Document Type:	Study Protocol
Official Title:	A multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding Phase II trial to study the efficacy, safety, pharmacokinetics and pharmacodynamic effects of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks in patients with chronic heart failure and preserved ejection fraction
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1. Title page

A multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding Phase II trial to study the efficacy, safety, pharmacokinetics and pharmacodynamic effects of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks in patients with chronic heart failure and preserved ejection fraction

Short title:	PANACHE		
Test drug:	neladenoson bialanate / BAY 1067197		
Study purpose:	dose finding		
Clinical study phase:	IIb	Date:	14 FEB 2017
Registration:	EudraCT no.: 2016-004062-26	Version no.:	1.0
Sponsor's study no.:	BAY 1067197 / 17582		
Sponsor:	Non-US: Bayer AG, D-51368 Leverkusen, Germany US territory: Bayer HealthCare Pharmaceuticals Inc., 100 Bayer Boulevard, P.O. Box 915, Whippany NJ 07981-0915, USA		

Sponsor's medical expert:
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The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final clinical study protocol as presented.

Name: PPD Role: Global Clinical Leader

Date: 14/2/2017 Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final clinical study protocol as presented.

Name:

Affiliation:

Date: Signature:

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

2. Synopsis

Title	A multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding Phase II trial to study the efficacy, safety, pharmacokinetics and pharmacodynamic effects of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks in patients with chronic heart failure and preserved ejection fraction
Short title	PANACHE
Clinical study phase	IIb
Study objective(s)	The objective of the study is to find the optimal dose of neladenoson bialanate for the Phase III trial by detecting and characterizing a significant dose-response relationship in the primary efficacy endpoint, absolute change from baseline in 6-minute walking distance (6MWD) at 20 weeks, in patients with chronic heart failure with preserved ejection fraction (HFpEF), and by characterizing the safety, tolerability and pharmacodynamic effects of the compound when given in addition to appropriate therapy for specific co-morbidities. An exploratory objective is to further assess pharmacokinetic parameters and blood and urine biomarkers.
Test drug(s)	
Name of active ingredient	neladenoson bialanate
Dose(s)	5 mg, 10 mg, 20 mg, 30 mg, and 40 mg once daily
Route of administration	Oral
Duration of treatment	20 weeks
Reference drug(s)	
Name of active ingredient	Placebo
Dose(s)	Not applicable
Route of administration	Oral
Duration of treatment	20 weeks
Background treatment	Appropriate therapy for specific co-morbidities given concomitantly with the test drug / placebo
Indication	Chronic heart failure (NYHA II-IV) with preserved ejection fraction
Diagnosis and main criteria for inclusion	1. Men or women aged 45 years and older 2. Diagnosis of chronic heart failure (CHF), NYHA class II-IV (without evidence of a non-cardiac explanation for dyspnea), LVEF ≥ 45% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) **within the previous 6 months** with no significant change in clinical status suggesting potential for deterioration in ejection fraction. 3. **In the 6 months prior to run-in**: a) Requirement of treatment with a diuretic AND b) Elevated natriuretic peptides, defined as *one* of: o BNP ≥ 75 pg/mL or NT-proBNP ≥ 300 pg/mL (sinus rhythm) o BNP ≥ 200 pg/mL or NT-proBNP ≥ 900 pg/mL (atrial fibrillation) AND

	c) At least *one* of the following: o *LA enlargement* (LA diameter ≥ 3.9 cm, LA volume ≥ 55 mL, LAVI ≥ 29 mL/m^2, or LAA ≥ 20 cm^2) (assessed by local imaging) o *LV hypertrophy* (septal or posterior wall thickness ≥ 1.1 cm) (local imaging) o *Elevated filling pressures* (invasive assessment) at rest (PAWP ≥ 20 mmHg or LVEDP ≥ 15 mmHg) or with exercise (PAWP ≥ 25 mmHg) (historical records) 4. 6MWD ≥ 100 m and ≤ 550 m at Visit 2 (baseline) 5. Written informed consent signed before any study-specific procedure
Diagnosis and main criteria for exclusion	1. Acute decompensated heart failure (defined as acute exacerbation of HF that may require IV therapy with diuretics, vasodilators or inotropic drugs and / or mechanical support) within the past 4 weeks 2. Initiation or dose modification of cardiovascular pharmacological therapy within the past 2 weeks (dose modification of pre-existing diuretic / anticoagulant medication is allowed based on patient-specific needs) 3. Inability to exercise: wheelchair / scooter / walker dependent; dependent on supplemental oxygen 4. HF is not the primary factor limiting activity as indicated by the patient affirming #1, #2 or #3 of the following questionnaire: My ability to be active is *most* limited by: #1 - Joint, foot, leg, hip or back pain #2 - Unsteadiness or dizziness impairing daily mobility #3 - Lifestyle, weather, or I just don't like to be active 5. Previous diagnosis of HFrEF (LVEF < 40%) 6. Known clinically significant persistent coronary ischemia (based on medical history, a preexisting or a recent clinical stress test) 7. Occurrence of any of the following within the previous 3 months: o Clinically evident myocardial infarction o Hospitalization for unstable angina o Stroke or transient ischemic attack o Coronary artery bypass graft (CABG) o Percutaneous coronary intervention (PCI) o Implantation of a cardiac resynchronization therapy device (CRTD) o Major surgery (that could interfere with patients' ability to exercise) 8. PCI, CABG or implantation of a CRTD planned between randomization and end of study 9. Sustained * systolic blood pressure ≤ 90 mmHg and / or signs and symptoms of hypotension prior to randomization 10. Sustained * systolic blood pressure ≥ 160 mmHg prior to randomization 11. Sustained * bradycardia with heart rate < 50 beats/minute or tachycardia with heart rate > 100 beats/minute prior to randomization * At two consecutive visits

12. Known clinically relevant ventricular arrhythmias (sustained ventricular tachycardia, ventricular flutter or fibrillation) within 3 months prior to randomization based on either medical history or device generated data (if applicable)
13. Clinically relevant permanent or intermittent AV-block ≥ grade II in patients without a permanent pacemaker or ICD / CRTD
14. Severe uncorrected valvular heart disease
15. Listing for heart transplantation and / or anticipated implantation of a ventricular assist device
16. Severe pulmonary disease with any of the following:
    - Requirement of continuous (home) oxygen or
    - History of chronic obstructive pulmonary disease ≥ GOLD III
    - Use of systemic corticosteroids
17. Asthma bronchiale with any of the following:
    - Symptoms *not* well-controlled within the past 6 months or
    - Ever intubated or in an intensive care unit for asthma
18. Anemia with hemoglobin < 10 g/dL within 3 months prior to randomization. If several values are available the latest result should be used.
19. Body mass index (BMI) > 45 kg/m^2 at randomization
20. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) formula within 3 months prior to randomization. If several values are available the latest result should be used.
21. Hepatic insufficiency classified as Child-Pugh B or C, or any of the following:
    - Primary biliary cirrhosis (PBC)
    - Primary sclerosing cholangitis
    - PBC-autoimmune hepatitis overlap syndrome
22. Concomitant use of any of the following therapy that cannot be discontinued:
    - Moderate or strong CYP3A4 inhibitors (Of note: grapefruit is a strong CYP3A4 inhibitor)
    - CYP3A4 inducers
    - Strong CYP2C8 inhibitors (Of note: clopidogrel is a strong CYP2C8 inhibitor)
    - Theophylline
    - Drugs having significant pre-systemic clearance via UGT1A1 in the intestine

    Respective substances must be stopped at least 7 days before randomization.
23. Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for > 12 months)
24. Known current heavy alcohol consumption or the use of illicit drugs that may interfere with the patient's safety and / or compliance
25. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s)
26. Previous assignment to treatment during this study

	27. Any condition or therapy, which would make the patient unsuitable for the study, or life expectancy less than 12 months (e.g. active malignancy) 28. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site) 29. Known allergies, intolerance or hypersensitivities to the study treatment (active substance or excipients), adhesives or hydrogel
Study design	Multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding
Methodology	The study will comprise a 1-week run-in period, 20-week treatment period, and a 6-week follow-up period (27 weeks total). Patients will have site visits at Weeks -1, 0 (baseline), 4, 8, 12, 20 (end of treatment visit) and 24 (safety follow-up visit). In addition, 2 phone calls at Weeks 2 and 26 will be made to assess patients' safety, and one additional phone call – to remind the patients of AVIVO self-application at Week 19. 6MWD test (including Borg CR 10 Scale) will be done during the run-in, to familiarize patients with the test, and at baseline, Week 8 and end of treatment / premature discontinuation visits. Safety will be monitored throughout the study. PK samples will be taken from all patients at dedicated time points. Biomarkers reflecting the pharmacodynamic activity of the drug will be examined, as well as candidate biomarkers that may predict drug response.
Type of control	Placebo control
Data Monitoring Committee	Yes
Number of patients	Approximately 288 patients are planned to be randomized.
Primary variable	Absolute change from baseline in 6MWD after 20 weeks of treatment
Time point / frame of measurement for primary variable	After 20 weeks of treatment
Plan for statistical analysis	The primary efficacy analysis will be performed on the primary efficacy variable in patients belonging to the per-protocol set using a type I error of 5%. For the assessment of a dose-response relationship in the absolute change in 6MWD, the MCP-Mod method, combining multiple comparison procedures (MCP) with modeling techniques under model uncertainty, will be used. A set with 5 candidate dose-response models has been specified. For the detection of a dose-response signal, each of the dose-response models in the candidate set will be tested at the corresponding type I error level, using a one-sided multiple contrast test based on pre-specified contrast coefficients. If a dose-response signal is established, a dose-response model will be fitted to the data and target dose(s) of interest will be estimated based on the estimated dose-response model. Other efficacy variables will be analyzed analogously to the primary variable or descriptively.

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6MWD	6-minute walking distance
A1R	A1 receptor
ACE	angiotensin-converting enzyme
ACEi	ACE inhibitor
ADHF	acute decompensated heart failure
ADP	adenosine diphosphate
AE(s)	adverse event(s)
AF	atrial fibrillation
ALT	alanine aminotransferase
AP	alkaline phosphatase
ARB(s)	angiotensin receptor blocker(s)
ARNI(s)	angiotensin receptor-neprilysin inhibitor(s)
AST	aspartate aminotransferase
ASWT	anteroseptal wall thickness
ATP	adenosine triphosphate
AUC	area under the time-concentration curve
AV	atrioventricular
BCRP	breast cancer resistance protein
BM	biomarker
BMI	body mass index
BNP	b-type natriuretic peptide
BSA	body surface area
%CV	percent coefficient of variation
CABG	coronary artery bypass graft
cAMP	cyclic adenosine monophosphate
CAD	coronary artery disease
CE mark	European Conformity mark (*Conformité Européenne*)
CEC	Clinical Events Committee
CHF	chronic heart failure
CI	cardiac index
CK	creatine kinase
CKD	chronic kidney disease
C_{max}	maximum drug concentration in plasma
CNS	central nervous system
CO	cardiac output
CRF	case report form
CRO	contract research organization
CRTD	cardiac resynchronization therapy device
CV	cardiovascular
CYP	cytochrome P450
DBP	diastolic blood pressure
DMC	Data Monitoring Committee

e.g.	for example (*exempli gratia*)
EC(s)	Ethics Committee(s)
ECG	electrocardiogram
eCRF	electronic CRF
EDC	electronic data capture
EF	ejection fraction
eGFR	estimated glomerular filtration rate
EMA	European Medicines Agency
EOT	end of treatment
EQ-5D-5L	EuroQol Group 5-dimensional, 5-level questionnaire
ESC	European Society of Cardiology
EU	European Union
EWDT	E-wave deceleration time
FAS	full analysis set
FDA	(US) Food and Drug Administration
FFA	free fatty acids
FU	follow up
FWER	family-wise error rate
Gal-3	galectin-3
GCP	Good Clinical Practice
GDF-15	growth differentiation factor 15
GFR	glomerular filtration rate
GGT	gamma glutamyl transpeptidase
GMP	Good Manufacturing Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GPV	global pharmacovigilance
HbA1c	hemoglobin A1c
HCl	hydrochloride
HDL	high-density lipoprotein
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalized heart failure
HIV	human immunodeficiency virus
HR	heart rate
hs-TNT	high sensitivity troponin T
i.e.	that is (*id est*)
IB	investigator's brochure
ICD	implantable cardioverter defibrillator
ICF	informed consent form

ICH	International Conference on Harmonization
IDMS	Isotope dilution mass spectroscopy
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ITT	intent-to-treat
IV	intravenous(ly)
IVSD	interventricular septum diameter
IxRS	interactive web / voice response system
KCCQ	Kansas City cardiomyopathy questionnaire
LA	left atrial
LAA	left atrial appendage
LAV	LA volume
LAVI	LA volume index
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LV	left ventricular
LVEDP	LV end-diastolic pressure
LVEDV	LV end-diastolic volume
LVEDVI	LVEDV index
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVESVI	LVESV index
MAP	mean arterial pressure
MCH	mean corpuscular hemoglobin
MCHC	MCH concentration
MCP	multiple comparison procedures
MCV	mean corpuscular volume
MDRD	modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mL	milliliter
mmHg	millimeter of mercury
MR-proANP	mid-regional pro-atrial natriuretic peptide
NGAL	neutrophil gelatinase-associated lipocalin
NONMEM	non-linear mixed effect modeling
NT-proBNP	N-terminal pro-hormone b-type natriuretic peptide
NYHA	New York Heart Association
OPN	osteopontin
PASP	pulmonary artery systolic pressure
PAWP	pulmonary artery wedge pressure

PBC	primary biliary cirrhosis
PCI	percutaneous coronary intervention
PD	pharmacodynamic
PDV	premature discontinuation visit
Pes	end-systolic pressure
pg	picogram
PK	pharmacokinetic
PKS	PK analysis set
PP	pulse pressure
PPS	per-protocol set
PRO(s)	patient-reported outcome(s)
PTT	partial thromboplastin time
PWT	posterior wall thickness
QC	quality control
QoL	quality of life
QTcB	QT interval frequency-corrected according to Bazett's formula
RV	right ventricular
SAC	systemic arterial compliance
SAE(s)	serious adverse event(s)
SAF	safety analysis set
SAP	statistical analysis plan
SBP	systolic blood pressure
SERCA	sarcoplasmic reticulum calcium adenoside triphosphatase
sST2	soluble suppression of tumorigenicity-2
SUSAR(s)	suspected unexpected serious adverse reaction(s)
SV	stroke volume
SVI	SV index
SVT(s)	supraventricular tachycardia(s)
TAPSE	tricuspid annular plane systolic excursion
TD	tissue Doppler
TIMP-4	tissue inhibitor of metalloproteinase-4
TPR	total peripheral resistance
UACR	urine albumin-to-creatinine ratio
UGT1A1	uridine diphosphate glucuronosyltransferase 1A1
ULN	upper limit of normal
US(A)	United States (of America)
VAS	visual analogue scale
WCHF	worsening chronic heart failure

3. Introduction

3.1 Background

Chronic heart failure (CHF) is a major public health problem characterized by significant mortality, frequent hospitalizations, and poor quality of life, with an overall prevalence that is increasing throughout the world. The European Society of Cardiology (ESC) represents countries with a population of > 900 million, and there are at least 15 million patients with heart failure (HF) in those 51 countries (1). An estimated 5.7 million patients have HF in the United States (US) with increasing prevalence, and the incidence approaches 10 per 1000 population after 65 years of age; the lifetime risk for developing HF is one in five for men and women (2). In developed countries 1-2% of the adult population has HF, with the prevalence rising to ≥ 10% among persons 80 years of age or older (3). HF carries a prognosis comparable to many forms of cancer with a 5-year survival rate of approximately 50% (4), which exceeds that of many cancers (5).

In the recent years, HF has been shown to occur in patients with near normal or preserved systolic function; a condition termed as “heart failure with preserved ejection fraction” (HFpEF). Currently, HFpEF accounts for approximately half of HF cases, and the prevalence of HFpEF, as well as its relative proportion compared with heart failure with reduced ejection fraction (HFrEF), has been increasing in recent years (6-8). Compared with HFrEF, patients with HFpEF are older, more often women and more commonly have a history of hypertension and atrial fibrillation (AF), while a history of myocardial infarction is less common (9).

