Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

Masking of dosing, and matching of placebo

Dosing was masked by instructing participants to take 2 study tablets once daily. All patients received the same number of tablets (only active, combination of active and placebo, or only placebo, depending on the treatment arm), to maintain blinding, as follows: placebo (2 placebo tablets); neladenoson 5 mg (5-mg tablet plus placebo tablet); neladenoson 10 mg (10-mg tablet plus placebo tablet); neladenoson 20 mg tablet (20-mg tablet plus placebo tablet); neladenoson 30 mg tablet (20-mg tablet plus 10-mg tablet); and neladenoson 40 mg tablet (2 20-mg tablets). Placebo was matched to treatment drug in appearance by adjusting the size and color of the film coat of the placebo tablet to the active tablet; both were pink coated tablets with a diameter of 8 mm and a weight of 185 mg.

MCP-Mod statistical approach

The MCP-Mod statistical approach consists of two key steps. Step 1 is the inferential part of the approach: a one-sided multiple contrast test for an efficacy signal (a non-flat dose-response curve) while controlling for type 1 error (α=5%). Five candidate shapes (linear model, E_{max} model, sigmoidal E_{max} models 1 and 2, and a quadratic model [**eFigure 2**]) were predefined to cover both plausible and diverse dose-response profiles, reflecting the range of candidate models believed to be capable of describing the dose-response relation at the study design stage. Step 2 is the estimation part of the approach: if a dose-response signal is established in step 1, a dose-response model and target dose(s) of interest were estimated. As pre-specified in the study protocol, a dose-response signal was defined to be present in the primary efficacy analysis if the null hypotheses related to the primary efficacy variable could be rejected. Prior to entry into the

aforementioned dose-response models, NT-proBNP and high-sensitivity troponin T were log-transformed due to a right-skewed distribution in both end points.

Treatment adherence and pharmacokinetics

To monitor treatment adherence, the investigators were required to document drug dispensing for each participant. Accountability was determined for all tablets at the scheduled visits, when participants were to return all remaining unused study drug, as well as all empty packaging. Any discrepancies between actual and expected amount of returned study medication was discussed and reconciled with the participant at the time of the visit. Treatment adherence was defined as 100*number of tablets taken / number of tablets planned. Plasma concentration of the study drug was measured in all study participants during the following study visits and times: baseline, 2 hours post-dose; Week 4 [Day 28], pre-dose; Week 8 [Day 56], pre-dose; Week 12 [Day 84], 2 and 4 hours post-dose; Week 20 [end-of-treatment]; and Week 24 [safety follow-up], 28-days after end-of-treatment.

eTable 1. Participating Sites and Principal Investigators

Country	Site investigator (first name)	Site investigator (last name)	Center
Austria	Christopher	Adlbrecht	Krankenhaus Hietzing
Austria	Johann	Auer	Krankenhaus St. Josef Braunau
Austria	Diana	Bonderman	Allgemeines Krankenhaus der Stadt Wien
Austria	Regina	Mascherbauer-Steringer	Krankenhaus der Elisabethinen Linz GmbH
Austria	Deddo	Moertl	Universitätsklinikum St. Pölten
Austria	Dirk	von Lewinski	Medizinische Universität Graz
Belgium	Michel	DE CEUNINCK	AZ Delta
Belgium	Etiënne	HOFFER	CHR de la Citadelle
Belgium	Philippe	Timmermans	Jessa Ziekenhuis
Bulgaria	Valentina	Grigorova	Medical Center Cardiohelp
Bulgaria	Ivan	Kamburov	MCOMH Preventsia-2000
Bulgaria	Kostadin	Kichukov	Spec Hosp for Active Treatm in Cardiology Sv Georgi Pernik
Bulgaria	Elena	Kinova	UMHAT Tsaritsa Joanna-ISUL EAD Sofia
Bulgaria	Sotir	Marchev	Specialized Hospital for Actrive Treatm of Card - Pleven
Bulgaria	Valentina	Mincheva	NMTH Tzar Boris III
Germany	Hans-Dirk	Düngen	Charité Campus Virchow-Klinikum (CVK)
Germany	Sabine	Genth-Zotz	St. Vincenz und Elisabeth Hospital, Kathol. Klinikum Mainz
Germany	Peter	Heymer	Klinische Forschung Dresden GmbH
Germany	Niels	Menck	HELIOS Klinikum Erfurt GmbH
Greece	Nikolaos	Kafkas	KAT General Hospital of Athens
Greece	Apostolos	Karavidas	G. Gennimatas General State Hospital of Athens
Greece	Athanasios	Manolis	Asklipieion General Hospital of Voulas
Greece	Ioannis	Mantas	General Hospital of Chalkida
Greece	Sotirios	Patsilinakos	Konstantopoulio General Hospital of Nea Ionia - Agia Olga
Greece	Vassilios	Vassilikos	Hippokration General Hospital of Thessaloniki
Israel	Yaron	Arbel	Tel-Aviv Sourasky Medical Center
Israel	Tal	Hasin	Shaare Zedek Medical Center
Israel	Amos	Katz	Barzilai Medical Center
Israel	David	Leibowitz	Hadassah University Hospital Mount Scopus
Israel	Gil	Moravsky	Assaf Harofeh Medical Center
Israel	Eugenia	Nikolsky	Rambam Health Corporation
Israel	Avraham	Shotan	Hillel Yaffe Medical Center
Italy	Giuseppe	Argiolas	A.O.U. di Sassari
Italy	Franco	Cosmi	AUSL 8 Arezzo
Italy	Lucio	Mos	AAS 3 Friuli Alto Medio Collin
Italy	Savina	Nodari	ASST Spedali Civili di Brescia
Italy	Claudio	Norbiato	A.O. Ordine Mauriziano
Italy	Michele	Senni	ASST Papa Giovanni XXIII
Italy	Massimo	Volpe	A.O. Sant Andrea
Japan	Takahiko	Aoyama	Fukui Prefectural Hospital
Japan	Hiroyuki	Fujinaga	Tokushima Prefectural Central Hospital

