
- [investigational] treatment dosage increased/reduced
- [investigational] treatment interrupted/withdrawn
- concomitant medication or non-drug therapy given
- non-drug therapy given
- patient hospitalized/patient's hospitalization prolonged (see Section 7.2 for definition of SAE)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent, and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB). This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the medicinal product that is identified between IB updates will be communicated as appropriate, for example, via an Investigator Notification or an Aggregate Safety Finding. New information might require an update to the informed consent and has then to be discussed with the subject.

The investigator must also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information must be recorded in the investigator's source documents; however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

[redacted]

7.2 Serious adverse events

7.2.1 Definition of SAE

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s)) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (specify what this includes)
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, e.g. defined as an event that jeopardizes the patient or may require medical or surgical intervention.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Life-threatening in the context of a SAE refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to Annex IV, ICH-E2D Guideline).

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to Annex IV, ICH-E2D Guideline).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

7.2.2 SAE reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] must be reported to Novartis within 24 hours of learning of its occurrence. Any

[redacted]

SAEs experienced after the 30 day period [after the last study visit/ following the last administration of study treatment if there are post-treatment follow-up visits with no required procedures] should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form; all applicable sections of the form must be completed in order to provide a clinically thorough report. The investigator must assess the relationship of each SAE complete the SAE Report Form in English, and submit the completed form within 24 hours to Novartis. Detailed instructions regarding the submission process and requirements for signature are to be found in the investigator folder provided to each site.

Follow-up information is submitted as instructed in the investigator folder. Each re-occurrence, complication, or progression of the original event must be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the blind was broken or not, and whether the subject continued or withdrew from study participation.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

7.3 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, patient or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE.

[redacted]

Table 7-1 Guidance for capturing the study treatment errors including misuse

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

7.4 Pregnancy reporting

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy must be recorded on the Pharmacovigilance Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during the pregnancy and unrelated to the pregnancy must be reported on a SAE form.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and (e)CRFs with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of patient records, the accuracy of entries on the (e)CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis CRA organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis Clinical Teams to assist with trial oversight.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical

[redacted]

information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the (e)CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the (e)CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to US CFR 21Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

CRO working on behalf of Novartis review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Diary data will be entered into an electronic diary by the subject who will fill in their PRO data in a site based tablet. The system will be supplied by a vendor(s), who will also manage the database. The database will be sent electronically to Novartis personnel (or designated CRO).

Randomization codes and data about all study drug(s) dispensed to the patient and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be

[redacted]

supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of relevant protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis management.

8.4 Data Monitoring Committee

Not required.

8.5 Angioedema Adjudication Committee

It is important that the investigator pays special attention to any swelling or edema that may resemble angioedema or angioedema-like events that may be reported by subjects. There will be a separate eCRF for angioedema events. If such an event occurs, the investigator will complete an Adjudication Questionnaire for Angioedema-like Event form (provided by Novartis) to summarize the event, its treatment, and its ultimate outcome and communicate this report to Novartis as soon as possible. Follow-up reports must be communicated to Novartis as soon as new information regarding the event becomes available. All hospital records related to the event must be communicated to Novartis.

Occasionally, the investigator may be contacted by Novartis regarding AEs that were reported on behalf of subjects that may resemble an angioedema-like event. The investigator or his/her

delegated staff must complete the required report forms and supply the required medical records for such events, regardless of whether the investigator views the event in question as angioedema or not.

All angioedema reports will be forwarded to an Angioedema Adjudication Committee (AAC) by Novartis for assessment. The adjudication committee will adjudicate all suspected angioedema events in a uniform and consistent manner, and will assign severity for each confirmed case.

The Angioedema Adjudication Committee (AAC) consists of a group of experts in clinical angioedema who have been selected according to their educational, clinical, and research experience and are independent from Novartis. The purpose of the AAC is to review and to adjudicate all suspected angioedema events in a uniform and consistent manner and to assign severity for each confirmed case for the project wide sacubitril/valsartan program. The AAC will remain blinded to treatment allocation during the adjudication process whenever possible and necessary.

The adjudication committee will remain blinded to treatment allocation during the adjudication process whenever possible and necessary.

[redacted]

Submission of an angioedema report is not a substitution for the submission of a SAE report. If an angioedema-like event satisfies the definition of a SAE, the investigator must submit a SAE report in addition to the Adjudication Questionnaire for an Angioedema-like Event.

9 Data analysis

The analysis will be conducted on all subject data at the time the trial ends. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

A designated Contract Research Organization will perform the statistical analysis.

It is planned that the data from all centers that participate in this protocol will be combined, so that an adequate number of subjects will be available for analysis.

Unless otherwise specified, all statistical tests will be conducted against a two-sided alternative hypothesis, employing a significance level of 0.05.

Efficacy, safety, and other data will be summarized. For continuous variables, summary statistics (mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum) at each time point and for change from baseline to each time point will be reported by treatment group. Discrete variables will be summarized by frequencies and percentages.

9.1 Analysis sets

The following subject sets will be used for the statistical reporting and analyses:

The Randomized Set will consist of all randomized subjects.

The Full Analysis Set (FAS) will consist of all subjects with the exception for those subjects who have not been qualified for randomization and have not received study drug, but have been inadvertently randomized into the study. Following the intent-to-treat principle, subjects will be analyzed according to the treatment to which they were assigned at randomization. Efficacy variables will be analyzed based on the FAS as the primary set.

The Safety Set (SAF) will consist of all randomized subjects who received at least one dose of study drug. Subjects will be included in the analysis according to the treatment actually received. The Safety Set will be used for the analyses of safety variables.

9.2 Subject demographics and other baseline characteristics

Baseline value is defined as the last non-missing assessment prior to the first dose of randomized study medication, unless specified otherwise in the protocol.

Summary statistics will be provided by treatment group for demographics and baseline characteristics. Categorical variables will be summarized using frequency and percentage.

The Randomized Set and FAS will be the subject sets for the above analyses.

[redacted]

9.3 Treatments

The overall duration on the double-blind study drug and during the open label treatment with study drug will be summarized by treatment group using mean, standard deviation, median, 25th and 75th percentiles, interquartile range, minimum, and maximum. Additionally, the number and percentage of subjects will be summarized by treatment group for duration category.

Concomitant medications and significant non-drug therapies, prior to and after the randomization date will be summarized (frequency and percent) by therapeutic class, preferred term, and treatment group.

The Safety Set will be used for the above analyses.

9.4 Analysis of the primary variable(s)

9.4.1 Primary Variable(s)

The primary endpoint is the change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline phase (mean of data collected each day during week -1) and the final randomized treatment phase measurement (mean of data collected each day during week 8), as measured by wrist-worn accelerometer collected actigraphy (total counts per 30 min period collected during the most active 30 minutes of each day).

9.4.2 Statistical model, hypothesis, and method of analysis

Let μ_j denote the population mean of change in mean activity count from baseline phase to Week 8 for treatment group j, j = 0, 1, where 0 corresponds to enalapril and 1 corresponds to sacubitril/valsartan.