HF is resulting in more than 1 million admissions per year as a primary diagnosis both in the US and Europe, representing 1% to 2% of all hospitalizations (2), thus being one of the leading causes of hospitalization. The relative proportion of HFpEF has increased to more than 45% of all HF hospitalizations (10) and hospitalization related to HF is the single most common cause of hospitalization in the HFpEF population, despite multiple significant comorbidities. Frequent hospitalizations, along with other direct and indirect costs, also place an enormous financial burden on healthcare systems; more is spent annually in the US for the treatment of HF by Medicare than on any other Medicare-covered condition (11).

Most patients with hospitalized heart failure (HHF) suffer from worsening of established HF (6). The prognosis of patients admitted to the hospital for HF is particularly unfavorable, as recurrent HF hospitalizations are representing an important marker of disease progression and an important indicator of poor outcomes (12, 13): within 60 to 90 days after discharge, patients with HHF continue to have a mortality and readmission rate approaching 15% and 30%, respectively, with the most common cause of death being progressive HF (14). Overall, patients with HFpEF have similar rates of post-discharge mortality compared with those with HFrEF, but the mode of death may differ (6). In addition, these patients have moderate to severe signs and symptoms throughout their course.

Exercise intolerance, with symptoms of dyspnea and fatigue with exertion and measured objectively with a variety of exercise test modalities, is the primary manifestation of chronic HFpEF, even when patients are stable and well-compensated (15). Exercise intolerance is associated with reduced health-related quality of life.

Mechanisms implicated in HFpEF include abnormal relaxation and reduced left ventricular compliance with resultant increase in ventricular filling pressures, increased vascular stiffness, abnormal systolic function despite preserved ejection fraction, interstitial fibrosis, coronary disease and microvascular dysfunction (7, 16-20). Furthermore, it is well established that energy deficiency contributes to the syndrome of HF (21, 22), and it has been shown that altered myocardial energetics underlie diastolic function abnormalities in HFpEF, especially under exercise conditions (23).

In addition, HFpEF is strongly influenced by aging, a systemic process affecting all organ systems. The impact of multiple comorbidities typical of older HFpEF patients contributes to the phenotypic heterogeneity and multifactorial pathophysiology of the disease (24). Owing to this complexity, among other things, currently no consensus diagnostic approach to HFpEF exists in the professional community. The recommendations essentially involve establishing that the HF clinical syndrome is present in the absence of other etiologies for dyspnea and volume overload. Therefore it seems reasonable to use a multitiered approach with the goal of identifying that there is a significant cardiovascular limitation driving the symptoms of dyspnea and functional intolerance, integrating the clinical presentation, the documentation of a preserved ejection fraction and the elevation of natriuretic peptide levels to support the diagnosis (25).

In contrast to the many studies that have shown a benefit of pharmacologic therapies in HFrEF, outcome trials including ACE inhibitors, mineralocorticoid receptor antagonists and ß-blockers have failed to show a benefit on the natural history of HFpEF (26-30). Almost no subgroups have revealed any favorable signals either, save for the possibility of mineralocorticoid antagonist effects in HFpEF patients enrolled in the Americas in the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial (31). In addition, there are several retrospective analyses which have shown that standard therapies do not work.

Pooled analysis of prospective HFpEF studies demonstrates that coronary heart disease (CAD) is common in HFpEF, with an estimated prevalence of approximately 45% (32). Slowing an elevated heart rate can prolong LV filling time in an abnormally stiff ventricle and also prolong coronary perfusion. However, a recent post-hoc analysis from the CHARISMA-trial in patients with CAD showed that β-blocker use was not associated with lower cardiovascular events in those without previous myocardial infarction (33).

Besides, limited heart rate increase (chronotropic incompetence) significantly contributes to low cardiac output augmentation with exercise in patients with HFpEF (34). There is a high prevalence of chronotropic incompetence in patients with HFpEF reported by clinical trials, which may already be a contributing factor to symptoms because of limited increase in cardiac output with exertion (23, 35). In these circumstances, further blunting heart rate by the use of ß-blockers seems unlikely to benefit HFpEF patients, as this could lead to worsening exercise capacity.

Accordingly, the evidence base for clinical efficacy for the use of ß-blocker therapy in HFpEF is inconclusive, and the results of ß-blocker trials in HFpEF are neutral. Therefore, current guidelines do not recommend the use of ß-blockers solely for HFpEF, unless they are used to

optimize treatment of comorbidity, such as controlling ventricular rate in atrial fibrillation or treating CAD (36-40).

In summary, there is no evidence-based therapy specific for HFpEF, but only general treatment recommendations exist, including the use of diuretics, caloric restriction diet, exercise training, and anticoagulation in the presence of atrial fibrillation (41). These are presumed to be beneficial to the vast majority of HFpEF patients because they address the presentation phenotype of lung congestion and the predisposition phenotype of overweight / obesity present in > 80% of HFpEF patients (42), as well as the common comorbid condition of arrhythmias like atrial fibrillation (43).

Thus, a substantial unmet medical need exists for clinical trials investigating therapeutic options targeting mechanisms involved in HFpEF (44-47). As evidence has suggested a crucial role of cardiac energetic impairment in the pathophysiology of HFpEF, cardiac energetics and altering cardiac substrate use represent promising targets for HFpEF therapy.

Apart from the fact that the treatment paradigm for patients with HFrEF, which centers on systemic blockade of the maladaptive neurohumoral response, does not seem to be working in the same way in HFpEF, the repeated stepwise addition of hemodynamically active medications raises tolerability and safety concerns (e.g. hypotension and bradycardia) (48), and hemodynamic compromise represents a frequent reason for failed HF drug development (49).

Therefore, addressing the failing heart directly might be a new option for the development of the next generation of hemodynamically silent HF drugs. In this context, neladenoson bialanate holds promise as a potentially hemodynamically neutral therapy for HF that could simultaneously improve cardiomyocyte energetics, calcium homeostasis, cardiac structure and function, and long-term clinical outcomes when added to background therapies. If positive, this study would provide a novel treatment strategy for this large group of patients with currently very limited treatment options.

3.2 Partial adenosine A1 receptor agonism in heart failure

The failing heart is characterized by abnormal mitochondrial structure and function including hyperplasia and reduced organelle size, poor organelle respiration, reduced mitochondrial membrane potential, opening of membrane permeability pores, and reduced rates of adenosine triphosphate (ATP) synthesis and thereby reduced energy supply in cardiomyocytes in HFpEF and HFrEF (16, 50-55). Additionally Ca^{2+} handling is disturbed and $SERCA_{2a}$ protein levels are decreased in HF (56), which changes the contraction / relaxation coupling in cardiomyocytes and leads to an intracellular calcium overload in the heart. Furthermore, systemic metabolic impairments in the skeletal muscle are increasingly recognized as contributing both to symptoms (muscle weakness, exercise limitation) and disease progression in HF (57). Preclinical studies have demonstrated that myocardial energy metabolism and utilization as well as calcium homeostasis are improved by the partial adenosine A1 receptor agonist capadenoson (50, 58). In the heart failure standard dog model, treatment with this drug showed fast improvement of cardiac energetics *(*ATP synthesis*)* via mitochondrial effects. Capadenoson further improved $SERCA_{2a}$ activity, leading to decreased intracellular calcium overload (50).

The high prevalence of CAD in patients with HFpEF is associated with greater deterioration in ventricular function and increased mortality (59, 60) based mainly on ischemia driven injury of cardiac tissue. The primary physiological undertaking of adenosine is to preclude tissue injury and promote repair in response to stress mainly through adenosine A1 receptors (A1R) activation. Preclinical data showed cardioprotection from ischemia-induced injury by preconditioning and improvement of endothelial function in animal models with partial A1R agonists including capadenoson (50, 61, 62). Potential benefit of this targeted approach to the treatment of HF lies in the ability of partial A1R agonism to afford protection to the failing myocardium by limiting triggers of cell injury and death. Furthermore, the prevention of deterioration of myocardial ATP levels matching the ATP production to oxygen supply seems to be an important factor for cardioprotection. Especially patients with high risk for cardiac events (e.g. HF patients with diabetes, chronic kidney disease [CKD], advanced CAD) might benefit from A1R activation.

Furthermore, excessive activation of the adrenergic nerve system is detrimental in HF patients, inducing systemic vasoconstriction, increased sodium / water retention, and ventricular remodeling, all of which contribute to disease progression. Adenosine carries anti-adrenergic properties that can protect the heart from adverse mechanical and metabolic over-response to excessive catecholamine stimulation, thereby limiting ischemia. Activation of the A1R may also inhibit norepinephrine release from cardiac presynaptic nerves (63, 64). Conceivably, these effects may be important for preventing disease progression and further adverse remodeling, particularly in those patients with concomitant CAD. Partial adenosine A1R agonism might offer a unique opportunity to selectively modulate the sympathetic control of cardiac function via presynaptic A1R activation and cAMP inhibition (63).

Heart failure is often associated with comorbidities like CKD and diabetes in HFpEF patients (65). Renal effects of adenosine A1R activation lead to vasoconstriction of the afferent arterioles in the kidneys (66) and thereby sodium retention and anti-diuretic effects. The effects were regarded as potential for renal benefit with adenosine antagonism in HF and led to large scale drug development programs with adenosine A1R antagonists, such as rolofylline in patients with acute decompensated heart failure (ADHF). But the Phase III trial failed to show any renal protection. Instead, higher rates of persistent renal impairment, seizure and stroke were noted in the rolofylline group (67, 68). In contrast, A1R activation shows reno-protective effects in preclinical models of ischemia-induced renal injury (69).

Increased plasma levels of free fatty acids (FFAs) are often found in patients with HF (70, 71) and result in an increase of insulin resistance and might be involved in the deterioration of heart function. A1R agonists can reduce plasma levels of FFAs in humans as shown in clinical trials (72). Furthermore, FFAs act as substrate for the energetic metabolism in the heart. HF is characterized by an added reliance on fatty acid oxidation, with downregulation of myocardial glucose transporters (73, 74). These changes characterize the transition of the failing heart to a fetal metabolic phenotype and gene profile, an adaptation that can further promote HF progression (73-75). Animal studies suggest that the partial A1R agonist capadenoson can augment expression of the GLUT-1 and GLUT-4 glucose transporters to near normal levels (50). Moreover, therapy with capadenoson has also been associated with normalization of protein levels that mediate fatty acid oxidation (50). Thus, A1R agonism

appears capable of partially correcting derangements in cardiac substrate utilization and restoring a physiologic metabolic profile in HF.

Previous attempts to address the A1 receptor, while offering potential therapeutic benefits, were limited by undesirable side effects that include bradycardia, atrioventricular blocks, sedation and antidiuretic effects. Furthermore, adenosine-like A1R agonists often have the drawback of a short half-life and low bioavailability making them not suitable for chronic oral therapy.

In contrast, partial adenosine A1 agonists may be used to modulate and trigger primarily favorable pharmacological responses for HF therapy, such as cardio- and renoprotection. A partial agonist is a low efficacy ligand, which elicits only a submaximal response from the receptor in contrast to a full agonist, even when all receptors are occupied. A partial agonist is expected to result in a robust signal response only in tissues with relative high receptor reserve, whereas a full agonist will elicit a robust signal also in tissue with a low receptor reserve. Thus, partial agonists are useful for achieving high selectivity for the target organ / tissue and minimizing toxicity and effects in non-target tissues (e.g. neurological effects, undesired kidney effects, AV conduction abnormalities). Hemodynamic effects evoked by A1R activation seem to have a lower receptor reserve in e.g. the AV node compared to cardioprotective effects. Furthermore, partial adenosine A1R agonists might induce less receptor desensitization than full agonists and be ideal for chronic treatment (76).

3.3 Neladenoson bialanate

Neladenoson bialanate (BAY 1067197, which is the free base of the hydrochloride BAY 86-8901) is the pro-drug of the pharmacologically active compound BAY 84-3174, a highly potent and selective non-adenosine like partial adenosine A1 receptor agonist suitable for once daily oral use.

Pharmacological actions seem to be at least partly based on an acute restoration and improved utilization of myocyte energetics (ATP production within the mitochondria), and chronic improvement of calcium handling by restoration of $SERCA_{2a}$ protein levels, which result in protection of cardiac function and improvement of contraction / relaxation coupling. These effects were seen after a short treatment period of one week in nonclinical models. In addition, neladenoson bialanate was characterized regarding mitochondrial function in isolated cardiomyocytes from normal and HF dogs (EF ~30%) produced by intracoronary microembolization as described in Sabbah et al (77). Neladenoson bialanate improved mitochondrial function (respiration, ATP synthesis, ATP / adenosine diphosphate [ADP] ratio, cytochrome c-dependent cyclooxygenase activity, membrane potential, and mitochondrial permeability transition pore opening) significantly and dose dependently in HF cardiomyocytes but had no effect on normal cardiomyocytes. Since both impaired myocardial energetics and disturbed calcium reuptake are considered key contributors to the pathophysiology of HFpEF, neladenoson bialanate has the potential to be a suitable treatment option for HFpEF patients to improve symptomatic status, morbidity and survival.

Furthermore, up to 80% of HFpEF patients are on a ß-blocker to optimize treatment of comorbidities, such as CAD or hypertension (29). However, ß-blockers can exacerbate chronotropic incompetence, an important cause of exercise intolerance in patients with HFpEF found in 50-80% of patients (23, 78, 79). Other than ß-blockers, neladenoson

bialanate shows no effects on heart rate in preclinical (39) and clinical models (49). Thus, it is a suitable option in patients with HFpEF, where a treatment not damping heart rate would be desirable.

Nonclinical data showed that neladenoson bialanate is cardio- and renoprotective at doses lower than needed to elicit the clinically relevant undesirable effects on heart rate, AV-conduction, blood pressure, renal function and the central nervous system.

In animal models and clinical studies in healthy volunteers, neladenoson bialanate significantly reduces plasma levels of free fatty acids vs. placebo. Abnormal energetic activity in heart failure correlates inversely with plasma free-fatty-acid concentrations. The excess of fatty acids may adversely affect the myocardium and in HF may be associated with uncoupled respiration (80).

Further details can be found in the investigator's brochure (IB), which contains comprehensive information on the study drug. The IB in its most current version is available in the study file.

3.4 Rationale of the study

The main limitations of using full A1R agonists in cardiovascular indications such as HF are undesired cardiac effects, such as bradycardia and higher degree AV block as well as negative cardiac inotropy and dromotropy. In contrast, preclinical data show that the partial adenosine A1R agonist neladenoson bialanate can be used to modulate and trigger primarily favorable pharmacological responses for HF therapy and avoid undesired effects such as AV conduction abnormalities and higher degree AV block. Nevertheless, based on the mode of action, there are theoretical concerns particularly with regard to undesired effects, such as bradycardia and higher degree AV block for an A1R agonist, which might be aggravated by concomitant use of heart rate decreasing drugs like ß-blockers.

The purpose of this clinical trial is to assess the safety, tolerability and the pharmacokinetic and pharmacodynamic response of 20 weeks' treatment with neladenoson bialanate compared to placebo in patients with chronic HFpEF on appropriate therapy for specific co-morbidities and to find the optimal dose for a further Phase III trial.

4. Study objectives

The objective of the study is to find the optimal dose of neladenoson bialanate for the Phase III trial by detecting and characterizing a significant dose-response relationship in the primary efficacy endpoint, absolute change from baseline in 6-minute walking distance (6MWD) at 20 weeks, in patients with chronic heart failure with preserved ejection fraction (HFpEF), and by characterizing the safety, tolerability and pharmacodynamic effects of the compound when given in addition to appropriate therapy for specific co-morbidities.

An exploratory objective is to further assess pharmacokinetic parameters and blood and urine biomarkers.

For variables please see Section 10.3.1.