Country	Site investigator (first name)	Site investigator (last name)	Center
Japan	Shinichi	Higashiue	Kishiwada Tokushukai Hospital
Japan	Masaaki	Hoshiga	Osaka Medical College Hospital
Japan	Masaaki	Hoshiga	Osaka Medical College Hospital
Japan	Masahiko	Koda	Chuno kosei Hospital
Japan	Mamoru	Manita	R.I.A.C Naha City Hospital
Japan	Seiji	Namba	Okayama Rosai Hospital
Japan	Haruhiko	Onaka	Takatsuki Red Cross Hospital
Japan	Satoru	Sakagami	National Hospital Organization Kanazawa Medical Center
Japan	Tsuyoshi	Shiga	Tokyo Women s Medical University Hospital
Japan	Shinji	Tanaka	Shonan Fujisawa Tokushukai Hospital
Japan	Ryoji	Taniguchi	Hyogo Prefectural Amagasaki General Medical Center
Japan	Takahisa	Yamada	Osaka General Medical Center
Poland	Janusz	Bednarski	Szpital Zachodni w Grodzisku Mazowieckim
Poland	Jaroslaw	Kasprzak	Wojewodzki Specjalistyczny Szpital im. dr Wl. Bieganskiego
Poland	Waldemar	Krysiak	109 Szpital Wojskowy z przychodnia SPZOZ
Poland	Ewa	Mirek-Bryniarska	Szpital Specjalistyczny im. J. Dietla
Poland	Wlodzimierz	Musial	Uniwersytecki Szpital Kliniczny w Bialymstoku
Poland	Joanna	Szachniewicz	IV Wojskowy Szpital Kliniczny z Poliklinika, SPZOZ
Poland	Dariusz	Wojciechowski	Szpital Wolski im. dr Anny Gostynskiej SPZOZ
Portugal	Candida	Fonseca	Hospital São Francisco Xavier
Portugal	Irene	Marques	Centro Hospitalar do Porto, EPE - Hospital de Santo Antonio
Portugal	Pedro	Monteiro	CHUC - Hospitais da Universidade de Coimbra
Portugal	Pedro	Moraes Sarmento	Hospital da Luz
Spain	Luís	Almenar Bonet	Hospital Universitari i Politècnic La Fe
Spain	Ramón	Bover Freire	Hospital Clínico Universitario San Carlos
Spain	Alberto	Esteban Fernández	Hospital Sanitas La Zarzuela
Spain	Núria	Farré López	Hospital del Mar
Spain	Francisco	Fernández Avilés	Hospital General Universitario Gregorio Marañón
Spain	José Manuel	García Pinilla	Hospital Virgen de la Victoria
Spain	Julio Eduardo	Núñez Villota	Hospital Clínico Universitario de Valencia
Spain	Domingo A.	Pascual Figal	Hospital Universitario Virgen de la Arrixaca
United States	Sadiya	Khan	Northwestern University
United States	Dalane	Kitzman	Wake Forest Baptist Health
United States	Keith	Miller	Bryan LGH Medical Center East
United States	Harvey	Serota	St. Louis Heart & Vascular, PC

eTable 2. Inclusion and Exclusion Criteria for PANACHE

Inclusion criteria:

1. Men or women aged 45 years and older
2. Diagnosis of chronic HF, 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, or 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 for 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) or
      - 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 LA area ≥ 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

Exclusion criteria:

1. Acute decompensated HF (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 CV 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 or a pre-existing or 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
   - CABG
   - PCI
   - implantation of a CRTD
   - major surgery (that could interfere with the patient's 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
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)

Exclusion criteria (continued):

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 for continuous (home) oxygen
    - history of chronic obstructive pulmonary disease ≥ GOLD III
    - use of systemic corticosteroids
17. Asthma bronchiale with either 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 > 45 kg/m^2 at randomization
20. eGFR < 30 mL/min/1.73 m^2 calculated by Modification of Diet in Renal Disease 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:
    - PBC
    - primary sclerosing cholangitis
    - PBC-autoimmune hepatitis overlap syndrome
22. Concomitant use of any of the following therapies 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 that 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. close relative of the investigator or 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

6MWD, 6-minute walk distance; AV, atrioventricular; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CRTD, cardiac resynchronization therapy device; CV, cardiovascular; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IV, intravenous; LA, left atrial; LAVI, left atrial volume index; LV, left ventricular; LVEDP, left ventricular end-diastolic pressure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; NYHA, New York Heart Association; PAWP, pulmonary artery wedge pressure; PBC, primary biliary cirrhosis; PCI, percutaneous coronary intervention.

eTable 3. Secondary Analysis: Pairwise Comparison of Change in 6-Minute Walk Distance From Baseline to 20 Weeks Between Neladenoson Doses vs. Placebo