The following null hypothesis (H_0) will be tested against the alternative hypothesis (H_A):

H_0: $\mu_1 - \mu_0 = 0$

H_A: $\mu_1 - \mu_0 \neq 0$

The primary efficacy variable will be analyzed by an analysis of covariance (ANCOVA) model with treatment and baseline activity as explanatory variables. The least squares means of the two treatment groups, least squares mean difference of the treatment groups, 95% confidence interval for the difference in the two treatment groups, and p-value based on the fitted linear model will be reported. If the p-value is < 0.05 and the least squares mean difference of the treatment groups favors sacubitril/valsartan, statistical significance in favor of sacubitril/valsartan will be declared.

Before performing the above analysis, tests of normality of the variable, change in mean activity counts collected during the most active 30 minutes of the subject's day between baseline and Week 8, and the log of the variable (log (Week 8 value) – log (baseline value)) will be performed. In the event the variable is not normally distributed (based on Shapiro-Wilk test p-value <0.05) but the lognormal distribution fits better, the above analysis will be performed using the log transformed data. Anti-log of the least squares mean difference of the

[redacted]

treatment groups will be used to report the ratio of the treatment difference in the original scale.

The primary analysis of the primary efficacy variable will be based on the Full Analysis Set.

9.4.3 Handling of missing values/censoring/discontinuations

Missing data will be imputed using the last-observation-carried-forward (LOCF) method. If a subject has no post-baseline value, the missing value will not be imputed and the subject will be removed from the analysis. If a subject's data is missing or unevaluable for the week preceding randomization, the data from the previous week will be used as the baseline measurement. If a subject's data is missing or unevaluable for each of these weeks, the subject will be excluded from the analysis.

9.4.4 Sensitivity analyses

A supportive nonparametric analysis will be performed to examine the consistency of results. For this supportive analysis, the primary efficacy variable will be analyzed using the Wilcoxon rank-sum test. The probability of one treatment being better than the other treatment will be estimated (based on the Wilcoxon rank-sum test) and the associated 95% confidence interval will be reported (Chen and Kianifard 2000).

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

The secondary efficacy variables are the following assessments defined based on actigraphy data:

- Change in mean activity (counts per minute) during sleep between baseline phase and week 8 (Randomized treatment phase)
- Change in mean activity during sleep between baseline phase and week 1 (Randomized treatment phase)
- Change in mean activity during sleep between baseline phase and week 9 and 16 (Open label extension phase)
- Change in mean activity counts during the most active 30 minutes of the subject's day between baseline phase and week 1 (Randomized treatment phase)
- Change in mean activity counts during the most active 30 minutes of the subject's day between baseline phase and week 9 and 16 (Open label extension phase)

During the randomized treatment phase, mean change from baseline for each continuous variable will be analyzed at each time point using the same ANCOVA model as for the primary efficacy variable, and missing data will be imputed using the LOCF method.

During the open label extension phase, change from baseline (mean of week -1) for each continuous variable will be analyzed at each time point using paired t-tests for the group randomized to sacubitril/valsartan. The analyses will be repeated using the week 8 measurement as baseline for the group randomized to Enalapril.

[redacted]

9.5.2 Safety variables

The safety and tolerability assessments are listed below:

- AEs and SAEs
- Sitting systolic, diastolic BP, and pulse pressure
- Heart rate
- Laboratory values

The assessment of safety will be based primarily on the frequency of adverse events, SAEs, and laboratory abnormalities. Other safety data will be summarized as appropriate.

The incidence of treatment-emergent adverse events (new or worsened) will be summarized by primary system organ class, preferred term, severity, and relationship to study drug. In addition, the incidence of death, SAEs, and AEs leading to discontinuation will be summarized separately by primary system organ class and preferred term.

Laboratory data will be summarized by presenting shift tables using extended reference ranges (baseline to most extreme post-baseline value), by presenting summary statistics of raw data and change from baseline values (mean, median, standard deviation, 25th and 75th percentiles, interquartile range, minimum and maximum) and by the flagging of notable values in data listings.

Data from other tests will be listed, notable values will be flagged, and any other information collected will be listed as appropriate.

Safety analyses will be performed based on the Safety Set. There will be no inferential analyses of the safety data.

9.5.3 Resource utilization

Not Applicable.

9.5.4 Pharmacokinetics

Not Applicable.

9.5.5 DNA

Not Applicable.

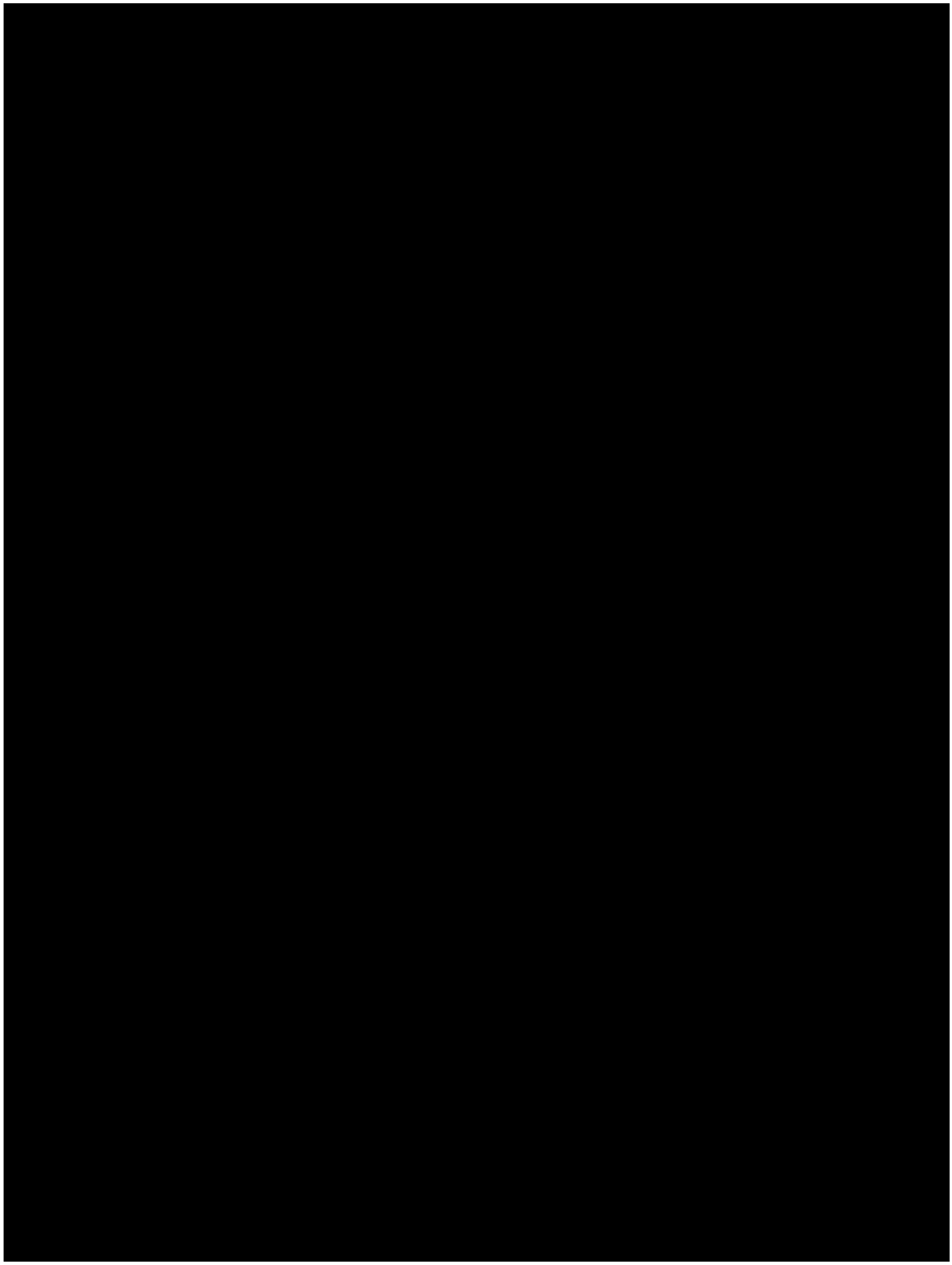
9.5.6 Biomarkers

Not Applicable.