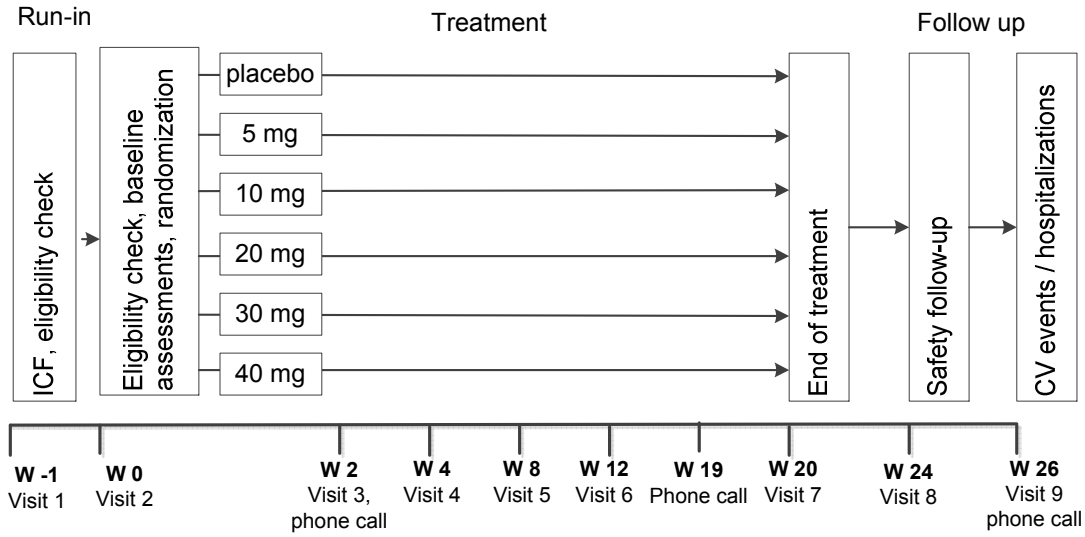
Considering the exploratory nature of phase II studies and the uncertainty around the most appropriate endpoints in HFpEF, the sponsor will take the totality of the data (including secondary / exploratory endpoints) into consideration regarding the benefit / risk assessment and the decision to move into phase III.

5. Study design

5.1 Design overview

Study 17582 is a multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding Phase II study. Figure 5—1 displays the overall study design.

Figure 5—1: Study design overview



Abbreviations: CV = cardiovascular; ICF = informed consent form; W = week

Approximately 288 patients from approximately 90 study centers worldwide will be randomized to one of the active treatment dose arms or placebo, in addition to their background therapy (for details see Section 7).

The study will comprise a 1-week run-in period, 20-week treatment period, and a 6-week follow-up period (27 weeks total).

Patients will have site visits at Weeks -1, 0 (baseline), 4, 8, 12, 20 (end of treatment visit) and 24 (safety follow-up visit). In addition, 2 phone calls at Weeks 2 and 26 will be made to assess patients' safety, and one additional phone call – to remind the patients of AVIVO self-application at Week 19.

6MWD test (including Borg CR 10 Scale) will be done during the run-in, to familiarize patients with the test, and at baseline, Week 8 and end of treatment / premature discontinuation visits. Safety will be monitored throughout the study. PK samples will be taken from all patients at dedicated time points. Biomarkers reflecting the pharmacodynamic activity of the drug will be examined, as well as candidate biomarkers that may predict drug response.

For detailed visit descriptions and rules for patients who discontinue study treatment earlier, please see Sections 9.1 and 9.2.

The anticipated duration of the study as a whole is approximately 19 months: this includes an anticipated recruitment period of 13 months followed by a run-in period of 1 week, a treatment period of 20 weeks and a follow-up period of 6 weeks after enrollment of the last patient into the trial.

5.2 Primary variable

- Absolute change from baseline in 6MWD after 20 weeks of treatment.

For secondary and other variables please see Section 10.3.1.

5.3 Justification of the design

A parallel group design was chosen to compare five different once-daily dose regimens and one placebo arm to find the best dose for Phase III. Placebo control is used to control for observer and subject bias, and randomization – to control for assignment bias. Based on Phase I data in healthy volunteers and Phase II data in heart failure patients, a sequential dose escalation design was not deemed necessary for neladenoson bialanate since the safety profile of the compound could be verified in dose ranges up to 40 mg. Evidence of A1R target engagement could already be achieved in different tissues across different clinical trials with 20 mg neladenoson bialanate. The dose range around 20 mg (5, 10, 30 and 40 mg) is to ensure different data points to feed the MCP mod predefined models and potential unforeseen variances. The doses studied will ensure a strong dose recommendation moving forward into phase III. Safety of the subjects in this parallel study design will be closely monitored by a Data Monitoring Committee (DMC).

5.4 End of study

The end of the study as a whole will be reached as soon as the last visit of the last patient has occurred in all centers in all participating countries (EU and non-EU).

6. Study population

6.1 Inclusion criteria

Patients must meet all of the following inclusion criteria to be included in the study:

1. Men or women aged 45 years and older
2. Diagnosis of chronic heart failure (CHF), NYHA class II-IV (without evidence of a non-cardiac explanation for dyspnea), LVEF ≥ 45% assessed by any imaging modality (e.g. echocardiography, cardiac magnetic resonance, cine levocardiography) **within the previous 6 months** with no significant change in clinical status suggesting potential for deterioration in ejection fraction.
3. **In the 6 months prior to run-in**:

   a) Requirement of treatment with a diuretic

   AND

   b) Elevated natriuretic peptides, defined as *one* of:

   - BNP ≥ 75 pg/mL or NT-proBNP ≥ 300 pg/mL (sinus rhythm)
   - BNP ≥ 200 pg/mL or NT-proBNP ≥ 900 pg/mL (atrial fibrillation)

   AND

c) At least *one* of the following:

- *LA enlargement* (LA diameter ≥ 3.9 cm, LA volume ≥ 55 mL, LAVI ≥ 29 mL/m^2, or LAA ≥ 20 cm^2) (assessed by local imaging)
- *LV hypertrophy* (septal or posterior wall thickness ≥ 1.1 cm) (local imaging)
- *Elevated filling pressures* (invasive assessment) at rest (PAWP ≥ 20 mmHg or LVEDP ≥ 15 mmHg) or with exercise (PAWP ≥ 25 mmHg) (historical records)

4. 6MWD ≥ 100 m and ≤ 550 m at Visit 2 (baseline)
5. Written informed consent signed before any study-specific procedure

6.2 Exclusion criteria

Patients who meet any of the following exclusion criteria will be excluded from the study:

1. Acute decompensated heart failure (defined as acute exacerbation of HF that may require IV therapy with diuretics, vasodilators or inotropic drugs and / or mechanical support) within the past 4 weeks
2. Initiation or dose modification of cardiovascular pharmacological therapy within the past 2 weeks (dose modification of pre-existing diuretic / anticoagulant medication is allowed based on patient-specific needs)
3. Inability to exercise: wheelchair / scooter / walker dependent; dependent on supplemental oxygen
4. HF is not the primary factor limiting activity as indicated by the patient affirming #1, #2 or #3 of the following questionnaire:

   My ability to be active is *most* limited by:

   #1 - Joint, foot, leg, hip or back pain

   #2 - Unsteadiness or dizziness impairing daily mobility

   #3 - Lifestyle, weather, or I just don’t like to be active
5. Previous diagnosis of HFrEF (LVEF < 40%)
6. Known clinically significant persistent coronary ischemia (based on medical history, a preexisting or a recent clinical stress test)
7. Occurrence of any of the following within the previous 3 months:
   - Clinically evident myocardial infarction
   - Hospitalization for unstable angina
   - Stroke or transient ischemic attack
   - Coronary artery bypass graft (CABG)
   - Percutaneous coronary intervention (PCI)
   - Implantation of a cardiac resynchronization therapy device (CRTD)
   - Major surgery (that could interfere with patients’ ability to exercise)

8. PCI, CABG or implantation of a CRTD planned between randomization and end of study
9. Sustained [1] systolic blood pressure ≤ 90 mmHg and / or signs and symptoms of hypotension prior to randomization
10. Sustained [1] systolic blood pressure ≥ 160 mmHg prior to randomization
11. Sustained [1] bradycardia with heart rate < 50 beats/minute or tachycardia with heart rate > 100 beats/minute prior to randomization
12. Known clinically relevant ventricular arrhythmias (sustained ventricular tachycardia, ventricular flutter or fibrillation) within 3 months prior to randomization based on either medical history or device generated data (if applicable)
13. Clinically relevant permanent or intermittent AV-block ≥ grade II in patients without a permanent pacemaker or ICD / CRTD
14. Severe uncorrected valvular heart disease
15. Listing for heart transplantation and / or anticipated implantation of a ventricular assist device
16. Severe pulmonary disease with any of the following:
    - Requirement of continuous (home) oxygen or
    - History of chronic obstructive pulmonary disease ≥ GOLD III
    - Use of systemic corticosteroids
17. Asthma bronchiale with any of the following:
    - Symptoms *not* well-controlled within the past 6 months or
    - Ever intubated or in an intensive care unit for asthma
18. Anemia with hemoglobin < 10 g/dL within 3 months prior to randomization. If several values are available the latest result should be used.
19. Body mass index (BMI) > 45 kg/m^2 at randomization
20. Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease (MDRD) formula within 3 months prior to randomization (see Appendix 16.1). If several values are available the latest result should be used.
21. Hepatic insufficiency classified as Child-Pugh B or C (see Appendix 16.2), or any of the following:
    - Primary biliary cirrhosis (PBC)
    - Primary sclerosing cholangitis
    - PBC-autoimmune hepatitis overlap syndrome

[1] At two consecutive visits

22. Concomitant use of any of the following therapy that cannot be discontinued:
    - Moderate or strong CYP3A4 inhibitors (Of note: grapefruit is a strong CYP3A4 inhibitor)
    - CYP3A4 inducers
    - Strong CYP2C8 inhibitors (Of note: clopidogrel is a strong CYP2C8 inhibitor)
    - Theophylline
    - Drugs having significant pre-systemic clearance via UGT1A1 in the intestine

    Respective substances must be stopped at least 7 days before randomization.
23. Women of childbearing potential (women are considered of childbearing potential if they are not surgically sterile or postmenopausal, defined as amenorrhea for > 12 months)
24. Known current heavy alcohol consumption or the use of illicit drugs that may interfere with the patient's safety and / or compliance
25. Previous (within 30 days or 5 half-lives of the investigational drug, whichever is longer) or concomitant participation in another clinical study with investigational medicinal product(s) or device(s)
26. Previous assignment to treatment during this study
27. Any condition or therapy, which would make the patient unsuitable for the study, or life expectancy less than 12 months (e.g. active malignancy)
28. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of the investigational site)
29. Known allergies, intolerance or hypersensitivities to the study treatment (active substance or excipients), adhesives or hydrogel

6.3 Justification of selection criteria

The selection criteria were chosen to exclude patients from the study who 1) may potentially be exposed to specific risks after administration of the study drug, 2) have conditions that may have an impact on the aim of the study, or 3) have a condition other than HFpEF that may be primarily responsible for their symptoms.

6.4 Withdrawal of patients from study

6.4.1 Withdrawal

An excessive rate of withdrawals (either patients discontinuing study medication or study withdrawal) can render the study non-interpretable. Therefore, un-necessary withdrawal of patients should be avoided and all efforts should be taken to motivate patients to comply with all the study specific procedures and to be followed until the end of the trial to detect the occurrence of cardiovascular events / assess vital status.

Before permanently discontinuing study medication (either initiated by the patient or the investigator) an interruption should be considered. Patients, who have temporarily discontinued study medication for any reason, should restart as soon as medically justified in

the opinion of the investigator; the patient can re-start at any time before the end of treatment (EOT) visit. In addition, patients should not be withdrawn from the study drug or from the study solely for reaching a potential cardiovascular event.

All patients who permanently discontinue study medication should come in for the EOT / premature discontinuation visit as soon as possible after discontinuation of the study medication and the safety follow-up visit 4 weeks after the last dose. In addition, they will be contacted by the investigator via the scheduled Week 26 phone call to assess occurrence of cardiovascular events.

The investigator should show due diligence and explore all possible options to reach a patient who fails to return to a visit. The site must document all attempts to try to contact the patient in the medical records / source documents.

In order to avoid loss-to-follow-up, the investigator should ask the patient at the study start for the contact details of a relative or friend who can be contacted in case the patient cannot be reached.

Patients should not be withdrawn from follow-up unless the patient explicitly withdraws consent to be contacted. All efforts should therefore be made to minimize the number of patients who withdraw such consent as, in general, no further information on cardiovascular events and survival status may be collected after that point.

Withdrawal criteria

Patients ***must*** **be withdrawn from the study** if any of the following occurs:

- At their own request or at the request of their legally acceptable representative. At any time during the study and without giving reasons, a patient may decline to participate further. The patient will not suffer any disadvantage as a result.

Patients ***may*** **be withdrawn from the study** if any of the following occurs:

- If, in the investigator's opinion, continuation of the study would be harmful to the patient's well-being.
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- If any investigational drug other than the study drug is used during the study period.

Depending on the time point of withdrawal, a withdrawn patient is referred to as either “screening failure” or “dropout” as specified below.

Screening failure

A patient who, for any reason (e.g. failure to satisfy the selection criteria), terminates the study before randomization is regarded a “screening failure”.

Re-screening is allowed once and only in the following cases:

- The patient had successfully passed the screening procedures, but could not be randomized to treatment on schedule.

- Initial screening occurred too early to complete the required washout period for prohibited substances.

In any case, the investigator has to ensure that the repeated screening procedures do not expose the patient to an unjustifiable health risk. For re-screening, the patient must sign a new informed consent form, even if its version was not changed after the patient's previous screening. In the event of re-screening the patient will be assigned a new patient identification number.

Dropout

A patient who discontinues study participation prematurely for any reason is defined as a "dropout" if the patient has already been randomized whether or not any study medication was taken.

General procedures

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records.

The patient may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.4.2 Replacement

Randomized patients who drop out or withdraw prematurely will not be replaced.

6.5 Patient identification

The patient number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current patient number within the center

7. Treatments

7.1 Treatments to be administered

Patients will receive either active treatment with neladenoson bialanate or placebo; treatment assignment is described in Section 7.3. Patients will be instructed to take two study tablets once daily, preferably in the morning, over a period of 20 weeks. On visit days, the study drug should be taken as specified in Table 9—1. The study drug should be taken with a glass of water, and can be taken with or without food. There will be no dose modifications; patients will stay on the dose which they were randomized to. For guidance regarding drug discontinuation please see Section 6.4.1

This treatment will be in addition to patients' regular treatment of specific co-morbidities (see Section 8.1.2).

7.2 Identity of study treatment

Three different "BAY-numbers" are used within this document, corresponding to three different chemical appearances of neladenoson bialanate:

BAY 1067197 is a pro-drug. BAY 1067197 represents the "pharmaceutical principle" of neladenoson bialanate, and thus this BAY number is used when generally speaking about neladenoson bialanate. Present dosages refer to BAY 1067197.

BAY 86-8901 is the hydrochloride salt of BAY 1067197. BAY 86-8901 is used to formulate the immediate release tablets to be administered to study patients. This BAY number is used when speaking about the oral preparation of neladenoson bialanate.

BAY 1067197 cannot be found in measurable concentrations, or only at very low concentrations in the blood plasma. Orally administered drug is converted by ester cleavage into the active metabolite **BAY 84-3174**, which is responsible for the pharmacodynamic effects. BAY 84-3174 is used in the context of plasma pharmacokinetic data measurements.

Details of BAY 1067197 are given in Table 7—1; details of placebo are given in Table 7—2. For more information please refer to the latest available version of the investigator's brochure.