Treatment comparison with Placebo	Difference of Means (Neladenoson - Placebo)	90% CI of Difference	Two-sided p-value	Adjusted 90% CI of Difference	Adjusted two-sided p-value
Neladenoson 5mg vs. Placebo	19.0	[-6.2, 44.1]	0.21	[-15.9, 53.8]	0.65
Neladenoson 10mg vs. Placebo	20.4	[0.5, 40.4]	0.09	[-7.2, 48.1]	0.35
Neladenoson 20mg vs. Placebo	12.5	[-7.8, 32.8]	0.31	[-15.6, 40.7]	0.80
Neladenoson 30mg vs. placebo	13.1	[-8.5, 34.6]	0.32	[-16.8, 42.9]	0.81
Neladenoson 40mg vs. placebo	14.6	[-6.5, 35.7]	0.25	[-14.6, 43.8]	0.72

6MWD = 6-min walking distance
Adjusted p-values and confidence limits were calculated with a Dunnett test. In the adjusted comparisons, baseline values of 6MWD, age, and gender were used as covariates.

eTable 4. Changes in Primary Endpoint (6-Minute Walk Distance) from Baseline to 20 Weeks: Neladenoson vs. Placebo Groups (Full Analysis Set with Multiple Imputation)

Treatment group	Mean change in 6MWD (m)	90% CI
Placebo	0.4	-9.8, 10.6
Neladenoson 5mg	19.4	-4.2, 43.0
Neladenoson 10mg	28.3	6.8, 49.7
Neladenoson 20mg	14.0	0.9, 27.1
Neladenoson 30mg	18.4	3.8, 33.1
Neladenoson 40mg	13.1	-3.2, 29.4
Multiple imputation is done by treatment group with 100 imputations. Baseline value of 6MWD and gender are included in the imputation model.		

Candidate model shape	P-value
Linear	0.35
SigmoidalEmax1	0.19
SigmoidalEmax2	0.45
Emax	0.05
Quadratic	0.16

MCP-Mod) was applied to calculate the p-values of the contrast tests for each candidate dose-response model.

eTable 5. Dose-Response Results for Primary and Secondary Endpoints: Per Protocol Set

End Points	Neladenoson bialanate					Placebo	MCP-Mod candidate model shape	P-value
	40 mg	30 mg	20 mg	10 mg	5 mg			
Primary End Point								
6-minute walk distance (m), mean (95% confidence interval [CI]) change from baseline to 20 weeks	n=37	n=34	n=41	n=44	n=22	n=65	-	-
	10.7 (-9.4, 30.8)	16.3 (-3.1, 35.6)	14.5 (-2.5, 31.6)	27.2 (-0.2, 54.6)	24.7 (-7.4, 56.9)	1.9 (-10.4, 14.2)	Linear	0.52
							SigmoidalEmax1	0.33
							SigmoidalEmax2	0.62
							Emax	0.09
							Quadratic	0.27
Secondary End Points								
Physical activity intensity (%), mean (95% CI) change from baseline to 20 weeks	n=32	n=30	n=33	n=34	n=20	n=52	-	-
	-0.1 (-0.3, 0.1)	-0.2 (-0.4, 0.0)	-0.1 (-0.3, 0.2)	-0.1 (-0.3, 0.1)	-0.2 (-0.5, 0.0)	-0.2 (-0.4, 0.0)	Linear	0.46
							SigmoidalEmax1	0.33
							SigmoidalEmax2	0.47
							Emax	0.43
							Quadratic	0.38
KCCQ overall summary score, mean (95% CI) change from baseline to 20 weeks*	n=37	n=33	n=41	n=44	n=22	n=65	-	-
	2.8 (-1.8, 7.5)	0.5 (-4.6, 5.5)	3.7 (-0.4, 7.9)	-0.7 (-6.7, 5.3)	7.0 (-0.7, 14.7)	2.9 (-0.4, 6.2)	Linear	0.77
							SigmoidalEmax1	0.87
							SigmoidalEmax2	0.75
							Emax	0.78
							Quadratic	0.82
NT-proBNP (pg/ml), mean (SD) mean (95% CI) change from baseline to 20 weeks	n=36	n=32	n=38	n=43	n=20	n=60	-	-
	301 (-71, 674)	185 (-14, 383)	163 (-115, 441)	143 (-77, 363)	50 (-394, 493)	26 (-124, 175)	Linear	>0.99
							SigmoidalEmax1	>0.99
							SigmoidalEmax2	>0.99
							Emax	>0.99
							Quadratic	>0.99
High-sensitivity troponin T (pg/ml), mean (95% CI) change from baseline to 20 weeks	n=36	n=33	n=38	n=44	n=22	n=60	-	-
	4.3 (1.0, 7.6)	3.0 (0.6, 5.3)	5.0 (2.0, 8.1)	3.1 (0.4, 5.8)	1.6 (-3.4, 6.5)	2.1 (0.1, 4.1)	Linear	0.96
							SigmoidalEmax1	0.98
							SigmoidalEmax2	0.98
							Emax	0.93
							Quadratic	0.98

KCCQ = Kansas City Cardiomyopathy Questionnaire; NT-proBNP = N-terminal pro-B-type natriuretic peptide
An increase (positive value) denotes improvement for 6-minute walk test distance, physical activity intensity, and KCCQ score, and denotes worsening for NT-proBNP and high-sensitivity troponin T. A decrease (negative value) denotes worsening for 6-minute walk test distance, physical activity intensity, and KCCQ score, and denotes improvement for NT-proBNP and high-sensitivity troponin T. See also text for calculation and meaning of physical activity intensity.
The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model. The P-values tested the hypothesis that a dose-response signal corresponding to the specified model types have been detected. Model shapes are shown in **eFigure 2, Supplement 2**.
*The KCCQ overall summary score ranges from 0-100; lower scores indicate lower quality of life. A 5-point increase is considered to be a clinically meaningful improvement.