9.5.7 PK/PD

Not Applicable.

[redacted]



9.7 Interim analyses

Not applicable.

9.8 Sample size calculation

Primary endpoint:

Assuming a significance level of 0.05, a total sample size of 136 subjects would provide 90% power to detect a difference of 5000 in the change from baseline in mean activity counts collected during the most active 30 minutes between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 7400 (Maurer 2009) and a 20% drop-out rate and a 10% rate of subjects with non-evaluable data. The assumed effect size of 68% (5000/7400) will be maintained in the event the log transformation is needed for the primary analysis thus not affecting the sample size calculation and power of the study.

Secondary endpoint:

Assuming a significance level of 0.05, a sample size of 136 subjects would provide 93% power to detect a 3.5 point difference in the change from baseline in mean activity value during the sleep (expressed as counts per minute) between the sacubitril/valsartan treatment group and the enalapril group during Week 8, assuming a common standard deviation of 4.9 and a 20% drop-out rate and a 10% rate of subjects with non-evaluable data (Peterson 2012).

10 Ethical considerations

10.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 Informed consent procedures

Eligible subjects may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative(s) of the subject. In cases where the patient's representative gives consent, the subject must be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he/she must indicate assent by personally signing and dating the written informed consent document or a separate assent form. Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they must not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

[redacted]

10.4 Publication of study protocol and results

The key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

10.5 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management (QM) system that includes all activities involved in quality assurance and quality control, including the assignment of roles and responsibilities, the reporting of results, and the documentation of actions and escalation of issues identified during the review of quality metrics, incidents, audits and inspections.

Audits of investigator sites, vendors, and Novartis systems are performed by Novartis Pharma Auditing and Compliance Quality Assurance, a group independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

11 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances is an investigator allowed to collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs under the protocol.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

11.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation. Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the reporting requirements identified in Section 7 Safety Monitoring must be followed.

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13 Appendix 1: Clinically notable laboratory values and vital signs

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

[redacted]

14 Appendix 2: Liver event and Laboratory trigger Definitions and Follow-up Requirements

Table 14-1 Liver Event and Laboratory Trigger Definitions

	Definition/ threshold
LIVER LABORATORY TRIGGERS	□ 3 x ULN < ALT / AST δ 5 x ULN □ 1.5 x ULN < TBL δ 2 x ULN
LIVER EVENTS	□ ALT or AST > 5 × ULN □ ALP > 2 × ULN (in the absence of known bone pathology) □ TBL > 2 × ULN (in the absence of known Gilbert syndrome) □ ALT or AST > 3 × ULN and INR > 1.5 □ Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) □ Any clinical event of jaundice (or equivalent term) □ ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia □ Any adverse event potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms
TBL: total bilirubin; ULN: upper limit of normal

[redacted]

Table 14-2 Follow Up Requirements for Liver Events and Laboratory Triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	□ Discontinue the study treatment immediately □ Hospitalize, if clinically appropriate □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	□ Discontinue the study treatment immediately □ Hospitalize if clinically appropriate □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	□ Discontinue the study treatment immediately □ Hospitalize, if clinically appropriate □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	□ Repeat LFT within 48 hours □ If elevation persists, continue follow-up monitoring □ If elevation persists for more than 2 weeks, discontinue the study drug □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN accompanied by symptoms[b]	□ Discontinue the study treatment immediately □ Hospitalize if clinically appropriate □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	□ Repeat LFT within the next week □ If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	□ Repeat LFT within 48 hours □ If elevation persists, establish causality □	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		

[redacted]

Criteria	Actions required	Follow-up monitoring
> 2 × ULN (in the absence of known Gilbert syndrome)	□ Repeat LFT within 48 hours □ If elevation persists, discontinue the study drug immediately □ Hospitalize if clinically appropriate □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	□ Repeat LFT within the next week □ If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	□ Discontinue the study treatment immediately □ Hospitalize the patient □ Establish causality □	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	□ Consider study treatment interruption or discontinuation □ Hospitalization if clinically appropriate □ Establish causality □	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

[redacted]

15 Appendix 3: Specific Renal Alert Criteria and Actions

Table 15-1 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute Kidney Injury: Serum creatinine increase ε 50% compared to baseline	Follow up within 24-48h if possible Consider study treatment interruption Consider patient hospitalization /specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR)≥150 mg/g or >15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Consider study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor patient regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months.	

16 Appendix 4: Guideline for the management of renal dysfunction

General principles:

Glomerular filtration rate in HF subjects depends on intrinsic renal function and on a balance between afferent and efferent glomerular arterial tonicity. This tonicity is partly regulated by a stimulation of angiotensin II and could be affected by either study medication. Moreover, renal dysfunction may develop or may deteriorate in some subjects after study drug administration. These recommendations have been developed to guide the investigators in managing subjects with renal dysfunction after randomization.

Two types of response to serum creatinine increase are described:

Surveillance situation

If, at any time after randomization, eGFR decreases by ≥ 25% from baseline (or if serum creatinine concentration increase to 2.5 mg/dL [221 µmol/L]), the investigator will check for potentially reversible causes of renal dysfunction such as:

- Non-steroidal anti-inflammatory drug intake, antibiotics, or other treatments known to affect creatininemia
- Volume decrease, including that resulting from excessive dosing of diuretics
- Urinary infection
- Urinary tract obstruction
- Study medication

Action situation

If a subjects eGFR decreases by ≥ 40% from baseline (or if serum creatinine concentration rises above 3 mg/dL (265 µmol/L), the investigator will check for potentially reversible causes of renal dysfunction (see above).

If the investigator judges that study medication has to be stopped, he/she will have to contact the Novartis medical monitor or his/her designee. Thereafter, serum creatinine assessments will have to be repeated at least each week until levels return to acceptable values. If study medication was stopped, every effort will be done to restart it again, according to clinical conditions.

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17 Appendix 5: Guidelines for the management of blood pressure

Guidelines

1. Investigator should monitor blood pressure closely
2. If symptomatic hypotension occurs:
   a. Correct any treatable cause, e.g. hypovolemia
   b. If hypotension persists, any antihypertensive drug and non-disease-modifying drugs, such as diuretics, CCBs, nitrates, and α-blockers, should be down-titrated or stopped first before down-titration of the study drug is considered
3. If hypotension persists, the study drug should be down-titrated or even temporarily withdrawn. The dose re-challenge and medication adjustment guidelines described in Section 5.5.4 should be adhered to as much as possible.