Table 7—1: Identity of neladenoson bialanate (BAY 1067197)

Sponsor's internal reference number	BAY 1067197
Formulation	Pink coated tablets
Galenical form	Round biconvex, diameter 8 mm Markings: One side PT; Other side blank
Composition	Active ingredient: *neladenoson bialanate hydrochloride, 2-{4-[2-({[2-(4-chlorophenyl)-1,3-thiazol-4-yl]methyl}sulfanyl)-3,5-dicyano-6-(pyrrolidin-1-yl)pyridin-4-yl]phenoxy}ethyl L-alanyl-L-alaninate hydrochloride (BAY 86-8901)* Empirical formula: C_{35} H_{34} Cl N_7 O_4 S_2 * HCl Molecular mass: 716.29 + 36.46 [g/mole] Excipients: Lactose anhydrous, Crospovidone and magnesium stearate Coating: Lacquer pink (Opadry Pink 02A34744)
Strength	5 mg,10 mg and 20 mg
Packaging	Blister

Table 7—2: Identity of placebo

Formulation	Pink coated tablets
Galenical form	Round, biconvex, diameter 8 mm Markings: One side PT; Other side blank
Composition	lactose monohydrate, cellulose microcrystalline and magnesium stearate Coating: Lacquer pink (Opadry Pink 02A34744)
Packaging	Blister

Storage requirements

Study drug will be stored at the investigational sites according to the label requirements in a place inaccessible to unauthorized personnel, i.e. in a locked cabinet.

All study drugs will be labeled according to the requirements of local law and legislation. Label text will be approved according to the sponsor's agreed procedures, and a copy of the labels will be made available to the study site upon request.

For all study drugs, a system of numbering in accordance with all requirements of GMP will be used, ensuring that each dose of study drug can be traced back to the respective bulk batch of the ingredients. Lists linking all numbering levels will be maintained by the sponsor's clinical supplies quality assurance group.

A complete record of batch numbers and expiry dates of all study treatment as well as the labels will be maintained in the sponsor's study file.

7.3 Treatment assignment

The intention is to randomize approximately 288 patients to the doses 5 mg, 10 mg, 20 mg, 30 mg, 40 mg of neladenoson bialanate, and placebo according to an allocation ratio of 1:2:2:2:2:3, respectively.

At the baseline visit, the investigator will first perform all required pre-treatment examinations and will then randomize the qualified patients to one of the six treatment arms.

The randomization will be stratified by atrial fibrillation (AF): yes vs. no.

Enrollment into the AF stratum may be stopped (after the discussion between the sponsor and the Steering Committee) when the AF stratum constitutes 30% of the total expected enrollment.

The randomization lists will be provided by Bayer's Global Randomization Management Group. Randomization will be done using an interactive voice / web response system (IxRS).

A handbook describing how to use the IxRS will be provided to each study site.

7.4 Dosage and administration

For dosage and administration please refer to Section 7.1.

7.5 Blinding

All patients will receive the same number of tablets (only active, combination of active and placebo or only placebo, depending on the treatment arm) to maintain the blind (Table 7—3).

Table 7—3: Assignment of tablets to dose groups

Treatment arm/ Formulation	5 mg	10 mg	20 mg	30 mg	40 mg	Placebo
5 mg	1	0	0	0	0	0
10 mg	0	1	0	1	0	0
20 mg	0	0	1	1	2	0
Placebo	1	1	1	0	0	2
Total tablets/day	2	2	2	2	2	2

The following parties will be unblinded: sponsor's IxRS and Medication Manager, Clinical Supply Manager and Clinical Pharmacometrics analyst (who will be provided with a randomization list for selected bioanalyses of the active metabolite BAY 84-3174 in plasma), the Fisher Project Manager, and the independent DMC.

For all other sponsor's study personnel, the Steering Committee and the Clinical Events Committee (CEC) the blinding will be strictly kept.

In compliance with applicable regulations, in the event of a SUSAR (see Section 9.6.1.5) related to the blinded treatment, the patient's treatment code will usually be unblinded before reporting to the health authorities, ethic committees and investigators (see Section 9.6.1.4). For exceptions please see Section 9.6.1.4.

Emergency unblinding by the investigator

In the event of emergency, and where knowledge of assigned treatment allocation is required for the acute treatment strategy, the investigator may unblind the case. Unblinding will be handled in IxRS.

The occurrence of SAEs should not routinely precipitate the immediate unblinding. The investigator is required to promptly document and explain to the sponsor any premature unblinding (e.g. unblinding due to an SAE) of the study drug. The investigator should report unblinding of treatment to the EC / IRB according to the EC / IRB's requirements.

7.6 Drug logistics and accountability

All study drugs will be stored at the investigational site in accordance with GCP and GMP requirements and the instructions given by the clinical supplies department of the sponsor (or its affiliate), and will be inaccessible to unauthorized personnel. Special storage conditions and a complete record of batch numbers and expiry dates can be found in the sponsor's study file; the site-relevant elements of this information will be available in the investigator site file. On the day of receipt, the responsible site personnel will confirm receipt of study drug via IxRS. The personnel will use the study drug only within the framework of this clinical study and in accordance with this protocol. Receipt, distribution, return and destruction (if any) of the study drug must be properly documented according to the sponsor's agreed and specified procedures.

Written instructions on medication destruction will be made available to affected parties as applicable.

7.7 Treatment compliance

To monitor compliance, the investigator will be required to document drug dispensing for each patient. Overall compliance with study drug intake should be between 80% and 120% of the scheduled dose at the end of study drug treatment. The date of dispensing the study drug to the patient will be documented.

Study drug will be dispensed according to the schedule provided in Section 9.1.

Patients will return at scheduled visits or at the premature discontinuation / EOT visit, if applicable, with all remaining unused study drug, when accountability will be determined for all tablets. To facilitate this, patients must be instructed to return all of the study drug packaging including unused study drug and empty packaging.

Any discrepancies between actual and expected amount of returned study medication must be discussed with the patient at the time of the visit, and any explanation must be documented in the source records.

8. Non-study therapy

8.1 Prior and concomitant therapy

8.1.1 Prohibited concomitant medication

Concomitant therapy with any of the following drug classes is prohibited:

- Moderate or strong CYP3A4 inhibitors (Of note: grapefruit is a strong CYP3A4 inhibitor)
- CYP3A4 inducers
- Strong CYP2C8 inhibitors (Of note: clopidogrel is a strong CYP2C8 inhibitor)
- Theophylline
- Drugs having significant pre-systemic clearance via UGT1A1 in the intestine

Respective substances must be stopped at least 7 days before randomization and can only be started 6 weeks after the last intake of study drug. A list of prohibited medications will be provided to the investigators.

If a prohibited concomitant medication (e.g. moderate / strong CYP3A4 inhibitor) is used during the study conduct, the study drug should be interrupted immediately and restarted as soon as possible, when the prohibited medication has been stopped. Prior to re-starting the study drug, a washout period of at least two days after discontinuation of the prohibited medication should be adhered to.

8.1.2 Permitted therapy

- All patients should be treated for specific co-morbidities as considered appropriate by the investigator and in accordance with standard therapy guidelines.
- Concomitant therapy is allowed unless listed in the prohibited medication section.

During the treatment period the background medications should be kept stable and changes in treatment should be based on clinical need.

Neladenoson bialanate is a weak BCRP inhibitor. The risk of clinically relevant drug–drug interactions at doses up to 40 mg BAY 1067197 due to inhibition of BCRP is regarded as low, but cannot be excluded (BCRP substrates are atorvastatin, simvastatin, rosuvastatin, fluvastatin, methotrexate, etc.; a list of BCRP substrates will be made available to the investigators).

If neladenoson bialanate is given concomitantly with other drugs that may increase the exposure of BCRP substrates, the respective drug labels should be consulted.

All concomitant medication will be documented in the eCRF.

8.2 Post-study therapy

The investigator must provide follow-up medical care for all patients who complete the study or who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care, as required.

Study medication will not be available to patients after completion of the study.

9. Procedures and variables

9.1 Tabular schedule of evaluations

Table 9—1: Schedule of evaluations

Study period	Run-in	Treatment [a]						EOT / PDV	Safety FU		Unscheduled [e]
Visit number	**1**	**2**	**3**	**4**	**5**	**6**		**7**	**8**	**9**	
Visit type	site	site	☎	site	site	site	☎ [b]	site	site	☎	
Week Day and allowed deviations	**-1** -7	**W0** 0+2	**W2** 14±2	**W4** 28±2	**W8** 56±2	**W12** 84±2	**W19** 133-2	**W20** [a] 140±2	**W24** [c] 168±2	**W26** [a] 182+7	
		pre-rand.									
Signed informed consent	●										
Inclusion / exclusion criteria	●	●									
KCCQ		●		●		●		●			
EQ-5D-5L		●						●			
Demographic data	●										
Medical and surgical history		●									
Smoking & alcohol history		●									
Caffeine & chocolate consumption		●						●			
Physical exam		●		●	●	●		●	●[d]		●
Height		●									
Weight		●		●	●	●		●	●		●
12-lead ECG		●				●		●			
NYHA class		●		●	●	●		●	●		●
BP and heart rate	●	●		●	●	●		●	●		●
Adverse events	●	●	●[e]	●	●	●		●	●	●[e]	●
Concomitant medication	●	●	●	●	●	●		●	●	●	●
6MWD test, Borg CR 10 Scale	●[f]	●[g]			●			●			
Echocardiography (central)		●						●			
AVIVO application, worn for 7 days	●	●			●	h	●				
Collection of AVIVO device		●		●		●		●			
Randomization via IxRS		●									
		post-rand.									
Laboratory (central lab)											
Blood sample for safety		pre-dose		●	●	●		●	●		●
Blood sample for biomarkers		pre-dose		●				●	●[i]		
Urine sample for biomarkers		pre-dose		●				●			
PK sample (exact time to be documented) [j]		2h post-dose		pre-dose	pre-dose	~2h & 4h post-dose		1 day post-dose	●		
Study drug [k]											
Study drug intake at the site		●		●	●						
Study drug intake before the visit						~2h before		1 day before			
Patients to remember the time of the study drug intake				day before	day before	●		day of last dose			
Dispense contact card	●										
Dispense study drug		●		●	●	●					
Collect unused study drug				●	●	●		●			

6MWD = 6-minute walking distance; BP = blood pressure, ECG = electrocardiogram; EOT = end of treatment; EQ-5D-5L = EuroQol Group 5-dimensional, 5-level questionnaire; FU = follow-up; h = hour(s); IxRS = interactive web/voice response system; KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association; PDV = premature discontinuation visit; post-rand. = post-randomization; PK = pharmacokinetics; pre-rand. = pre-randomization; W = week

Table 9-1: Schedule of evaluations (continued)

a For patients who discontinue study medication prematurely:

- EOT / premature discontinuation visit must be performed as soon as possible after discontinuation of the study drug.
- Safety FU visit must be scheduled 4 weeks after the last dose (± 2 days).
- Week 26 follow-up call will be made 26 weeks after the start of treatment (+7 days).

b Phone call to remind patients to self-apply AVIVO device. The phone can be made up to 2 days before Week 19, but not later than Week 19, to have 7 days of data for evaluation at the Week 20 visit.

c Safety FU visit is relative to the last dose of study medication and is 4 weeks after the last dose.

d Targeted physical examination based on symptoms

e If there is an AE reported during a phone call, the investigator, at his / her discretion, may ask the patient to come for an unscheduled visit at the patient's earliest convenience (Section 9.2.11).

f 6MWD test (including Borg CR 10 Scale) at Visit 1 (run-in visit) is to familiarize patients with the test.

g Patients are only allowed to be randomized, if the walking distance determined *at Visit 2* (Week 0) is ≥ 100 m and ≤ 550 m; the distance walked in the familiarization test *at run-in* (Week -1) will not be taken into account to decide if patients can move forward to randomization.

h At Visit 6 (Week 12) the site will hand over an AVIVO device to patients for self-application at Week 19 and instruct them how to apply the device

i Only NT-proBNP

j **At Visit 2**: One PK sample will be drawn not earlier than 2 hours and not later than 6 hours after the first dose of study medication. The exact time of the first dose must be recorded by the investigator.

At Visits 4 and 5: One PK sample at each of the visits will be drawn pre-dose. Patients must not take study medication before the visit but should remember the exact time of the previous dose.

At Visit 6: Two PK samples will be drawn post-dose

1. 2 hours after the study drug intake (range 1:30 hour to 3:29 hours)
2. 4 hours after the study drug intake (range 3:30 hours to 5:30 hours)

The minimum time between the two samples should be at least 1 hour.

Patients will be instructed to take the study drug about 2 hours before the visit and to remember the exact time. If a patient does not take the study drug before the visit, he / she can take it at the start of the visit, in which case PK sampling will occur as described above.

At Visit 7: One PK sample will be drawn 1 day after the last dose. Patients should remember the exact time of their last dose.

k It is important that the patients remember the time of the tablet intake as precisely as possible (i.e. exact hour and minute) on the following days:

1. On the day before Visits 4 and 5
2. On the day of Visit 6
3. On the day of their last dose

This information will be recorded in the patient's file. A phone call to remind the patients is recommended. The investigator must record the time of the dose when the study drug is taken at the site.

9.2 Visit description

9.2.1 Visit 1 (Week -1, run-in)

- Confirm signed informed consent is available (Section 13.4)
- Allocate unique patient identification number (Section 6.5)
- Eligibility assessment (Sections 6.1 and 6.2)
- Demographic data collection and recording (Section 9.3.1)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- 6MWD test, to familiarize the patient with the procedure (Section 9.4.1)
- Borg CR 10 Scale (Section 9.4.2)
- AVIVO device application, worn for 7 days (Section 9.6.3.5)
- Contact card dispensing

9.2.2 Visit 2 (Week 0, baseline)

At Visit 2 eligibility must be re-assessed before the patient is randomized to a treatment arm. Please note: laboratory eligibility criteria are based upon local historical records, not central laboratory findings. Even retrospectively, central laboratory results from the baseline visit will not render a patient ineligible for the study. If a patient is not eligible for randomization, or withdraws for other reasons before randomization, he / she will be considered a screening failure even though the visit is not named a screening visit (for details see Section 6.4.1).

The following procedures will be performed **before randomization**:

- Review in/exclusion criteria and confirm patient eligibility
- Quality of life questionnaires (KCCQ and EQ-5D-5L), to be completed by the patient (Section 9.4.6)
- Medical and surgical history collection and recording (Section 9.3.2)
- Tobacco smoking and alcohol history collection and recording
- Assessment of caffeine-containing beverage and chocolate consumption during the previous 4 weeks
- Physical examination (Section 9.6.3.2)
- Weight and height measurement (BMI will be calculated automatically)
- 12-lead ECG (Section 9.6.3.3)
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- 6MWD test (Section 9.4.1)

- Borg CR 10 Scale (Section 9.4.2)
- Collection of AVIVO device applied at Visit 1 (Week -1)
- Echocardiography (Section 9.4.3)
- AVIVO device application, worn for 7 days (Section 9.6.3.5)

After all above procedures are done, the patient can be randomized via IxRS (Section 7.3).

The following procedures should be performed **after randomization and before study medication intake**:

- Blood sampling for safety (Section 9.6.3.1).
- Blood and urine sampling for biomarkers (Section 9.4.4)
- Study drug dispensing (Section 7.7)

The following procedures should be performed **during and after study medication intake:**

- Start of study medication (Section 7.1). The first dose of study medication will be taken after all previous procedures are completed; the time of intake should be recorded. The patients will be instructed to remember the time of medication intake as precisely as possible on selected days.
- PK sampling not earlier than 2 hours and not later than 6 hours after the first dose of study medication; the exact time of PK sampling and drug intake is to be documented in the patient's file (Section 9.5).

9.2.3 Visit 3 (Week 2, phone call)

After 2 weeks of treatment (± 2 days) the site personnel will call the patient to inquire about adverse events and to collect information on concomitant medications. If there is an AE reported during the phone call, the investigator may ask the patient to come for an unscheduled visit (Section 9.2.11). Information collected during the phone call must be recorded in the patient's medical records / source documents.

9.2.4 Visit 4 (Week 4)

- Quality of life questionnaire (KCCQ), to be completed by the patient (Section 9.4.6)
- Physical examination (Section 9.6.3.2)
- Weight measurement
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- Collection of AVIVO device applied at Visit 2 (Week 0)
- Blood sampling for safety (Section 9.6.3.1)
- PK sampling (pre-dose). Please note: on this day the patient should not take the study medication before the visit but only after the PK sampling. Ideally, the study

personnel should contact the subject prior to Visit 4 to remind them not to take the study drug as usual in the morning at home. The patient should remember the time of the previous study drug intake as precisely as possible. The exact time of PK sampling and drug intake is to be documented in the patient's file.