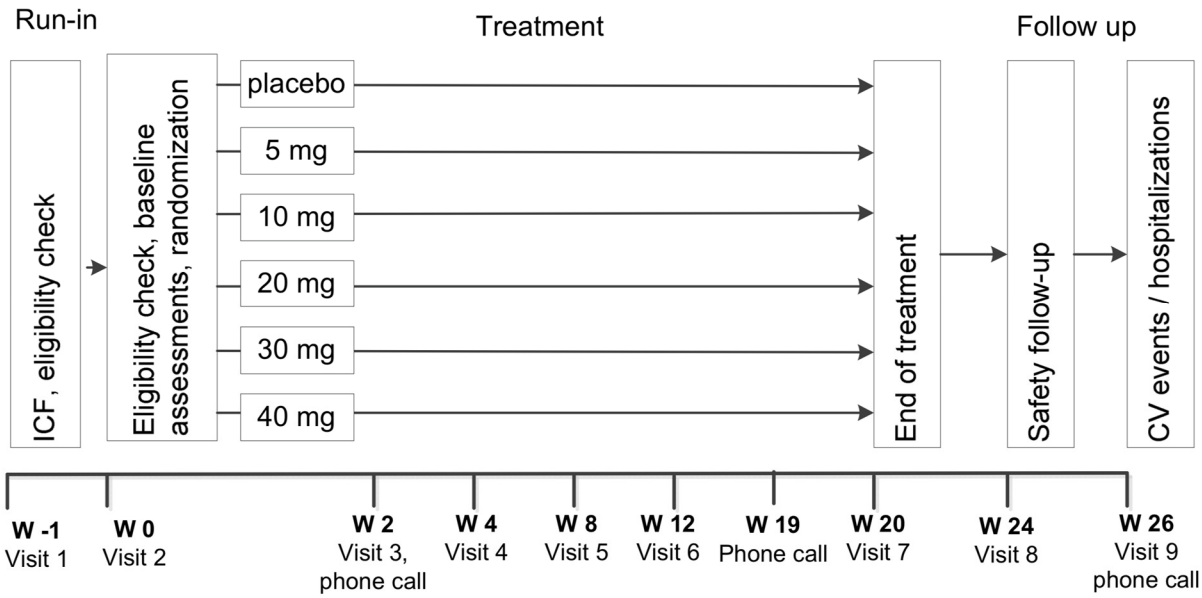
eTable 6. Echocardiographic Outcomes: Full Analysis Set

End Points	Neladenoson bialanate					Placebo	MCP-Mod candidate model shape	P-value
	40 mg	30 mg	20 mg	10 mg	5 mg			
Primary End Point								
6-minute walk distance (m), mean (95% confidence interval [CI]) change from baseline to 20 weeks	n=33	n=30	n=30	n=31	n=19	n=56	-	-
	-1.45 (3.6)	-2.40 (3.2)	-1.03 (3.9)	-0.60 (3.2)	0.03 (2.6)	-0.73 (3.7)	Linear	0.52
							SigmoidalEmax1	0.33
							SigmoidalEmax2	0.62
							Emax	0.09
							Quadratic	0.27
E/e' ratio, mean (SD) change from baseline to 20 weeks (higher change value = worsening)	n=35	n=24	n=27	n=25	n=17	n=45	-	-
	0.96 (5.4)	0.05 (3.2)	0.27 (5.5)	0.45 (5.0)	2.21 (7.82)	-0.28 (3.0)	NA	NA
LA volume (ml), mean (SD) change from baseline to 20 weeks (higher change value = worsening)	n=31	n=30	n=30	n=32	n=19	n=54	-	-
	6.8 (23.6)	6.9 (14.4)	3.9 (21)	6.6 (21.8)	3.7 (20.0)	3.0 (15.9)	NA	NA

LV = left ventricular; LA = left atrial; NA = not applicable.