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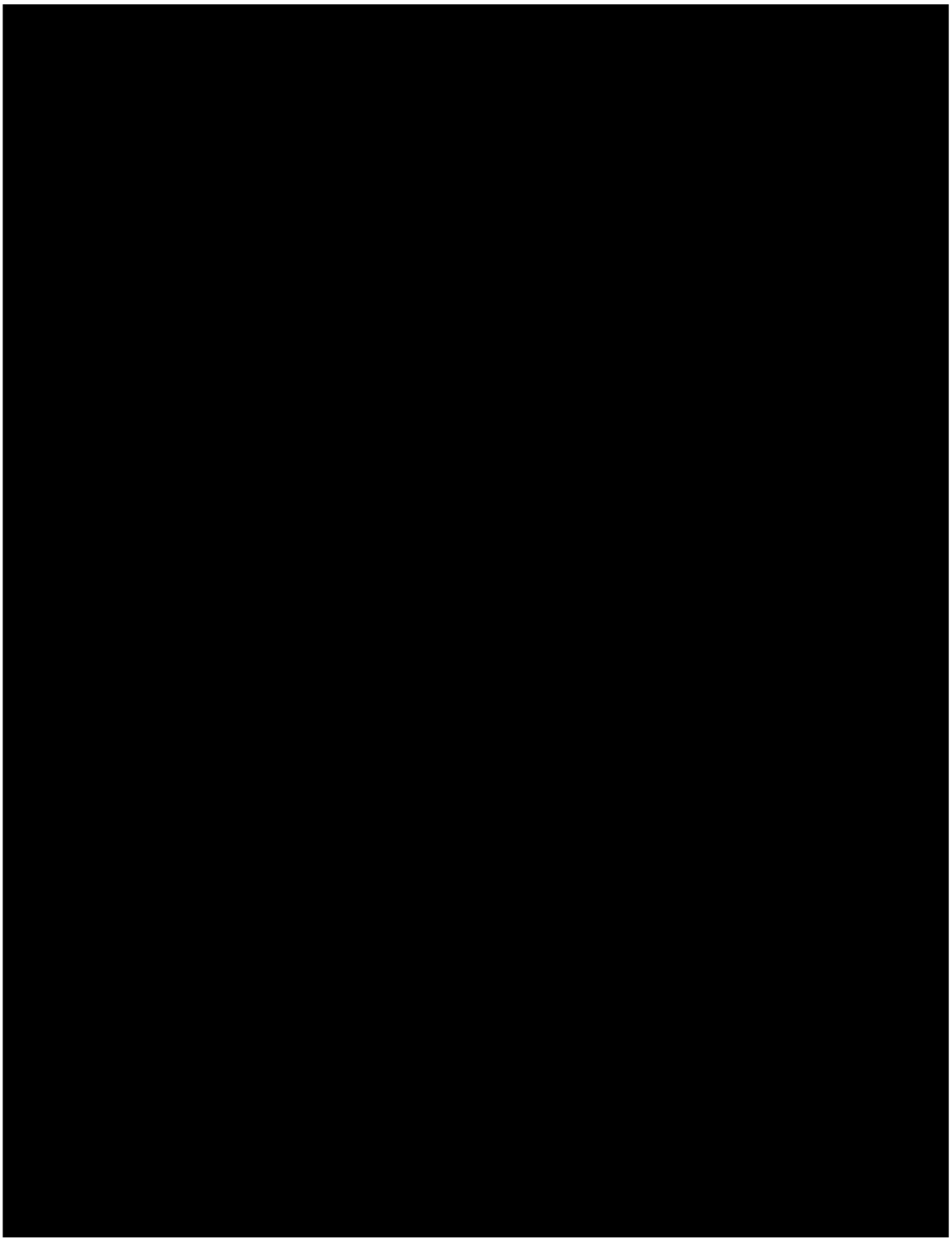