- Blood and urine sampling for biomarkers (Section 9.4.4)
- Study drug dispensing and unused study drug collection (Section 7.7)

9.2.5 Visit 5 (Week 8)

- Physical examination (Section 9.6.3.2)
- Weight measurement
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- 6MWD test (Section 9.4.1)
- Borg CR 10 Scale (Section 9.4.2)
- AVIVO device application, worn for 7 days (Section 9.6.3.5)
- Blood sampling for safety (Section 9.6.3.1)
- PK sampling (pre-dose). Please note: on this day the patients should not take the study medication before the visit but only after the PK sampling. Ideally, the study personnel should contact the subject prior to Visit 5 to remind them not to take the study drug as usual in the morning at home. The patient should remember the time of the previous study drug intake as precisely as possible. The exact time of PK sampling and drug intake is to be documented in the patient's file.
- Study drug dispensing and unused study drug collection (Section 7.7)

9.2.6 Visit 6 (Week 12)

- Quality of life questionnaire (KCCQ), to be completed by the patient (Section 9.4.6)
- PK sampling (Section 9.4.6.2):
  - Study drug is to be taken at home approximately 2 hours before the visit; it is important that the patient remembers the time of study drug intake as precisely as possible; a phone call on the previous day to remind the patient is recommended. This information will be documented in the patient's file.
  - The first PK sample is to be taken approximately 2 hours after study drug intake (range 1:30 hour to 3:29 hours). Time of sampling should be precisely documented in the patient's file.
  - The second PK sample is to be taken approximately 4 hours after study drug intake (range 3:30 hours to 5:30 hours). Time of sampling should be precisely documented in the patient's file.
  - The minimum time between the two samples should be at least 1 hour.

If a patient does not take the study drug before the visit, he / she can take it at the start of the visit, in which case PK sampling will occur as described above.

- Physical examination (Section 9.6.3.2)
- Weight measurement
- 12-lead ECG (Section 9.6.3.3)
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- Collection of AVIVO device applied at Visit 5 (Week 8)
- Handing-over AVIVO device to patients for self-application at Week 19 (Section 9.2.7) and instruction of patients how to apply the device
- Blood sampling for safety (Section 9.6.3.1).
- Study drug dispensing and unused study drug collection (Section 7.7)

9.2.7 Reminder phone call at Week 19

After 19 weeks of treatment (- 2 days) the site personnel will call the patients to remind them to self-apply the AVIVO device provided at Visit 6 (Week 12); if the device has not been provided at site, it should have been shipped to the patients. If there is an AE reported during the phone call, the investigator will have to make sure this is further assessed at the Week 20 visit or at an unscheduled visit prior to this. Information collected during the phone call must be registered in the patient's medical records / source documents.

Every effort should be made that the Week 20 visit at the site is conducted 7 days after the patient has applied the AVIVO device to have 7 days of data for evaluation. Accordingly, scheduling of Week 19 reminder-call and Week 20 visit should be aligned to achieve this. If the site prefers to have an on-site visit at Week 19 for the purposes mentioned above, an unscheduled visit (Section 9.2.11) can be conducted instead of the phone call (the patient's preference should also be considered).

9.2.8 Visit 7 (Week 20, EOT or premature discontinuation)

The last dose of study drug should be taken the day before the visit. The patients should remember the time of the last dose as precisely as possible; this information will be recorded in the patient's file. It is recommended to make a reminder phone call to the patients on the previous day.

If a patient discontinues study treatment prematurely this visit should be completed as soon as possible after the last dose.

- Quality of life questionnaires (KCCQ and EQ-5D-5L), to be completed by the patient (Section 9.4.6)
- Physical examination (Section 9.6.3.2)
- Weight measurement
- Assessment of caffeine-containing beverage and chocolate consumption during the previous 4 weeks
- 12-lead ECG (Section 9.6.3.3)
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- 6MWD test (Section 9.4.1)
- Borg CR 10 Scale (Section 9.4.2)
- Collection of AVIVO device applied at Week 19
- Echocardiography (Section 9.4.3)
- Blood sampling for safety (Section 9.6.3.1).
- PK sampling one day after the last dose (Section 9.4.6.2).
- Blood and urine sampling for biomarkers (Section 9.4.4)
- Unused study drug collection (Section 7.7)

9.2.9 Visit 8 (Week 24, safety follow-up)

If a patient discontinues study treatment prematurely this visit should be completed 4 weeks ±2 days after the last dose.

- Physical examination (targeted examination based on symptoms) (Section 9.6.3.2)
- Weight measurement
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- Blood sampling for safety (Section 9.6.3.1)
- PK sampling (Section 9.4.6.2)
- Blood sampling for NT-proBNP (Section 9.4.4)

9.2.10 Visit 9 (Week 26, phone call)

Twenty-six weeks after the start of study treatment the site personnel will call the patients to inquire about adverse events, including cardiovascular events, and to collect information on concomitant medications. For patients who discontinue study drug treatment early, the phone call will still be made 26 weeks after the start of study treatment. Information collected during the phone call must be recorded in the patient's medical records / source documents.

9.2.11 Unscheduled Visit

If a patient experiences an adverse event for which the investigator determines a follow-up site visit is necessary (either before the next scheduled study visit or during the Week 26 phone call), then the following assessments will be performed:

- Physical examination (Section 9.6.3.2)
- Weight measurement
- NYHA class assessment (Section 9.4.5.2)
- Blood pressure and heart rate measurement (Section 9.6.3.4)
- Adverse events assessment (Section 9.6.1.3)
- Concomitant medication collection and recording (Section 8.1)
- Blood sampling for safety (Section 9.6.3.1)

9.3 Population characteristics

9.3.1 Demographic and vital signs

The following demographic and vital signs data will be collected and recorded in the eCRF:

- Year of birth
- Age (to be calculated by the investigator)
- Gender
- Race / ethnicity (collection may be restricted per local regulations)
- Weight
- Height

BMI will be calculated automatically.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Pertaining to the study indication
- Considered relevant to the study (e.g. cardiovascular and metabolic diseases)
- Considered relevant for the patient's study eligibility
- Related to concomitant medication

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Other baseline characteristics

In addition, the following baseline characteristics will be collected and recorded:

- Pre-defined medical history
- NYHA class
- Tobacco smoking history
- Alcohol consumption history
- Recent caffeine-containing beverage and chocolate consumption history

9.4 Efficacy

9.4.1 6MWD test

The 6MWD test is designed to evaluate a patient's exercise capacity while performing an everyday activity. During this study, a 6MWD test including Borg CR 10 Scale will be conducted at different time points as specified in Table 9—1, for further details on assessment refer to Section 16.3. A familiarization 6MWD test will be performed during the run-in phase. To avoid any interactions, it is not permitted to perform the familiarization test on the same day as the baseline (Week 0) 6MWD test. It is only allowed to randomize patients, if the walking distance determined at baseline is ≥ 100 m and ≤ 550 m.

9.4.2 Borg CR 10 Scale

The score on the Borg CR 10 Scale will always be measured in conjunction with the 6MWD test. For details on time points refer to Table 9—1, for further details on assessment refer to Section 16.4.

The Borg CR 10 Scale will be explained to the patients before starting the 6MWD test (questionnaires and instructions will be provided in local language). Patients will be asked to rank their exertion at the end of the 6MWD test. If a patient has problems understanding the principles of rating, an attempt should be made to explain the principles in a neutral and unpersuasive manner. The test result will be entered on same work sheet as the 6MWD test result. Later on the results will be transferred into the eCRF.

9.4.3 Echocardiography

Transthoracic echocardiography and tissue Doppler will be performed at the time points specified in Section 9.1. The readings will be assessed centrally. SBP, DBP, and HR will be measured during echocardiography in addition to acquisition of echo data. The following parameters (but not limited to) will be analyzed by the central reader:

- LV ejection fraction (LVEF, %)
- LV end-diastolic volume (LVEDV), LVEDV index (LVEDVI, calculated as LVEDV/BSA)
- LV end-systolic volume (LVESV), LVESV index (LVESVI, calculated as LVESV/BSA)
- LA size (LA diameter, area, volume index [LAVI, calculated as LAV/BSA])
- Lateral e' (early diastolic mitral annular relaxation velocity at the lateral mitral annulus by Tissue Doppler, TD)
- Septal e' (early diastolic mitral annular relaxation velocity at septal mitral annulus by TD), including calculation of average e'
- Global longitudinal strain (%)
- Pulmonary artery systolic pressure (PASP), estimated by tricuspid regurgitation velocity and inferior vena cava diameter, including its change with respiration, and hepatic vein flow in patients with tricuspid regurgitation
- Tricuspid annular plane systolic excursion (TAPSE), right ventricular (RV) s' (velocity of the tricuspid annular systolic excursion at the RV free wall by TD)
- Mitral regurgitation
- LV mass, LV mass index (calculated as LV mass/BSA)
- Wall thicknesses, incl. interventricular septum diameter (IVSD), posterior wall thickness (PWT), anteroseptal wall thickness (ASWT)
- E, A (if in sinus rhythm), calculation of E/A and E/e' (using lateral, septal, average e') ratios
- E-wave deceleration time (EWDT)
- Stroke volume (SV, calculated by LVEDV - LVESV) and derived parameters, including SV index (SVI, calculated as SV/BSA), cardiac output (CO, calculated as SV*HR), cardiac index (CI, calculated as CO/BSA), systemic arterial compliance (SAC, calculated as SV/PP), total peripheral resistance (TPR, calculated as MAP/CO*80)
- Effective arterial elastance (Ea), estimated as end-systolic pressure (Pes) [Pes calculated as SBP times 0.9 (82)] divided by SV (SBP*0.9/SV)

Final details of all echocardiography parameters to be measured and analyzed will be included in a separate echocardiography manual.

9.4.4 Biomarker investigations

Biomarker investigations in the present study will include the biomarkers listed below.

Mandatory (sampled at all time points):

- NT-proBNP (baseline disease status & efficacy)
- High sensitivity troponin T (hs-TNT) (baseline disease status)
- Cystatin C (baseline disease status & efficacy)
- Free fatty acid (FFA) (target engagement / mechanistic marker)
- Urine albumin-to-creatinine ratio (UACR)
- Hemoglobin A1c (HbA1c) (target engagement / mechanistic marker)
- Neutrophil gelatinase-associated lipocalin (NGAL) (baseline disease status & efficacy)

Additional exploratory biomarker sampling:

- Soluble suppression of tumorigenicity-2 (sST2) (baseline disease status & efficacy)
- Galectin-3 (Gal-3) (baseline disease status & efficacy)
- Growth differentiation factor 15 (GDF-15) (baseline disease status & efficacy)
- Mid-regional pro-atrial natriuretic peptide (MR-proANP) (baseline disease status & efficacy)
- Copeptin (baseline disease status & efficacy)
- Osteopontin (OPN) (baseline disease status & efficacy)
- Tissue inhibitor of metalloproteinase-4 (TIMP-4) (baseline disease status & efficacy)
- Additional newly emerging HF or safety biomarkers

Blood sampling for biomarkers is scheduled for the time points as given in Section 9.1. All biomarkers will be measured using validated assay systems. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of the QC samples will be reported in a separate analytical report. Details on the collection, processing, storage and shipment of biomarker samples will be provided in separate documents (e.g. sample handling sheets or lab manual). Additional exploratory biomarkers sampling is to be used for research purposes to identify and / or verify biomarkers that are predictive or correlate with the efficacy / safety and the response in terms of tolerability of neladenoson bialanate. The analysis of exploratory biomarker may include the listed above exploratory biomarkers, safety biomarkers or new emerging HF biomarkers. Exploratory biomarker statistics may be reported separately. Exploratory biomarker analysis completed in the first year after the end of the study will be reported back to the investigator, if this provides additional meaningful information. Pure exploratory measures without an established interpretation might be withheld of reporting, considering that this will be of no value to the investigator or patient. The steering committee will provide guidance to the sponsor on reporting of exploratory biomarkers to investigators and patients.

In addition to the biomarkers listed above, other biomarkers deemed relevant to gain further knowledge about the pathomechanism of the disease or about the drug (i.e. mode of action related effect or safety of the drug) may be measured, based on newly emerging data from other ongoing studies and / or literature data.

Table 9—2: Sample types used for biomarker investigations

Sample type, short form	Description
Biomarker serum	Blood sample for serum preparation for biomarker analysis
Biomarker plasma	Blood sample for plasma preparation for biomarker analysis
Biomarker urine	Urine sample for biomarker analysis

9.4.5 Clinical efficacy variables

9.4.5.1 Clinical outcome events

The following clinical outcome events will be collected:

- All deaths (CV and non-CV)
- HF hospitalizations and urgent visits for HF
- Myocardial infarction
- Stroke

The CEC will adjudicate all deaths as either CV or non-CV, and other events listed above in accordance with the pre-specified endpoint criteria in the adjudication charter. Investigators are mandated to report all suspected potential endpoints for adjudication by the CEC.

Events for adjudication should be reported as soon as critical data (as defined in the eCRF page) to the event adjudication is available. A query will be posted for events that require additional supporting documentation from the sites in order to render an adjudicated result and will be followed up by the sponsor. Every effort will be made to provide the CEC with clean eCRF data and required clinical data prior to event adjudication.

9.4.5.2 NYHA class assessment

NYHA class	Symptoms
I	Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Source: (83)

9.4.6 Patient-reported outcomes

At study visits where the questionnaire is required (see Table 9—1), patients should complete it before any other study procedures or assessments.

At collection, the questionnaire will be reviewed for completeness, and the patient will be encouraged to answer any blank data fields. Subsequently, a member of the investigator's team will enter the responses into the eCRF. Details about scoring and calculating algorithms will be provided in the statistical analysis plan (SAP).

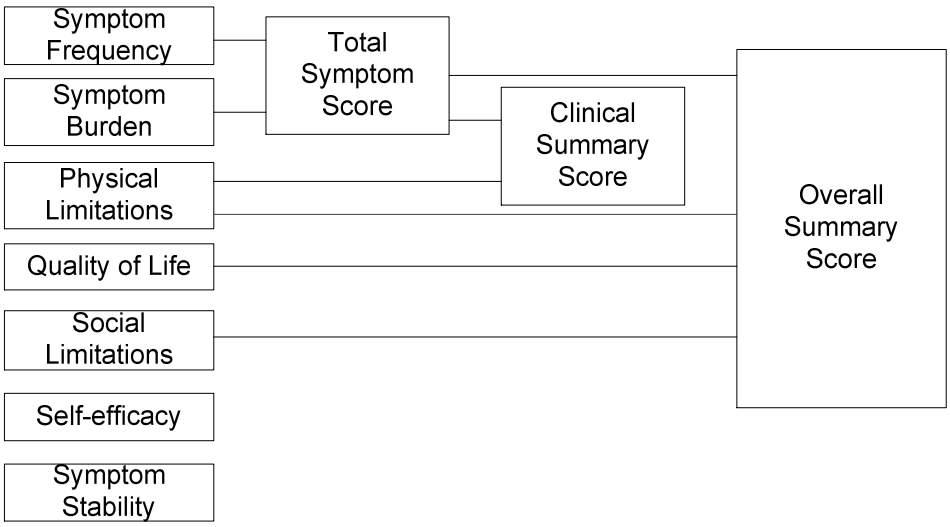
9.4.6.1 KCCQ

The **KCCQ** is the leading health-related quality-of-life measure for patients with CHF. It was developed in the late 1990s to early 2000s by Dr. John Spertus at the Mid-America Heart Institute, Kansas City, MO, USA. It is a 23-item questionnaire that independently measures the impact of patients' HF, or its treatment, on 7 distinct domains:

1) Symptom Frequency – the KCCQ Symptom scale quantifies the frequency of clinical symptoms in HF, including fatigue, shortness of breath, paroxysmal nocturnal dyspnea, and edema / swelling.
2) Symptom Burden – the KCCQ Symptom burden scale quantifies the severity of clinical symptoms in HF, including fatigue, shortness of breath and edema / swelling.
3) Physical Limitation – the KCCQ Physical limitation scale measures the limitations patients experience, due to their HF, in performing routine activities.
4) Quality of Life – the KCCQ Quality of life scale is designed to reflect patients' assessment of their quality of life, given the current status of their HF.
5) Social Limitations – the KCCQ Social limitation scale quantifies the extent to which HF symptoms impair patients' abilities to interact in social roles.
6) Self-efficacy – numerous studies have underscored the importance of patients being engaged in the management of their disease. The KCCQ Self-efficacy scale quantifies patients' perception of how to prevent HF exacerbations and manage complications when they arise.
7) Symptoms Stability– unlike the other 5 domains that provide cross-sectional quantification of patients' current status, the KCCQ Symptom stability domain measures recent changes in patients' symptoms. As a measure of change, it is most interpretable as a baseline assessment of the stability of patients' symptoms at the start of the study and thereafter.