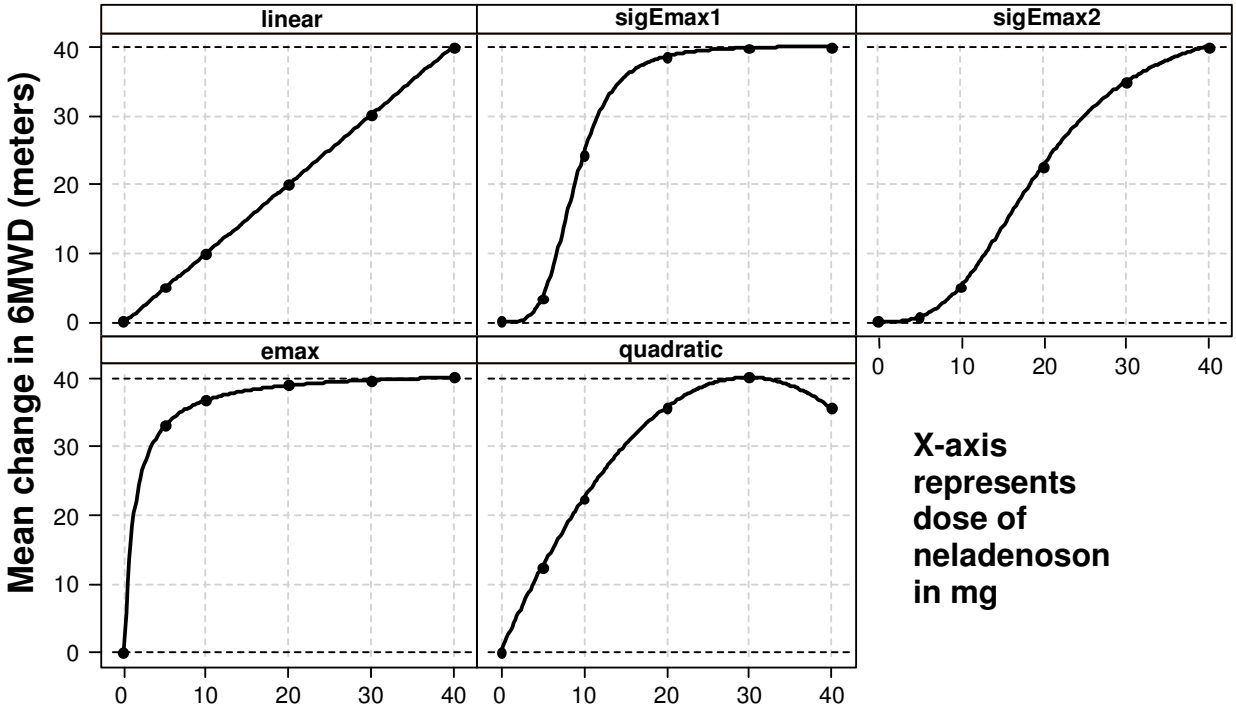
*The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model. Formal statistical testing was not done for E/e' ratio and LA volume because these were exploratory endpoints and changes were similar across groups.

eFigure 1. Study Design Overview of the PANACHE Trial



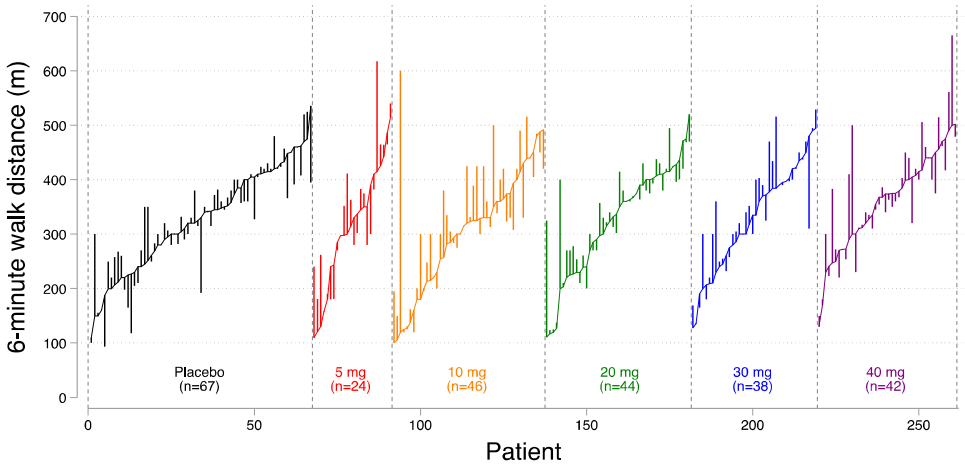
CV = cardiovascular; ICF = informed consent form; W = week

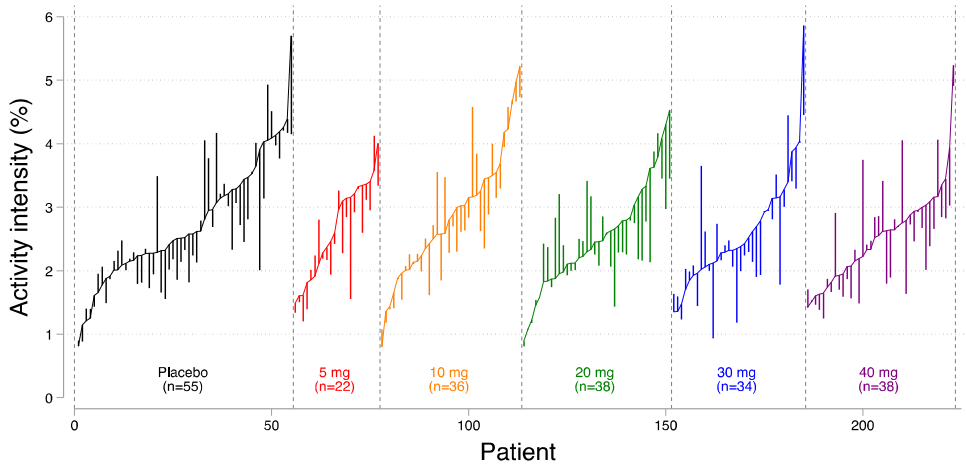
eFigure 2. Dose-Response Curves Showing Various Model Types Tested Using the MCP-Mod Approach