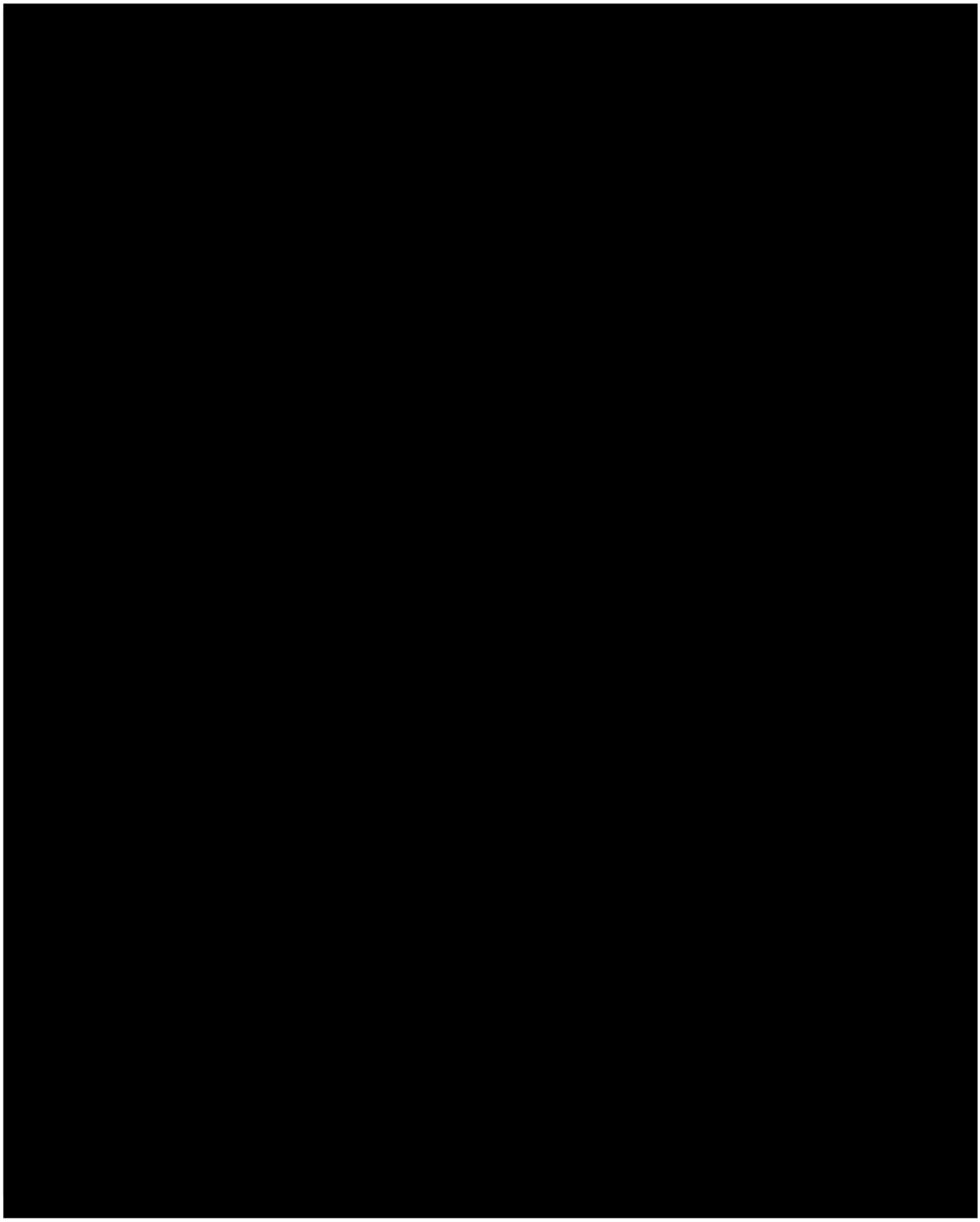

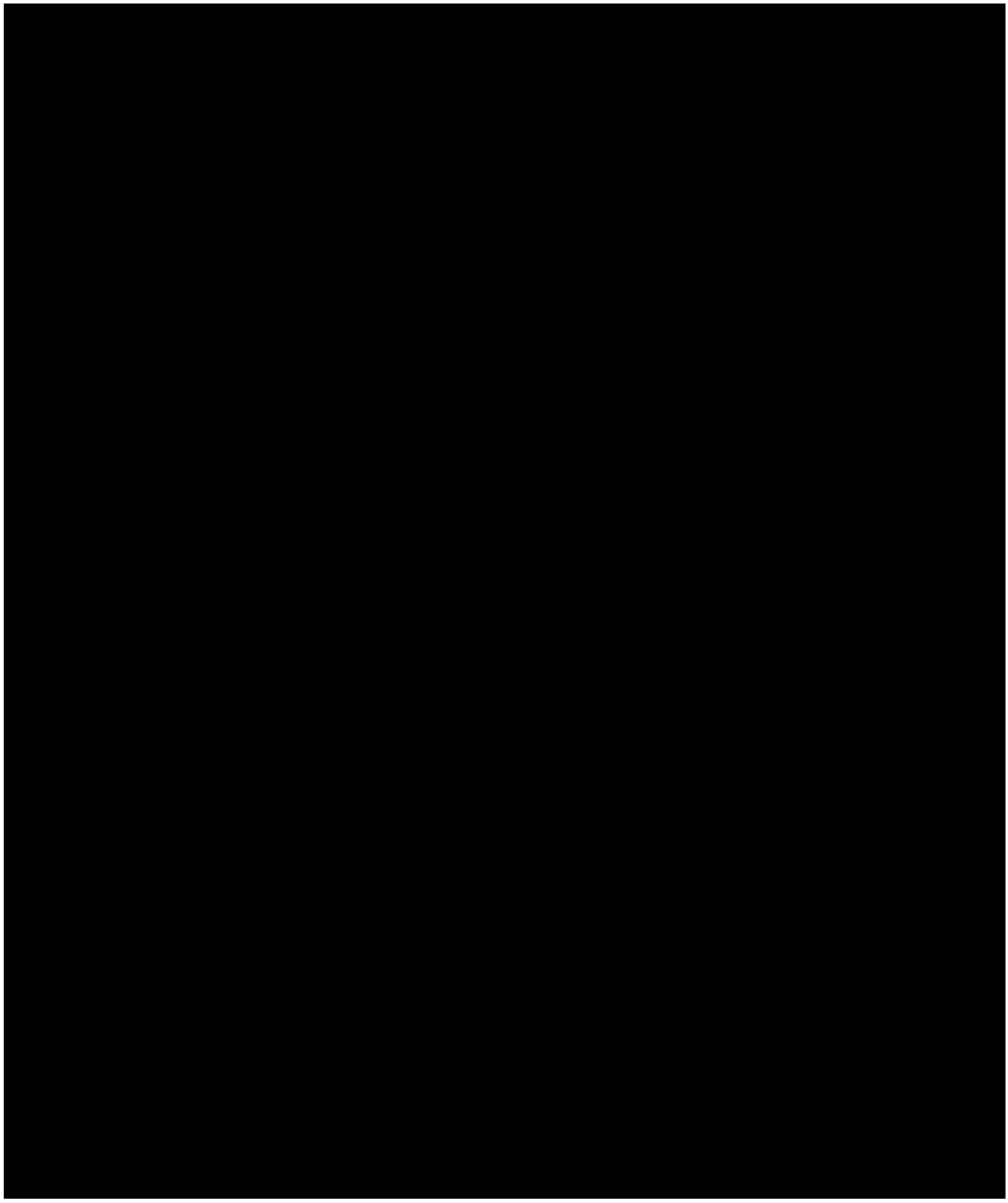

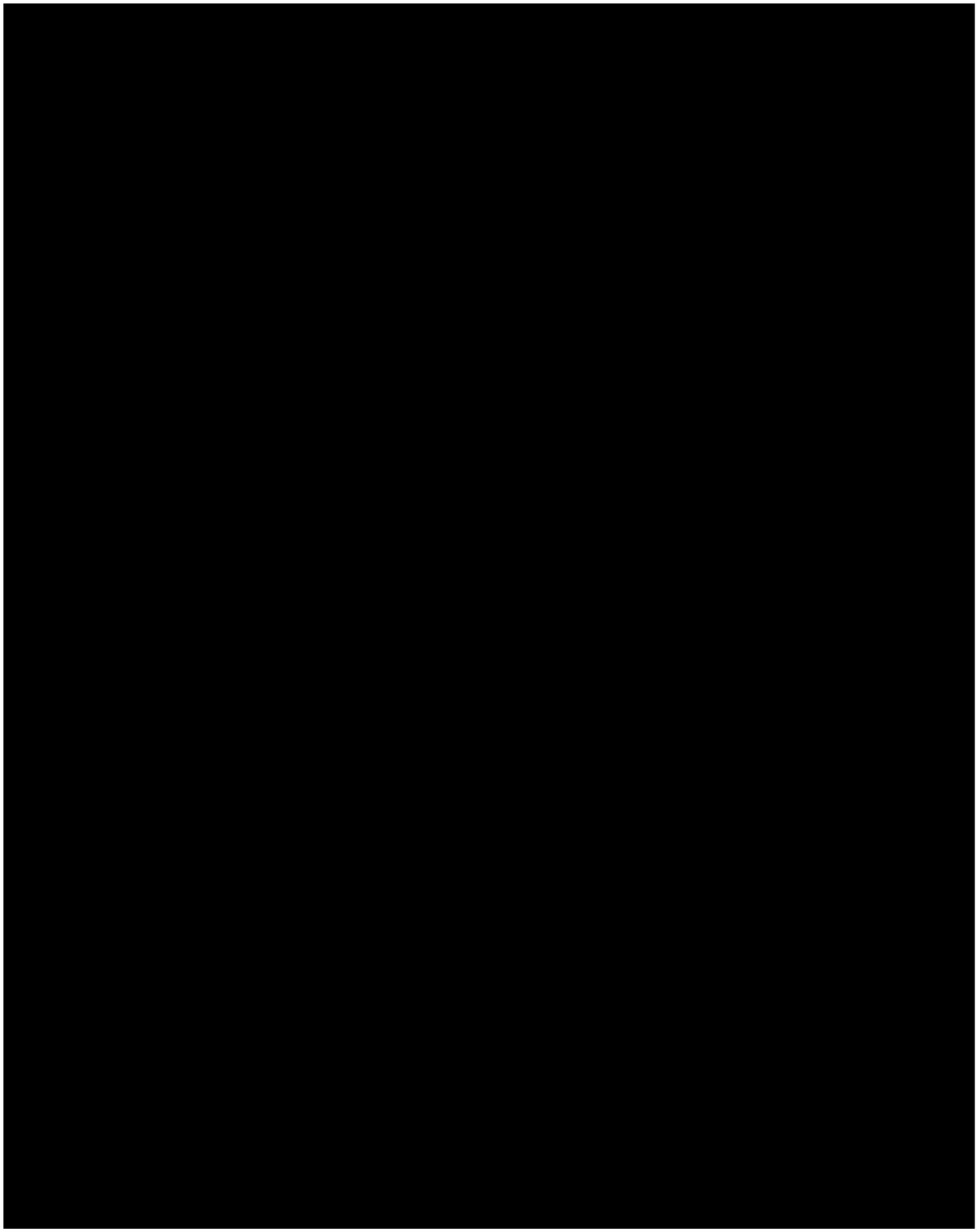

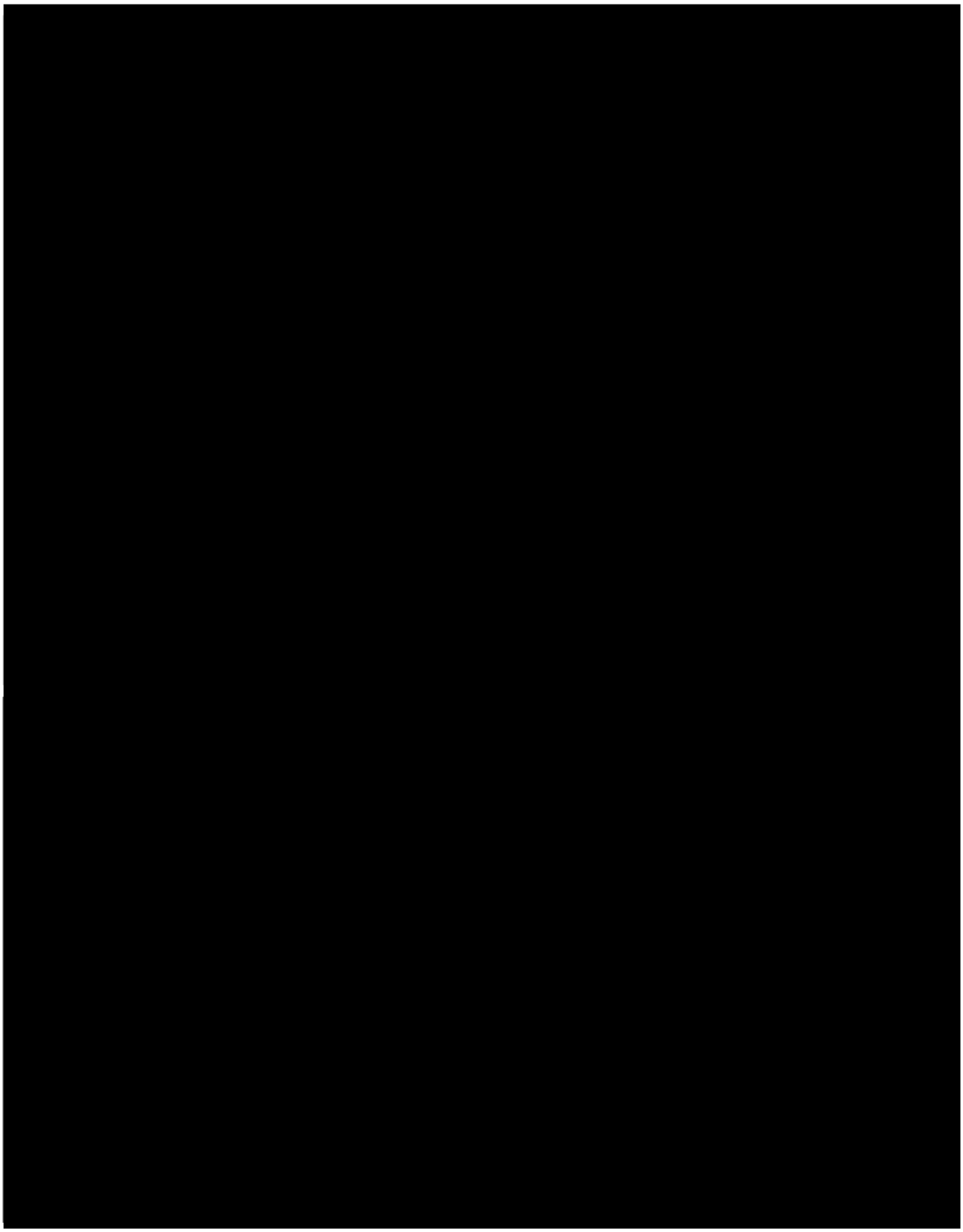

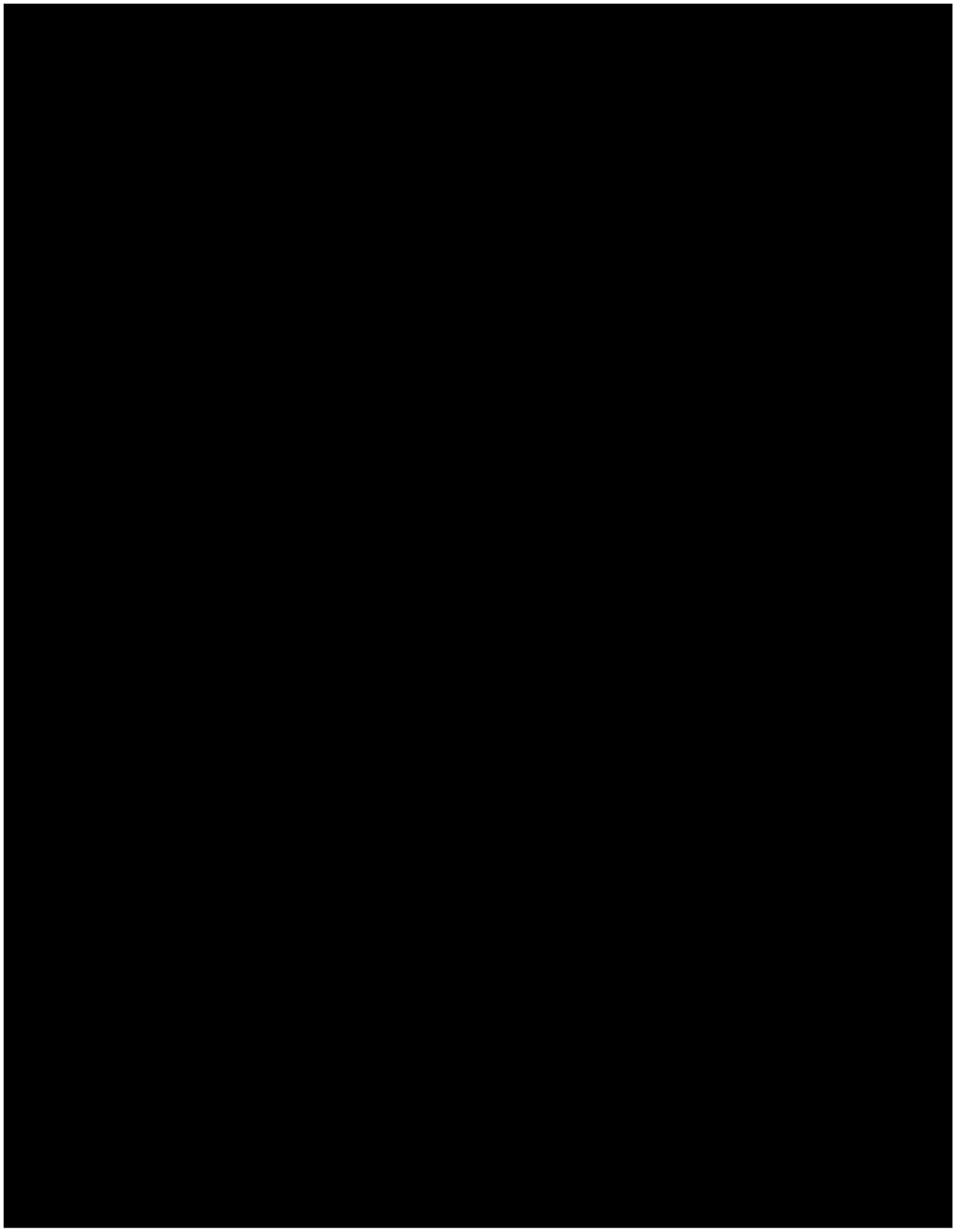

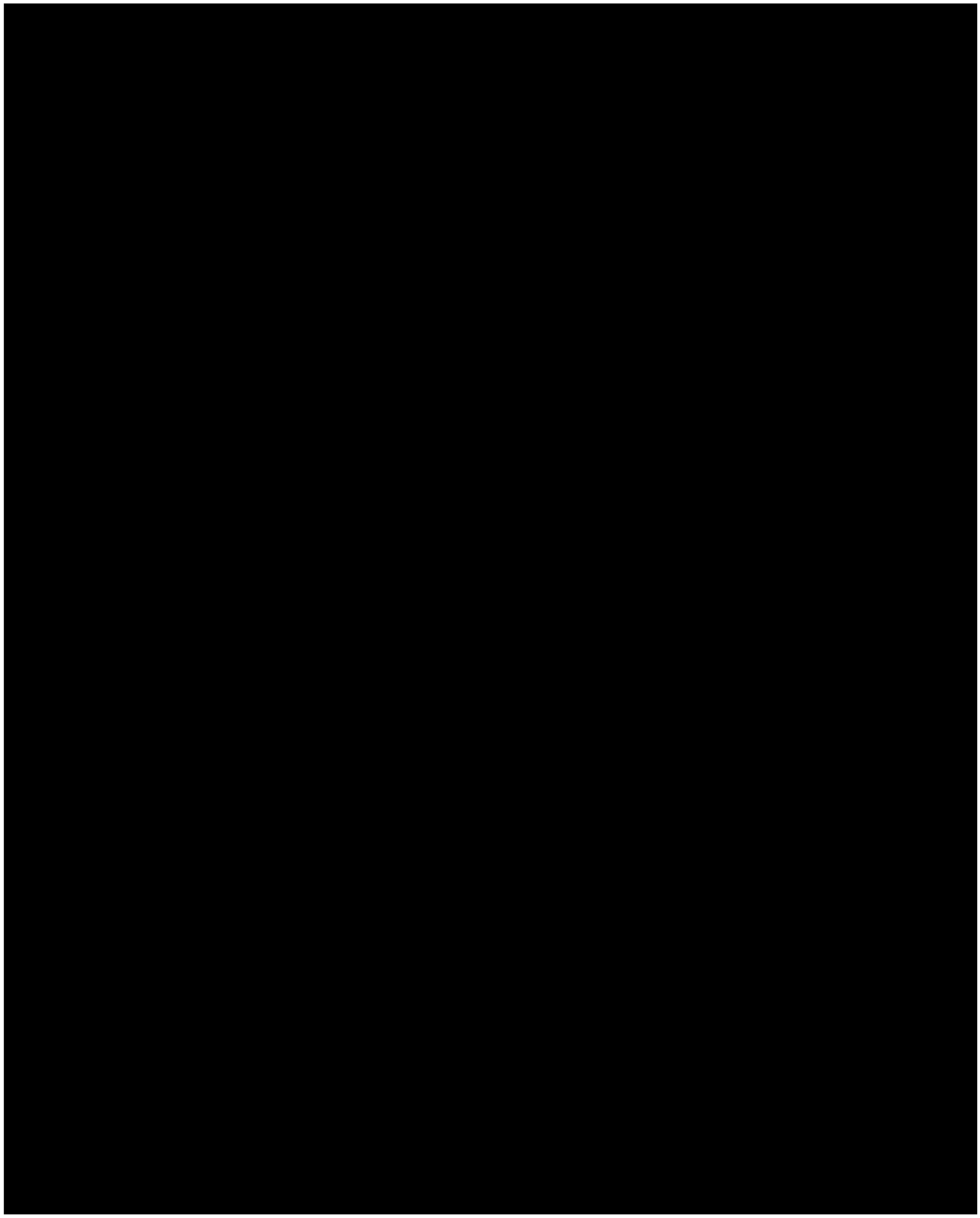

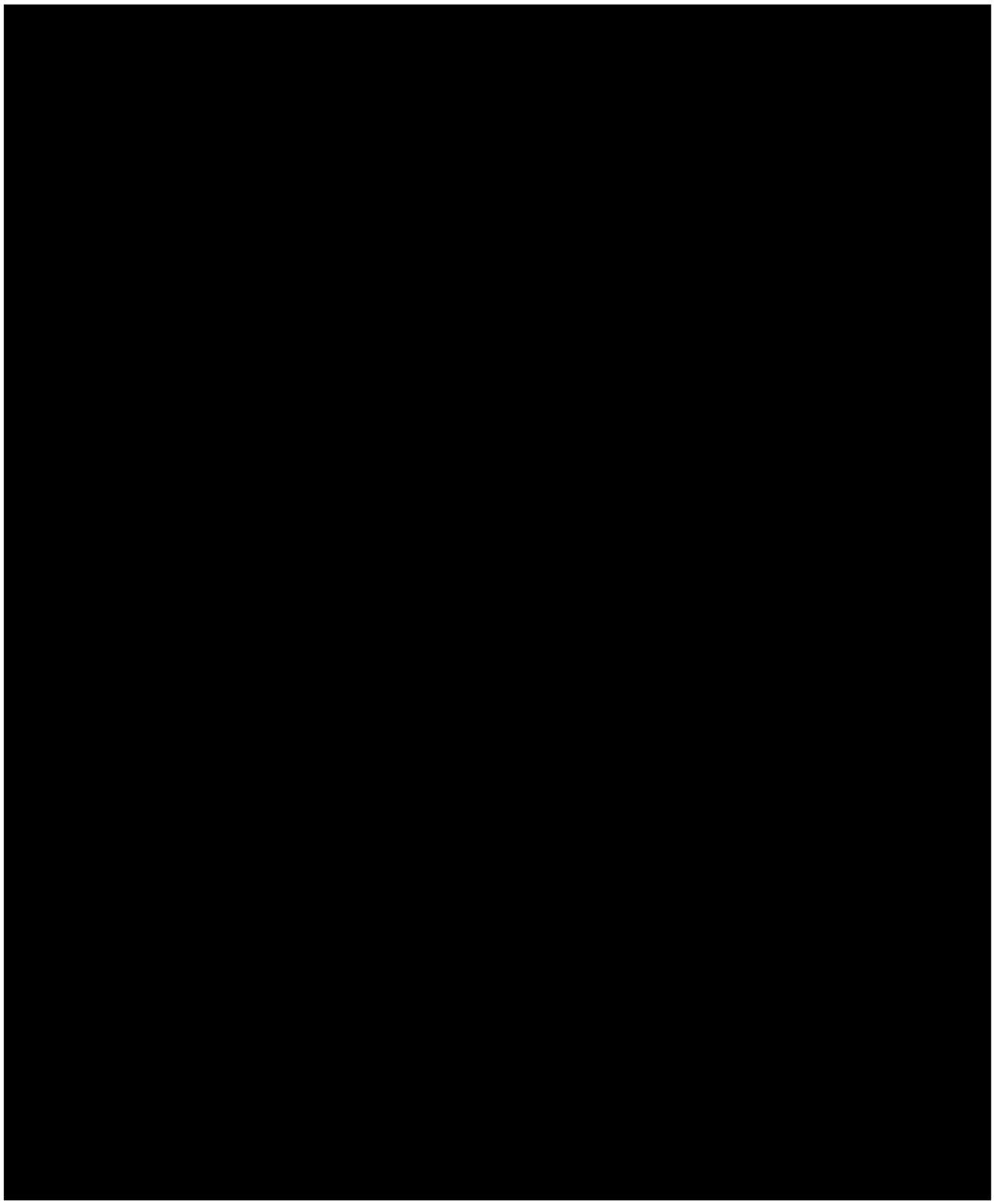

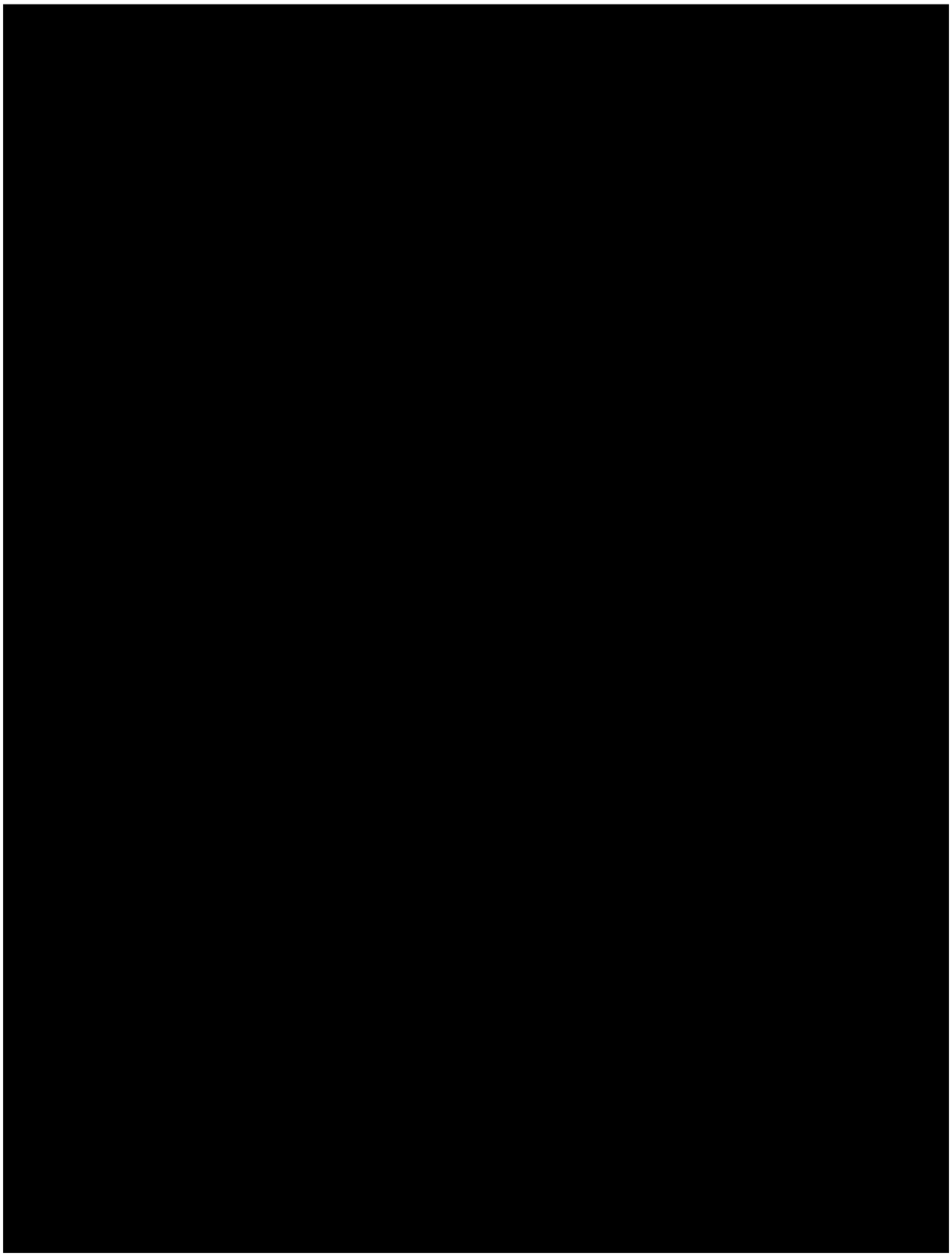

21 Appendix 9: Prohibited Medications: Prescription and non-prescription medications taken for insomnia or to induce sleep

CATAGORY	EXAMPLES