In addition, there are 3 summary scores, a Total Symptom Score that combines the Symptom Frequency and the Symptom Burden scores, a Clinical Summary Score that combines the Total Symptom and Physical Limitation scores to replicate the NYHA classification; and an Overall Summary Score that includes the Total Symptom, Physical Limitation, Social Limitations, and Quality of Life scores (Figure 9—1).

Figure 9—1: KCCQ Scores



9.4.6.2 EQ-5D-5L

The EQ-5D-5L consists of 2 pages: the EQ-5D-5L descriptive system and the EQ visual analogue scale (EQ VAS). The EQ-5D-5L descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain / discomfort, and anxiety / depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems and extreme problems. The respondent is asked to indicate his / her health state by ticking (or placing a cross) in the box against the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labeled 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health outcome as judged by the individual respondents.

9.5 Pharmacokinetics / pharmacodynamics

It is planned to collect PK samples from all patients randomized. The data collected are intended to be used for PK analysis of the study population as a whole and should also give information about individual exposure to BAY 84-3174. Only the active metabolite BAY 84-3174 will be measured from the plasma samples collected (see Section 7.2 for details regarding different BAY numbers).

A sparse sampling scheme has been developed, which will allow for a limited number of PK samples to be obtained from each patient. The sampling time points have been included in the flow chart (see Table 9—1). The PK sampling schedule is detailed in the visit description (Section 9.2). It is important to exactly record in the patient's file the time point when the PK sample is taken, as well as the times of the most recent medication intake prior to the blood sampling. The sampling variability will be used for modelling the PK and PD characteristics of the study medication.

Details about the collection, processing, storage and shipment of samples will be provided separately (e.g. sample handling sheets or laboratory manual).

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

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

A surgical procedure that was planned prior to the start of the study by any physician treating the patient should not be recorded as an AE (however, the condition for which the surgery is required may be an AE).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal physical examination findings, symptoms, diseases, laboratory, or ECG findings.

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at unchanged intensity, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death
b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the patient was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   – The admission results in a hospital stay of less than 12 hours
   – The admission is pre-planned
   – (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)

– The admission is not associated with an AE
(e.g. social hospitalization for purposes of respite care).

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

Definition of treatment-emergent adverse event

An AE is classified as treatment-emergent if it occurs or worsens after the first dose of study drug up to 6 weeks after the last dose of study drug.

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild - usually transient in nature and generally not interfering with normal activities
- Moderate - sufficiently discomforting to interfere with normal activities
- Severe - prevents normal activities

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question.

Possible answers are "yes" or "no".

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the patient is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the AE is reasonably associated with the use of the study treatment.

Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Patient's response after de-challenge or re-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication or treatment:
  The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug.
- Exposure to physical and / or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual patient's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedure(s)

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no".

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

– None
– Remedial drug therapy
– Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

– Recovered / resolved
– Recovering / resolving
– Recovered / resolved with sequelae
– Not recovered / not resolved
– Fatal
– Unknown

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective CRF pages all adverse events occurring in the period between the signing of the informed consent and the end of the follow-up phase (Visit 9); after the end of the follow-up phase there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

“Death” should not be recorded as an AE on the AE page. Instead, “death” is the outcome of an underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

If an SAE is unexpected, i.e. the event is not previously documented in the investigator’s brochure (IB) (new occurrence) and is suspected to be related to the study drug, this event is considered a Suspected Unexpected Serious Adverse Reaction (SUSAR). In general, SUSARs will be unblinded by the sponsor for regulatory reporting (see below for exceptions).

Investigator’s notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator’s reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator’s awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient

detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page and the complementary SAE pages in the CRF must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, SUSARs) will be performed by the sponsor and / or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

Protocol-specific exceptions to SAE unblinding / reporting

If reported as SUSARs, the following clinical events will be exempted from unblinding and expedited reporting by the sponsor to investigators, IECs / IRBs, and regulatory agencies, since they are considered, consistent with the underlying condition, as disease related in the defined study population:

- CV death
- Worsening of heart failure
- Non-fatal myocardial infarction
- Non-fatal stroke
- Transient ischemic attack
- Cardiac arrhythmias
- Coronary revascularization procedures.

Note that all of these events will be reviewed and monitored by an external DMC unblinded to treatment as part of the overall assessment of safety and efficacy for neladenoson bialanate. Based upon their regular review of unblinded safety results, the DMC is empowered to make recommendations with regard to trial conduct to assure the continuing appropriate safety of the subjects participating in the study.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB) for neladenoson bialanate.

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.1.6 Adverse events of special interest

Adverse events of special interest have to be reported to the sponsor along the timelines set for serious adverse events (even though they may not be classified as serious), i.e. within 24 hours of the investigator's awareness, as described in section 9.6.1.4.

Adverse events of special interest are:

- Symptomatic bradycardia (HR < 50 bpm)
- Findings in ECG and / or AVIVO device as follows:
  - Mobitz type I AV-block leading to withdrawal or interruption of study drug
  - Mobitz type II AV block leading to withdrawal or interruption of study drug or leading to any change in therapy
  - Third degree AV blocks

9.6.2 Pregnancies

Females of childbearing potential are excluded from the study. However, the investigator must report to the sponsor any pregnancy occurring in a female study patient during her participation in this study. The outcome of the pregnancy should be followed up carefully, and any outcome of the mother and the child at delivery should be reported.

The child's health should be evaluated at birth.

For a pregnancy in the partner of a male study patient, all efforts will be made to obtain similar information on course and outcome, subject to the partner's consent.

For all reports, the forms provided are to be used. The investigator should submit them within the same timelines as an SAE.

9.6.3 Further safety

9.6.3.1 Laboratory evaluations

All laboratory evaluations will be done by central laboratory. Additional re-tests for liver monitoring (Section 9.6.3.6) will be done locally.

Hematology: erythrocytes, hemoglobin, hematocrit, MCV, MCH, MCHC, reticulocytes, leukocytes, differential blood count, platelets

Clinical chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (AP), gamma glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), creatine kinase (CK), amylase, lipase, glucose, cholesterol (HDL, LDL, total), triglycerides, creatinine, urea, uric acid, bilirubin, total protein, albumin, sodium, potassium, calcium, chloride, magnesium, anorganic phosphate

Coagulation: partial thromboplastin time (PTT), international normalized ratio (INR)

9.6.3.2 Physical examination

The physical examination (by means of inspection, palpation, auscultation) will be performed by a physician at the investigational site covering at least the organs of the cardiovascular, respiratory, abdominal and neurological system.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.6.3.3 12-lead ECG

The standard 12-lead ECG will be evaluated by the investigator and the following parameters will be recorded in the eCRF: HR, PR interval, QRSD interval, QT interval (uncorrected). QTcB (QT interval frequency-corrected according to Bazett's formula) will also be calculated but will not be valid for evaluation. The frequency-corrected QT interval will be calculated by data management according to the formulas of both Bazett and Fridericia.

All ECGs recorded during the study will be evaluated by a physician. He / she will document the diagnosis(es) including an overall assessment of the findings and their clinical relevance. Any clinically relevant abnormality will be documented as an AE or SAE.

9.6.3.4 Blood pressure and heart rate

Heart rate and blood pressure (systolic and diastolic) will be measured by a member of the investigator's study team with the patient at rest.

9.6.3.5 AVIVO monitoring

AVIVO Mobile Patient Management System will be used to monitor patients' cardiovascular status as part of the safety assessment. The cardiac monitoring device will be worn as specified in Section 9.1.

The system is intended to continuously measure, record and periodically transmit ECG data. The system can detect (but is not limited to) higher degree AV-blocks > I°, SVTs (e.g. atrial fibrillation [AF], atrial flutter, paroxysmal SVTs), ventricular ectopy, bradyarrhythmias, conduction disorders and heart rate variability. Included in the service is the monitoring center - an independent certified diagnostic testing center staffed with ECG-trained technicians who read through the transmitted events 24h/7d. An electrophysiologist is also on staff for interpretation of difficult rhythms. The system has achieved CE mark and has US FDA clearance.

AF will be assessed as subclinical AF and AF burden as an exploratory endpoint. No patient symptoms will be captured as part of this analysis, if not reported by the patient at routine visits.

Apart from safety assessments, also the patient's everyday physical activity (e.g. duration, intensity) will be tracked by the AVIVO device. This is part of the secondary efficacy variables. Details of the cardiac monitoring and the device to be worn by the patient will be outlined in a manual that will be provided to all participating centers. All collected variables will be described in the SAP.

9.6.3.6 Liver function monitoring

Any patient with an ALT or AST > 3 x ULN or alkaline phosphatase (AP) > 2 x ULN must be re-tested as soon as possible but at the latest within 48-72 hours of the investigator becoming aware of the result. This re-testing and any subsequent testing based on elevated levels should include measurement of ALT, AST, total and direct bilirubin, and AP, and will be assessed by local laboratory. Every effort should be made to clarify the etiology of elevated levels. Patient management is at the discretion of the investigator but the treating physician may continue the study drug during retesting. Liver function test monitoring should be performed as above for all patients even if the study drug is interrupted until tested values have normalized or returned to patient's baseline. If close liver monitoring is not possible then the patient should discontinue study medication.

For ALT or AST > 3 x ULN concurrent with a total bilirubin > 2 x ULN, every effort should be made to clarify any possible underlying disease(s).

The frequency of liver function tests based on re-test values is shown in Table 9—3.

Table 9—3: Liver function monitoring

ALT, AST or AP level at re-test	Frequency	Further notice
ALT or AST > 3 x ULN	2-3 times a week	Obtain details on liver related symptoms and exclude other causes of liver enzyme elevations
ALT or AST ≤ 3 x ULN	Once a week	Until return to normal or patient baseline levels
AP > 2 x ULN	2-3 times a week	Obtain details on liver related symptoms and exclude other causes of liver enzyme elevations

ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; ULN = upper limit of normal

Discontinuation of treatment should be considered if:

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or INR > 1.5)
- ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and / or eosinophilia (> 5%)
- AP > 2 x ULN or ALT/AP < 2 for more than 2 weeks if other causes of cholestasis are excluded

9.7 Other procedures and variables

Not applicable.

9.8 Appropriateness of procedures / measurements

All parameters, as well as the methods to measure them, are standard variables / methods in clinical studies and / or clinical practice. They are widely used and generally recognized as reliable, accurate, and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analyses will be performed by or under the supervision of the sponsor's study statistician and the assigned study statistical analyst using statistical analysis system (SAS); the version used will be specified in the SAP.

A general description of the statistical methods to be used to analyze efficacy and safety in this is study is outlined below. A detailed SAP will be provided as a separate document that will be finalized and approved before database lock. The SAP will accommodate protocol amendments or unexpected issues in study execution or data that affect planned analyses and will provide more details on the analytical approaches, output tables and figures.

A meta-analysis of this study (17582) and of the study 15128 in patients with HFrEF, which is conducted at the same time, will be specified in a separate SAP.

10.2 Analysis sets

Documentation of protocol deviations and assignment of patients to analysis sets will be performed according to the sponsor's applicable Standard Operating Procedures and / or Operation Instructions.

The primary efficacy variable will be analyzed using the per-protocol set (PPS) and the full analysis set (FAS) for sensitivity analyses.

Data for all patients who signed informed consent but were not randomized will not be included in any statistical analyses except standard disposition tables and listings provided in the clinical study report (Screening failures and discontinued patients).

The statistical analysis sets are defined as follows:

Full analysis set (FAS)

The FAS population consists of all randomized unique patients. According to the ICH E9 guideline, this analysis set is as complete as possible and as close as possible to the intent-to-treat (ITT) ideal. Patients will be analyzed as randomized. The FAS will be used to display baseline characteristics and to display efficacy analyses.

Safety analysis set (SAF)

The SAF population consists of all randomized patients who received at least one dose of study medication after randomization. The SAF will be used to display safety analyses. For safety analyses, patients will be analyzed as treated.

Per-protocol set (PPS)

The PPS population consists of all FAS population patients without validity findings. Validity findings may include adherence and compliance issues and the violation of inclusion / exclusion criteria affecting efficacy evaluation.

A list of potential validity findings will be provided in a separate protocol deviation document which will be finalized before database lock. The detailed definitions and the assignment of patients to this analysis set will be based on the validity review meeting. Patients will be analyzed as treated.

Pharmacokinetic analysis set (PKS)

The PKS population consists of all patients treated with neladenoson bialanate with at least 1 valid BAY 84-3174 plasma concentration and without protocol deviation that would interfere with the evaluation of the PK data.

10.3 Variables and planned statistical analyses

10.3.1 Variables

10.3.1.1 Primary efficacy variable

- Absolute change from baseline in 6MWD after 20 weeks of treatment

10.3.1.2 Secondary efficacy variables

Secondary efficacy variables across different domains are:

- Activity (e.g. duration, intensity) reported values and absolute change from baseline at 20 weeks
- NT-proBNP (pg/mL), measured values (log transformed) and absolute / relative change from baseline at 20 weeks to assess elevated filling pressures
- High sensitivity troponin T (hs-TNT; ng/L), measured values (log transformed) and absolute / relative change from baseline at 20 weeks as a biomarker of myocardial injury
- KCCQ, as described in Section 9.4.6.1, measured values and absolute / relative change from baseline

10.3.1.3 Other exploratory variables

- Echocardiographic parameters, as described in Section 9.4.3, measured values and absolute / relative change from baseline at 20 weeks
- Mandatory biomarkers, as described in Section 9.4.4, measured values and absolute / relative change from baseline at 20 weeks, including UACR, cystatin-C, NGAL for the evaluation of kidney function
- CV mortality, HF hospitalization and urgent visits for HF as clinical outcomes
- All-cause mortality, non-fatal myocardial infarction, non-fatal stroke
- EQ-5D QoL, as described in 9.4.6.2, measured values and absolute / relative change from baseline
- Change in NYHA class
- Absolute change in score on Borg CR 10 Scale

10.3.1.4 Safety variables

Safety and tolerability variables are:

- Adverse events (Section 9.6.1), including
  - SAEs, AEs, treatment-emergent AEs and AEs of special interest, including AV blocks > I°
  - SAEs and AEs leading to discontinuation of interruption of study drug, including AV blocks in particular
- Laboratory abnormalities (Section 9.6.3.1), measured values and change from baseline, in particular
  - Change in renal function measured by eGFR change from baseline
  - Change in liver function measured by bilirubin (total and fractions), AST and ALT from baseline
- 12-ECG abnormalities (Section 9.6.3.3) and PR interval duration
- Blood pressure and heart rate (Section 9.6.3.4); measured values and change from baseline
- Number of clinically significant findings in ECG and / or AVIVO device report

10.3.2 Statistical and analytical plans

All data will be listed and all variables will be summarized by means of descriptive statistics according to their type.

Summaries by treatment group using appropriate descriptive statistics will be provided for all study variables including demographic and baseline characteristics. Summary statistics will be presented for the original data as well as for the difference to baseline. Descriptive statistics such as mean, median, standard deviation, quantiles, minimum, and maximum will be used to summarize continuous variables. Counts and percentages will be used to summarize categorical variables. Life tables and Kaplan-Meier estimates will be used to summarize time-to-event variables. Graphical data displays may also be used to summarize the data. Confidence intervals will be provided at a 2-sided level of 90% unless otherwise stated.