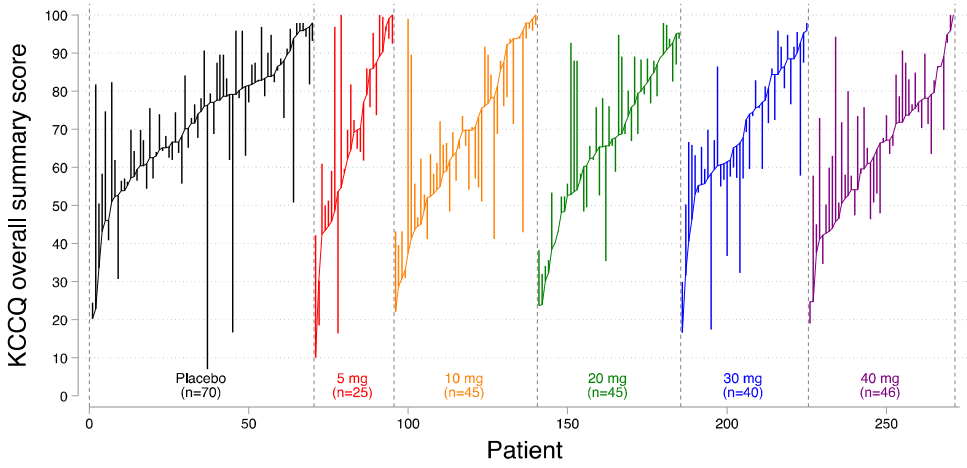


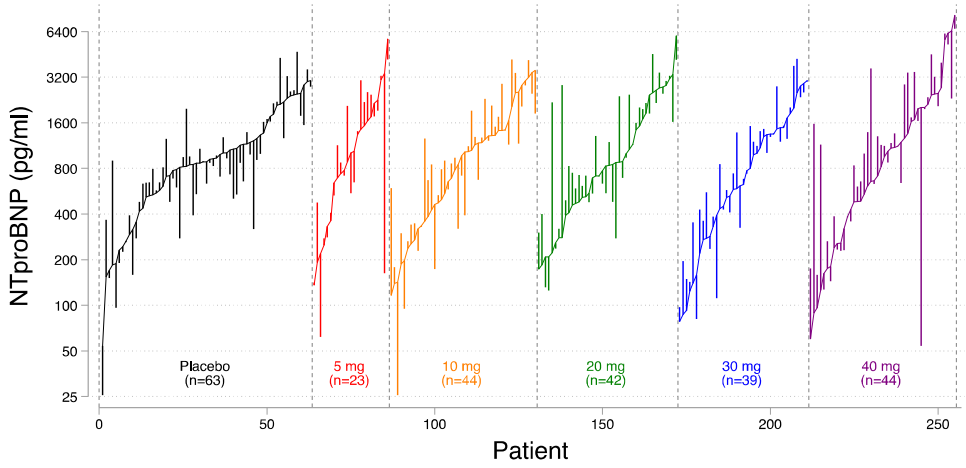
6MWD = 6-minute walk distance

eFigure 3. Changes in Primary and Secondary Efficacy Endpoints From Baseline to 20 Weeks, Neladenoson vs. Placebo Treatment Groups: Parallel Line Plots (Full Analysis Set)