Benzodiazepines with sedating properties for insomnia; or alternative indications taken at bedtime	*Examples include:* Alprazolam (Xanax) Clonazepam (Clozaril) Diazepam (Valium) Estazolam (Prosom) Flurazepam (Dalmane) Lorazepam (Ativan) Quazepam (Doral) Oxazepam (Serax) Temazapem (Restoril) Triazolam (Halcion)
Non-benzodiazepines for insomnia	Examples include: Eszopiclone (Lunesta) Ramelteon (Rozerem) Suvorexant (Belsomra) Tasimelteon (Hetlioz) Zaleplon (Sonata) Zolpidem (Ambien, Ambien CR, Edluar, Intermezzo, Zolpimist)
Antidepressants with sedating properties for insomnia; or alternative indications taken at bedtime	*Examples include:* Amitriptyline (Elavil), Doxepin (Silenor, Sinequan) Mirtazapine (Remeron) Trazodone (Oleptro, Desyrel)
Other prescriptions with sedating properties for insomnia; or alternative indications taken at bedtime	*Examples include:* Baclofen (Lioresal, Gablofen) Cyclobenzaprine (Flexeril) Gabapentin (Neurontin) Hydroxyzine (Atarax) Olanzapine (Zyprexa) Phenobarbital (Phenobarb) Quetiapine (Seroquel) Tiagabine (Gabitril)
Non-prescription Drugs for sleep/insomnia or designated for “nighttime” or “PM” use containing any of the following active ingredients: Diphenhydramine, Doxylamine, Chlorpheniramine	*Examples include:* Advil P.M. Aleve P.M. Benadryl Chlorphen Nytol Nyquil Sominex Tylenol P.M Unisom ZzzQuil
Non-prescription Herbs/Supplements for sleep/insomnia or designated for “nighttime” or “PM”	*Examples include:* 5-HTP Kava Kava Melatonin Valerian Root

[redacted]