For this combined proof-of-concept and dose-finding study, an overall one-sided type I error level of 5% is planned to be used. The type I error will be controlled for the primary analysis of the primary variable.

There will be no formal control of the type I error for secondary or explorative analyses of the primary variables and any analysis of other efficacy variables.

10.3.2.1 Subgroups

In order to assess the homogeneity of the dose response across the most important prognostic and predictive factors, subgroup analyses will be performed.

'Key' subgroups comprise:

- LVEF(%) at baseline: < 55 vs. ≥ 55
- NT-proBNP (pg/ml) at baseline: ≤ median vs. > median
- NYHA class at baseline: II vs. III / IV
- Prior ß-blocker: yes vs. no

Truly exploratory analyses, i.e., mainly summary statistics, will be provided for a spectrum of demographic, disease and clinical characteristics, including

- Age (years): < 65, 65-75, > 75
- Gender: male vs. female
- Race: White vs. non-white
- Region: North America / South America / West Europe / East Europe / Asia
- Region: Japan vs. rest-of-the-world (analysis to be included in reports specific for Japan only)
- BMI at baseline (kg/m²): ≤ 30 vs. > 30
- Time of CHF diagnosis to randomization (months): ≤ 3 vs. > 3
- Prior hospitalization for heart failure: yes vs. no
- Etiology of CHF: ischemic vs. non-ischemic
- Diabetes: yes vs. no
- Atrial fibrillation: yes vs. no
- Hypertension: yes vs. no
- Prior medication:
    - Prior ß-blocker in max tolerated dose: yes vs. no
    - Prior use of aldosterone antagonist: yes vs. no
    - Prior use of ACE inhibitor: yes vs. no
    - Prior use of ARB: yes vs. no
- Estimated GFR (ml/min/1.73 m^2): ≤ 60 vs. > 60

Further details will be described in detail in the SAP.

10.3.2.2 Analysis of the primary efficacy variable

It is planned to perform a test for a dose-response signal under the assumption of a nearly monotone dose-response relationship in the dose range considered. The MCP-Mod method (84) combining multiple comparison procedures (MCP) principles with modeling techniques will be used for the primary statistical analysis of the primary efficacy variable. This method allows the flexibility of modeling for dose estimation, while preserving the robustness to model misspecification associated with MCP procedures.

Assumptions

Five active doses of neladenoson bialanate will be used in this study: 5 mg, 10 mg, 20 mg, 30 mg, and 40 mg, as well as a placebo arm corresponding to a 0 mg dose.

The measurements of the primary efficacy variable are assumed to be normally distributed with the same standard deviation σ and independent between patients.

The following assumptions were made for the absolute change from baseline in 6MWD over 20 weeks:

- the expected mean effect under the placebo dose is assumed as an absolute difference from baseline of Δ = 0 m with a standard deviation of σ = 80 m
- while the maximum observable mean effect under neladenoson bialanate within the dose range considered is assumed as an absolute increase of Δ = 40 m with a standard deviation of σ = 80 m.

This results in an expected maximum effect size of (40-0)/80 = 0.5.

It is assumed that the primary efficacy variable, denoted as Y, is observed for the 6 parallel groups corresponding to doses levels: (placebo =) $d_1 < d_2 < \ldots < d_k$, where $k = 6$.

For patient j within treatment group i the response can then be described by the following model:

$$Y_{ij} = f(d, \boldsymbol{\theta}) + \varepsilon_{ij}, \quad \varepsilon_{ij} \sim N(0, \sigma^2), \quad i = 1, \ldots, k, \; j = 1, \; \ldots, \; n_i,$$

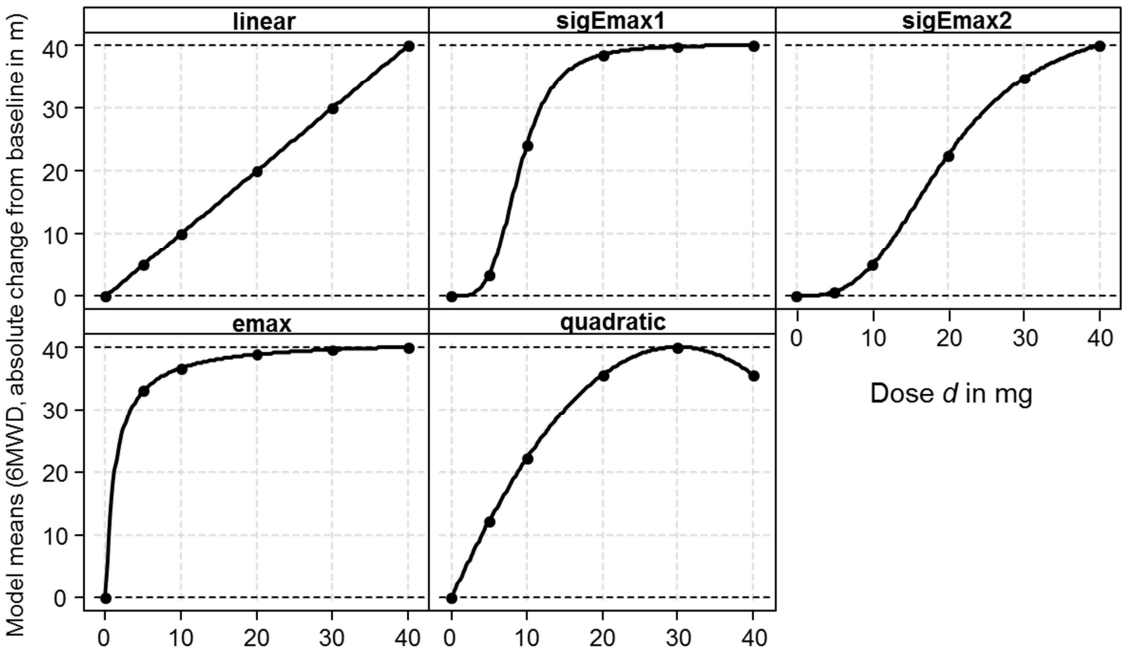
where $f(.)$ is parameterized by a vector of parameters $\boldsymbol{\theta}$ and ε_{ij} is the error term.

A candidate set with M=5 different dose response shapes $f(.)$ based on four models was chosen for the MCP-Mod method. Table 10—1 displays the response expressions for the shapes in the candidate set. Figure 10—1 shows the corresponding dose-response shapes. The model parameters were obtained through discussions with experts in the clinical team, taking prior beliefs and uncertainty into account.

Table 10—1: Dose-response shapes used in the candidate set

Model	Response as function of dose *d*
Linear	d
Sigmoidal E_{max} 1	$40.1\, d^4 / (9^4 + d^4)$
Sigmoidal E_{max} 2	$45\, d^3 / (20^3 + d^3)$
E_{max}	$41.25\, d / (1.25 + d)$
Quadratic	$2.667\, d - 0.044\, d^2$

Figure 10—1: Dose-response shapes used in the candidate set



Based on the standardized versions of the models in the candidate set and the sample size allocation planned for this study, the optimum contrast coefficients for the 5 contrast tests on the dose-response shapes can be derived.

Analysis

Step 1: Detection of dose-response signal

For detecting an overall trend, or a dose-response signal, each of the M=5 dose-response shapes in the candidate set will be tested, using a single contrast test based on the updated version of contrast coefficients taking the actual sample sizes per treatment group into account.

For each model m, m = 1, …, 5, in the candidate set

the null hypothesis $H_{0m}: c_m\mu_m^0 = 0$

will be tested against

the respective 1-sided alternative hypothesis $H_{1m}: c_m\mu_m^0 > 0$,

where $\mu_m^0 = (\mu_{m1}^0, \dots, \mu_{m6}^0)' = (f_m^0(d_1, \boldsymbol{\theta}_m^0), \dots, f_m^0(d_6, \boldsymbol{\theta}_m^0))'$ and

f^0 is the standardized version of the dose-response model $f(d, \boldsymbol{\theta}) = \theta_0 + \theta_1 f^0(d, \boldsymbol{\theta}^0)$. In this parameterization, θ_0 is a location parameter and θ_1 is a scale parameter such that only $\boldsymbol{\theta}^0$ determines the shape of the model function.

A “proof-of-concept” dose-response relationship is detected if at least one single contrast test, is statistically significant, while controlling the family-wise error rate at level α.

This analysis will be performed for the FAS and PPS populations, where the PPS analysis is the primary analysis.

If no candidate model is statistically significant, the procedure stops, indicating that a dose-response relationship cannot be established from the observed data.

Out of the statistically significant models in the candidate set a best model can be selected for the next step: modeling and estimation.

Step 2: Modeling and estimation of target doses

If a dose-response signal is established, the selected dose-response model(s) will be fitted to the observed data to estimate the model parameters.

The estimated dose-response model will be plotted against the doses including 90% confidence bands. Once the dose-response model has been successfully fitted to the data, target dose(s) of interest are estimated. Given a clinically relevant effect Δ , a minimum effective dose (MED_Δ) associated with model $f(d, \boldsymbol{\theta})$ is defined as

$$MED_\Delta = \text{argmin}_{d\in(d_1,d_6]}\{f(d,\boldsymbol{\theta}) \geq f(d_1,\boldsymbol{\theta}) + \Delta\}.$$

Estimates of MED_Δ will be calculated for a clinically relevant change in 6MWD assumed as $\Delta = 40$ m and potentially a plausible range of Δ values which will be defined in the SAP. In addition, estimates considering confidence bounds for the predicted value at a certain dose may be used. The final choice of the target dose depends on the evaluation of the primary efficacy variable and other efficacy variables, as well as safety considerations.

Modeling and estimation will be performed for the FAS and PPS populations as well as for relevant subgroups.

Further details will be described in the SAP.

As a secondary analysis pairwise comparisons of the active neladenoson bialanate dose groups with the placebo group will be performed without controlling the family-wise error rate.

10.3.2.3 Analysis of the secondary efficacy variables

The primary analysis of secondary efficacy variables will be performed in PPS, sensitivity analyses might be performed in the FAS. The secondary efficacy variables will be analyzed using similar statistical methods as for the primary efficacy variable, i.e. the MCP-Mod method with the same standardized candidate dose-response shapes and corresponding coefficients as for the primary variable. In addition to analyses comparing population means in the different dose groups, the number of patients in whom the individual change from baseline value crossed clinically meaningful thresholds will be analyzed. The totality of evidence for the primary and secondary efficacy variables will be combined and used to assess the drug effect over dose levels.

All other efficacy variables will be analyzed descriptively.

Further details will be described in the SAP.

10.3.2.4 Analysis of the safety variables

If not indicated otherwise, evaluation of safety variables will be done using the SAF.

Adverse events

The adverse events (AE) analysis will be performed as treated in the SAF. All tabulations will be descriptive only.

Individual listings of AEs will be provided. The incidence of treatment-emergent AEs and drug-related (treatment-emergent) AEs will be tabulated by treatment group using MedDRA terms. Separate tables and listing for serious AEs and death will be provided.

Further safety parameters

The safety evaluation of laboratory data will include:

- Descriptive analysis of continuous laboratory parameters, and their changes from baseline by visit and treatment group.
- Incidence rates of treatment-emergent laboratory values outside of normal range by treatment group.
- Listings of laboratory data out of normal range.

Vital signs and their changes from baseline will be analyzed descriptively by visit and by treatment group.

ECG-findings (like AV-conduction abnormalities) will be summarized in frequency tables. A table displaying the number of patients with AV-block > I° will be provided.

Data from the AVIVO monitoring will be summarized; details will be described in the SAP.

Summary statistics and figures of heart rate and blood pressure (systolic, diastolic, and mean arterial pressure) will be created.

10.3.2.5 Pharmacokinetic analyses

Pharmacokinetic analyses will be performed on the population valid for pharmacokinetics.

For the investigation of systemic exposure to BAY 84-3174 and its relationship with treatment effects, the plasma concentrations of BAY 84-3174 will be determined at different time points using a sparse sampling approach in all participating patients (see Section 9.5). The plasma concentration vs. time data will be evaluated descriptively separated by dose and visit. Plots will be prepared pooling all individual plasma concentrations (naive pooling) vs. actual relative study times (time of sample collection after time of study drug administration).

Furthermore, the pharmacokinetic data and the relationship of markers of BAY 84-3174 exposure (e.g. C_{max}, AUC) with treatment effects will be evaluated using non-linear mixed effect modeling (NONMEM). The latter evaluation will be described in a separate analysis plan and will be reported under separate cover.

The PK bioanalysis will be performed under the responsibility of the Sponsor's Bioanalytics Laboratory.

10.3.2.6 Biomarker analyses

Biomarker data will be described by the following summary statistics: arithmetic mean, standard deviation, median, quantiles, minimum, and maximum.

Graphical displays of individual data as well as mean values with standard deviation will be included.

10.3.3 Missing data, censoring due to death, and drop outs

Generally, missing data will be handled as such, i.e., no imputation of missing data will be performed. An exception is the analysis of the primary and secondary efficacy variables, as described below, and the timing of events relative to other events. For this purpose, data rules for the handling of missing or incomplete dates will be described in the SAP.

All missing or partial data will be presented in the patient data listing as they are recorded in the eCRF.

A number of descriptive analyses will be performed to better understand missing data patterns. The frequency, proportion and the reasons for premature discontinuation of both the study and study treatment will be reported. Kaplan-Meier plots for "time to end of study treatment (calculated as days from first dose to the earliest date of last dose, including premature stop of study medication, and death)" and "time to end of study" will be provided, by treatment group and overall.

The number of patients who prematurely discontinue study participation or intake of study medication will be carefully evaluated with respect to the key baseline characteristics, which will be further specified in the SAP, and the reasons for premature discontinuation of study and / or study treatment. If the proportion of patients who withdraw across the dose groups is not fairly balanced, the impact on the primary variable will be further explored. To further explore the missingness pattern with regards to the "missing at random" assumption, the mean of the baseline values of the efficacy variable will be summarized for patients with and without post-baseline observations, by treatment group and overall.

For the analysis of the primary and secondary variables, it cannot necessarily be assumed that data are missing at random. As the choice of primary analysis will be based on assumptions that cannot be verified, the robustness of the results of the primary analysis will be investigated through appropriate sensitivity analyses making different assumptions, in accordance with the EMA "Guideline on missing data in confirmatory clinical trials".

Efficacy analysis using the PPS

The primary efficacy analysis aims at evaluating the dose-response relationship of the primary and secondary efficacy variables for all randomized patients, who have remained in the study and adhered to study treatment according to the study protocol until Week 20 ("completers and treatment adherers" analysis). Therefore, the primary analysis will be performed in the per protocol set, a subset of the FAS comprising "compliant and adherent" patients (as much as possible, defined via validity criteria). To avoid bias, the PPS will also include those "compliant and adherent" patients who are "censored" due to CV death or a hospitalization for HF preventing the assessment of the relevant efficacy endpoints 20 weeks after randomization, to take place as planned. It is expected, that these are the only patients for

whom missing observations need to be considered in the primary analysis. A "worst case" approach will be used, where the missing change from baseline value will be imputed with a multiple of the worst change from baseline value, which is possible given the individual baseline value observed in the respective treatment group, or 0 if the worst change in that treatment group is positive.

As a sensitivity analysis, a "completers and treatment adherers" only analysis excluding the censored patients in the per protocol analysis set will be performed. This strategy leads to unbiased estimates only if missing values are "missing completely at random" (MCAR), i.e. the missingness – including missing data due to death – is independent of both observed and unobserved outcomes. This condition is unlikely to hold exactly but rather approximately.

Further sensitivity analyses on the PPS may be performed if the missing data patterns suggest further exploration.