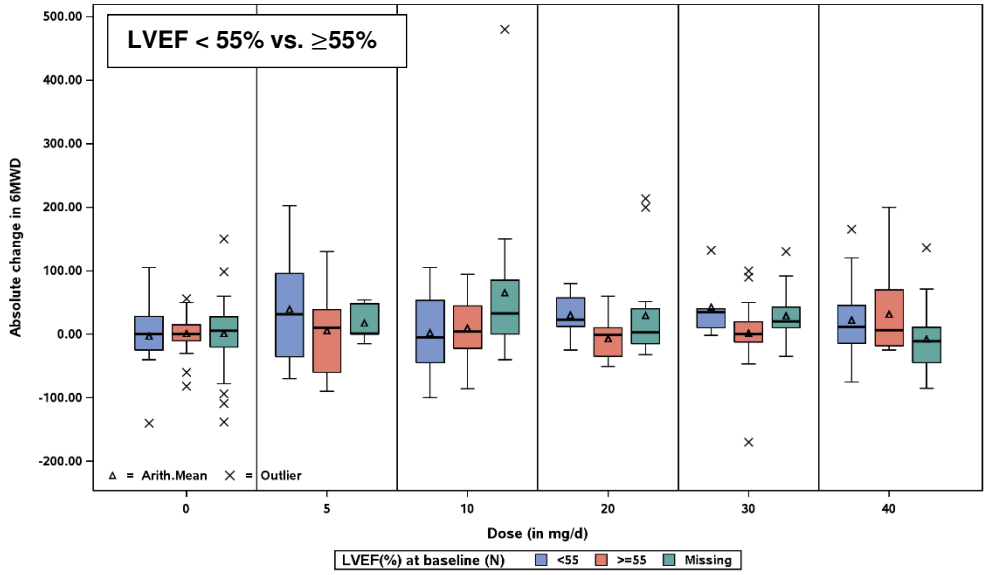




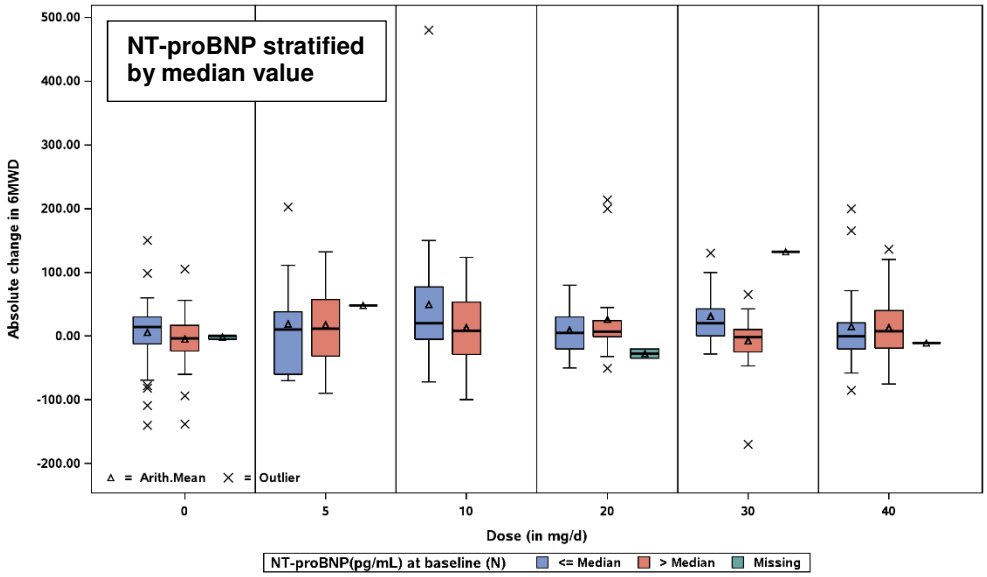




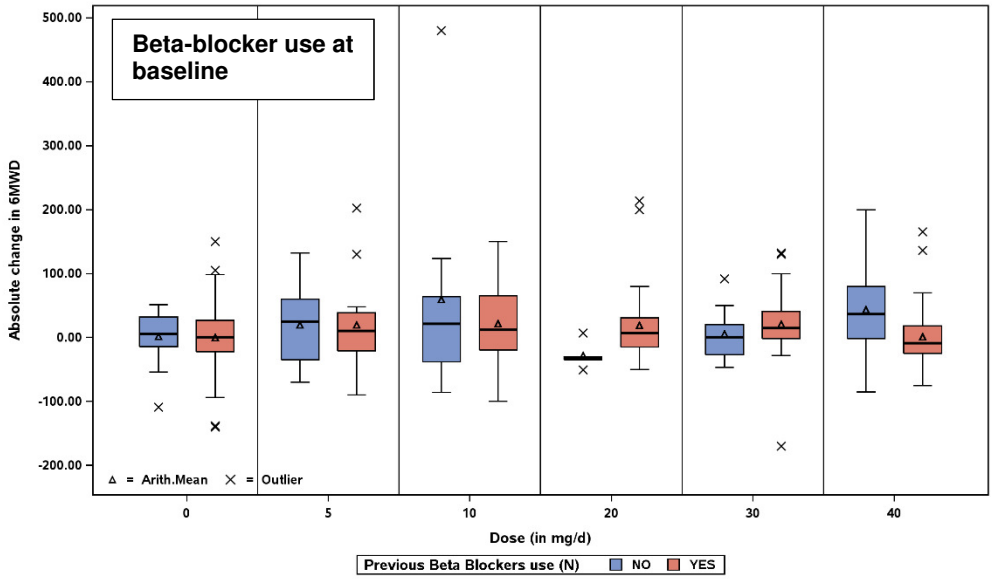
eFigure 4. Subgroup Analyses for the Primary End Point (6MWD): Full Analysis Set



LVEF < 55%:	
Model shape	**P-value**
Linear	0.28
SigmoidalEmax1	0.31
SigmoidalEmax2	0.27
Emax	0.18
Quadratic	0.20
LVEF >= 55%:	
Model shape	**P-value**
Linear	0.31
SigmoidalEmax1	0.55
SigmoidalEmax2	0.41
Emax	0.47
Quadratic	0.56
LVEF missing:	
Model shape	**P-value**
Linear	0.78
SigmoidalEmax1	0.30
SigmoidalEmax2	0.85
Emax	0.10
Quadratic	0.29