Efficacy analysis using the FAS

The efficacy analysis in the FAS aims at evaluating the dose-response relationship of the primary and secondary efficacy variables for all randomized patients. Efficacy analyses in the FAS will include the following:

- Generally, it will be assumed that missing observations for the respective efficacy variables are missing at random. This implies that the behavior of the post dropout observations can be predicted from the observed variables using appropriate imputation models. Likely exceptions to the missing at random assumption are observations which are missing due to a patient's CV death or HF hospitalization prior to the visit in Week 20. These observations can be assumed to be missing not at random (MNAR), i.e., that missingness depends both on observed and unobserved outcomes and that an explicit model for the patient's statistical behavior after drop-out (or death) is required. Therefore, an analysis based on a pattern mixture framework (85) with different imputation rules depending on the reason for missingness will be used using a multiple imputation model, followed by a modification of the imputed data applying penalties:

  1. First, multiple imputation will be applied to draw sets of completed data, using an appropriate imputation model. Baseline characteristics which should be considered in the imputation model include but are not restricted to the baseline values of the respective efficacy variable, the treatment group, and sex.
  2. The imputed data will be modified by applying penalties. The choice of the penalty may be guided by the worst observed change from baseline for the respective outcome in the corresponding treatment group, e.g. by choosing the penalty as a multiple of the worst observed change from baseline value.
  3. After modifying the completed data sets, the primary analysis using the MCP-step of the MCP-Mod methodology will be applied to the multiply imputed datasets and the results will be combined.

- An analysis where for each patient without an observation at the visit in Week 20 the missing value will be imputed according to a last observation carried forward approach, including the baseline value. Such an analysis is usually biased but will make use of the observations obtained at early EOT visits.

For reproducibility, the SAS seed number for creating the random numbers for the multiple imputation will be set to the study number. More details will be described in the SAP.

10.4 Determination of sample size

This combined proof-of-concept and Phase IIb dose-finding study has been powered for the detection of a dose response signal in the primary efficacy variable.

The sample size for the primary efficacy variable was evaluated under the assumptions described in Section 10.3.2.2 and a type I error level = 5% with the aim to achieve at least 80% power for the one-sided primary multiple contrast test. The overall randomization ratio was assumed to be 3:1:2:2:2:2 for doses 0, 5, 10, 20, 30, and 40 mg.

Table 10—2 displays the power for the multiple contrast test in the MCP-Mod approach, used as primary analysis, for the set of specified alternatives.

Table 10—2: Power for multiple contrast test for set of different alternatives

Sample size		Power for alternative based on respective dose-response model (in %)					
Overall	Per group [a]	Linear	Sigmoidal E_{max} 1	Sigmoidal E_{max} 2	E_{max}	Quadratic	Minimum
180	30	74.10	86.84	81.84	82.96	80.59	74.10
192	32	76.54	88.75	84.07	85.11	82.82	76.54
204	34	78.83	90.39	86.05	87.04	84.86	78.83
216	*36*	*80.84*	*91.81*	*87.80*	*88.72*	*86.61*	*80.84*
228	38	82.76	93.03	89.36	90.23	88.23	82.76
240	40	84.48	94.05	90.73	91.51	89.62	84.48
252	42	86.06	94.97	91.92	92.67	90.88	86.06
264	44	87.45	95.72	92.96	93.65	91.96	87.45

a Number of patients randomized to dose levels 10 mg, 20 mg, 30 mg, and 40 mg of neladenoson bialanate, for placebo sample size per group to be multiplied by 3/2, for dose level 5.0 mg sample size per group to be divided by 2.

To achieve at least 80% power for the multiple contrast test in the MCP-Mod approach under all different alternatives, a minimum of 36 patients per treatment group (54 patients for the placebo and 18 patients for the 5 mg group) is needed, resulting in an overall sample size of 216 patients.

Based on this estimation, a total of 288 patients are planned to be randomized to the 6 treatment groups:

- 72 patients are planned to be randomized to placebo (0 mg),
- 48 patients each are planned to be randomized to the dose levels 10 mg, 20 mg, 30 mg, and 40 mg of neladenoson bialanate, and
- 24 patients are planned to be randomized to the dose level 5 mg of neladenoson bialanate.

These numbers already include adequate assumptions on expected drop-out after randomization and invalid or missing data. In the selected population it is expected that only about 75% of all randomized patients, i.e. about 216 patients, will contribute complete data to the primary analysis in the PPS.

All power estimations and simulations were performed with the DoseFinding package in R, version 3.2.3 (2015-12-10).

10.5 Planned interim analyses

A formal interim analysis is not planned. Periodic data review by a DMC will be performed to monitor safety.

11. Data handling and quality assurance

11.1 Data recording

The data collection tool for this study will be a validated electronic data capture system called RAVE. Patient data necessary for analysis and reporting will be entered / transmitted into a validated database or data system (e.g. TOSCA, SAS).

Data required according to this protocol will be recorded by investigational site personnel via data entry into the internet based EDC software system RAVE, which Bayer has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Bayer for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered by the site personnel. Bayer extensively applies the logic to ensure data are complete and reflect the clinical data requirements of the study. Data queries resulting from the application of the software logic are resolved by the site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Bayer's internal computer system via a secure Virtual Private Network.

All access to the RAVE system is through a password-protected security system that is part of the RAVE software. All internal Bayer and external investigator site personnel seeking access must go through a thorough RAVE training process before they are granted access to RAVE for use in Bayer's clinical studies. Training records are maintained.

All personnel with access to the RAVE system are supported by a Service Desk staffed with trained personnel to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

The RAVE System contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why the change was made and the date and time it was made. This information is available both at the investigator’s site and at Bayer. Data entries made in the RAVE EDC screens are supported by source documents maintained for all patients enrolled in this study.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (patient number; year of birth / age; sex; if permitted locally, race / ethnicity)
- Date of informed consent
- Inclusion / exclusion criteria
- Reason for premature discontinuation
    - AE information, if applicable
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE, the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE such as:
    - The SAE itself
    - Concomitant medication
    - Medical history
    - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's / CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor / designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of patients are being protected
- Study is conducted in accordance with the currently approved protocol
  (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with sponsor's applicable standards and data cleaning procedures. This is applicable for data recorded in the eCRF as well as for data from other sources (e.g. IxRS, laboratory, ECG, AVIVO).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following additional data: pharmacokinetic data and biomarker data.

11.4 Missing data

The following measures will be implemented to minimize the amount of missing data.

- Encourage further participation in the study, i.e. phone call 26 weeks after the start of treatment, even if the study medication is discontinued early.
- If the patient does not attend the visits in person, the investigator should make every effort to collect information on mortality and / or hospitalization from other sources, e.g. family / friend / general physician / etc.
- Ask sites to call patients the day before certain study visits to remind them to remember the time they take their study medication and to remind them in case study medication should not be taken at home the next day.
- Educate patients on the AVIVO device and train sites to prepare the patient's skin for adherence of the sensor. Ask sites to call patients at the end of the wearing period to provide instructions for removal, storage and return at the next visit.
- Try to avoid unnecessary patient withdrawals (see Section 6.4).

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator / institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s) / IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator / institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his / her time and the time of his / her staff to the auditor / inspector to discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor (minimum is 25 years; longer if required by local regulation), alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator / institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator / institution will contain reference to all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
  - Safety findings from this study (e.g. SAEs)
  - Results of parallel clinical studies
  - Results of parallel animal studies
    (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his / her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s) / IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing patients, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual patient's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigator(s) and other study personnel

Sponsor's study medical expert is identified on the Title page.

Coordinating investigators in this study will be:

PPD
USA
Tel. PPD
Fax PPD
E-mail: PPD

PPD
USA
Tel. PPD
Fax PPD
E-mail: PPD

All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before patient recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must receive all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

External data evaluation bodies

Steering Committee

The main task of the Steering Committee, which is composed of a panel of experts in the field, is to support the conduct of the study and to advise the sponsor on clinical, medical, and scientific questions. Details of the committee will be specified in the Steering Committee charter.

Data Monitoring Committee

Ongoing safety monitoring during the conduct of the study will be performed by an external and unblinded DMC. Analysis periods and procedures will be defined in an operational charter (DMC Charter) filed in the study file. Following data review, the DMC will provide written recommendations that will be transferred to Bayer. All other definitions will be provided in the DMC charter.

Clinical Events Committee

Blinded adjudication of all HF hospitalizations, urgent visits for HF and deaths will be performed by a central CEC as described in the CEC charter. Data entry procedures and documentation necessary for case adjudication will also be described in the CEC charter. Adjudication results will be the basis for the final analysis.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and / or any sub investigators) who is directly involved in the treatment or evaluation of research patients has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s) / IRBs will be obtained for all participating centers / countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC / IRB

approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC / IRB, head of the study center / medical institution) must supply to the sponsor, upon request, a list of the EC / IRB members involved in the vote and a statement to confirm that the IEC / IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC / IRB / sponsor approval / favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC / IRB / head of medical institution / sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Patient information and consent

All relevant information on the study will be summarized in an integrated patient information sheet and informed consent form provided by the sponsor or the study center. A sample patient information and informed consent form is provided as a document separate to this protocol.

Based on this patient information sheet, the investigator or designee will explain all relevant aspects of the study to each patient prior to his / her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB / IEC has been obtained.

Each patient will be informed about the following aspects of premature withdrawal:

- Each patient has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The patient's consent covers end-of-study examinations as specified in the visit description described in Section 9.2 to be conducted after withdrawal of consent to treatment.
- The patient's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Patient-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The patient has the right to object to the generation and processing of this post-withdrawal data. The patient's oral objection may be documented in the patient's source data.

Each patient will have ample time and opportunity to ask questions.

Only if the patient voluntarily agrees to sign the informed consent form and has done so, may he / she enter the study. Additionally, the investigator will personally sign and date the form. The patient will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note / file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or patient´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to patients will be revised whenever important new information becomes available that may be relevant to the patient's consent, or there is an amendment to the protocol that necessitates a change to the content of the patient information and / or the written informed consent form. The investigator will inform the patient of changes in a timely manner and will ask the patient to confirm his / her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC / IRB's approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his / her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of patients / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and / or regulations, will not be made publicly available.

Patient names will not be supplied to the sponsor. Only the patient number will be recorded in the CRF, and if the patient name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the patients will be informed in writing that representatives of the sponsor, IEC / IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the patient's identity will remain confidential.

The investigator will maintain a list to enable patients to be identified.

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15. Protocol amendments

Not applicable.

16. Appendices

16.1 Calculating glomerular filtration rate

In accordance with established nephrology practice and guidelines, renal function at baseline and throughout the study will be assessed by means of the estimated glomerular filtration rate (eGFR), calculated using the Modification of Diet in Renal Disease (MDRD) study abbreviated formula.

Isotope dilution mass spectroscopy (IDMS)-traceable MDRD Study Equation:

Conventional units (serum creatinine level is measured in mg/dL)

GFR (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

GFR can be estimated using the calculator provided in the following link:
http://www.kidney.org/professionals/kdoqi/gfr_calculator

For further information on assessing renal function using GFR estimates, see reference (86).

16.2 Calculating the Child-Pugh score

The severity of liver disease (Table 16–1) will determine the Child-Pugh score (Table 16–2).

Table 16–1: Grading of severity of liver disease

Factor	+1	+2	+3
Bilirubin (mg/dL)	< 2	2 – 3	> 3
Albumin (g/dL)	> 3.5	2.8 – 3.5	< 2.8
International Normalized Ratio	< 1.7	1.7 – 2.3	> 2.3
Ascites	None	Mild	Moderate / Severe
Encephalopathy	None	Grade I - II	Grade III – IV

Source: adapted from (87)

Table 16–2: Classification using the added score from Table 16–1

Child-Pugh Class	A	B	C
Points	5 – 6	7 – 9	10 – 15

Source: adapted from (87)

16.3 6-minute walking distance (6MWD) test

The 6MWD test must be performed in accordance with the American Thoracic Society Guideline (81).

According to the guideline, the 6MWD test should be carried out indoors, along a long, flat, straight, enclosed corridor with hard surface that is seldom traveled. The walking course should be preferably 30 m in length, but not less than 25 m (longer walking courses should be shortened to 30 m). The length of the corridor and turnaround points should be marked.

Patients will be instructed to walk alone, not run, from one end to the other end of the walking course, at their own pace, while attempting to cover as much ground as possible in 6 minutes.

During the walk, patients are allowed to stop, lean against the wall and rest, but should resume walking as soon as they feel able to do so. The resting time will be included in the 6 minutes.

A "warm-up" period before the test should not be performed. The patients should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts.

Investigators should not walk with the patients. Moreover, only standardized phrases for encouragement must be used during the test. To allow reproducibility, standardized phrases should be used every minute according to the following pattern:

- After the first minute, tell the patient the following (in even tones): "You are doing well. You have 5 minutes to go."
- When the timer shows 4 minutes remaining, tell the patient the following: "Keep up the good work. You have 4 minutes to go."
- When the timer shows 3 minutes remaining, tell the patient the following: "You are doing well. You are halfway done."
- When the timer shows 2 minutes remaining, tell the patient the following: "Keep up the good work. You have only 2 minutes left."
- When the timer shows only 1 minute remaining, tell the patient: "You are doing well. You have only 1 minute to go."

To reduce the variability of the 6MWD tests, it is *of utmost importance that familiarization-6MWD test, baseline-test and all following tests are performed under the same conditions*.

- Wheelchair or scooter dependent / supplemental oxygen patients or those on continuous oxygen for severe pulmonary disease are excluded from the study.
- The use of a cane is allowed in cane dependent patients, but then these patients need to use the same cane at every 6MWD test throughout the study. If the need for walking aids should arise at the baseline visit, the same walking aids should also be used at every subsequent test.
- If a supplemental oxygen therapy should be implemented already at baseline, all subsequent 6MWD tests have to be performed under the same "baseline" conditions (same flow of oxygen, same application route, and same way of carrying the oxygen bottle).

- Even if a supplemental oxygen therapy is implemented or modified during the trial (e.g. increase of oxygen flow), it is not permitted to perform the subsequent 6MWD tests under conditions other than the baseline conditions.

However, a change of test conditions should be avoided, if reasonably possible at least after baseline, to have the same conditions in all 6MWD tests.

For quality reasons, the inhalation of supplemental oxygen and the use of walking aids during the 6MWD tests must be documented in the eCRF.

16.4 Borg CR 10 Scale and test instructions

Use this rating scale to report how strong your perception of exertion is. First look at the verbal expressions. Start with them and then the numbers. Of these ten (10) or "Extremely strong – Maximal" is a very important intensity level. This is the most intense perception or feeling you have ever had.

If your experience or feeling is "Very weak", you should say "1", if it is "Moderate", say "3". Note that "Moderate" is "3" and thus weaker than "Medium", "Mean" or "Middle". If the experience is "Strong" or "Heavy" (it feels "Difficult") say "5". Note that "Strong" is about half of "Maximal". Is your feeling "Very strong", choose a number from 6 to 8. If your perception or feeling is stronger than "10", "Extremely strong – Maximal" you can use a larger number, e.g. 12 (that's why "Absolute maximum" is marked with a dot "●").

It is very important that you report what you actually experience or feel, not what you think you should report. Be as spontaneous and honest as possible and try to avoid under- or overestimating. Look at the verbal descriptors and then choose a number.

When rating your exertion give a number (in principle any kind of decimal number is allowed) that corresponds to how hard and strenuous you perceive the work to be. The perception of exertion is mainly felt as strain and fatigue in your muscles and as breathlessness or any aches.

0 "Nothing at all", means that you don't feel any exertion whatsoever, no muscle fatigue, no breathlessness or difficulties breathing.

0.3

0.5 "Extremely weak", "Just noticeable"

0.7

1 "Very weak" means a very light exertion. As taking a shorter walk at your own pace.

1.5

2 "Weak", "Light"

2.5

3 "Moderate" is somewhat but not especially hard. It feels good and not difficult to go on

4

5 "Strong – Heavy". The work is hard and tiring, but continuing isn't terribly difficult. The effort and exertion is about half as intense as "Maximal".

6

7 "Very strong" is quite strenuous. You can still go on, but you really have to push yourself and you are very tired.

8

9

10 "Extremely strong – Maximal" is an extremely strenuous level. For most people this is the most strenuous exertion they have ever experienced previously in their lives.

11

//

● Is "Absolute maximum – Highest possible" for example "12" or even more