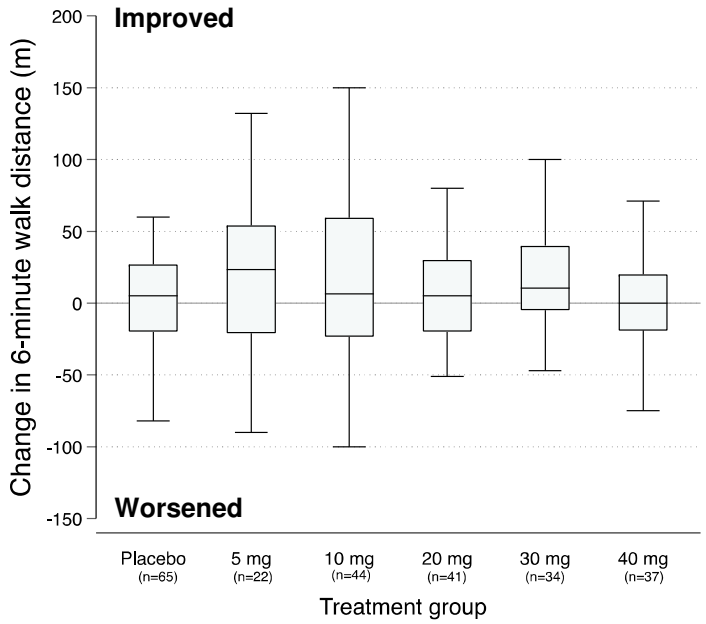


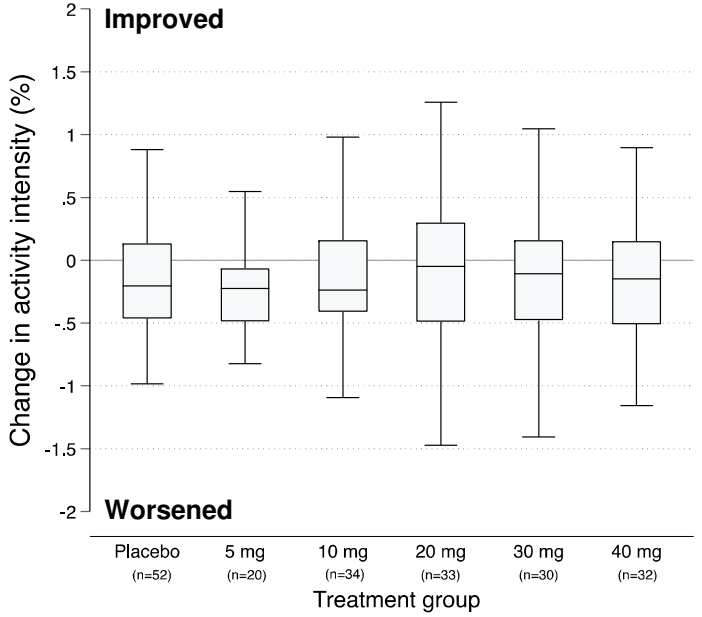
NT-proBNP <= median value	
Model shape	**P-value**
Linear	0.53
SigmoidalEmax1	0.38
SigmoidalEmax2	0.63
Emax	0.18
Quadratic	0.35
NT-proBNP > median value	
Model shape	**P-value**
Linear	0.46
SigmoidalEmax1	0.31
SigmoidalEmax2	0.54
Emax	0.15
Quadratic	0.30

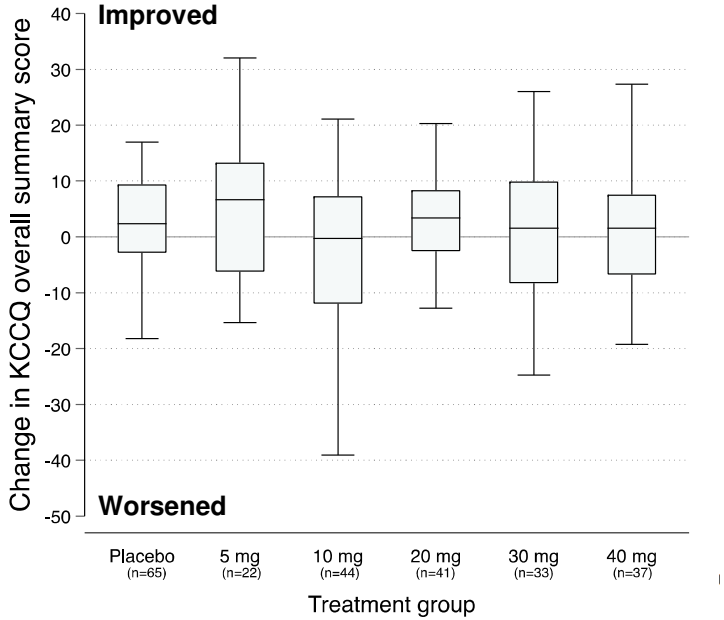


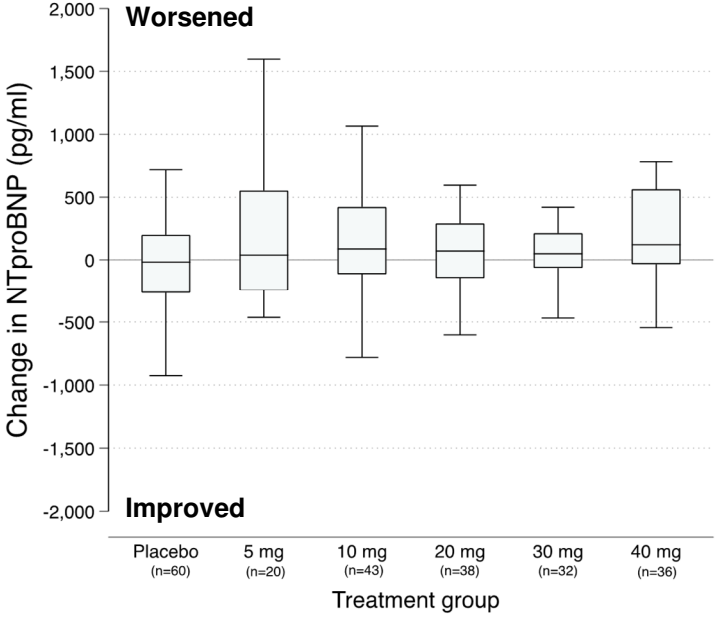
Beta-blocker use: No	
Model shape	**P-value**
Linear	0.53
SigmoidalEmax1	0.21
SigmoidalEmax2	0.55
Emax	0.08
Quadratic	0.16
Beta-blocker use: Yes	
Model shape	**P-value**
Linear	0.41
SigmoidalEmax1	0.46
SigmoidalEmax2	0.56
Emax	0.27
Quadratic	0.48

eFigure 5. Changes in Primary and Secondary Efficacy Endpoints From Baseline to 20 Weeks, Neladenoson vs. Placebo Treatment Groups: Box Plots (Per-Protocol Set)

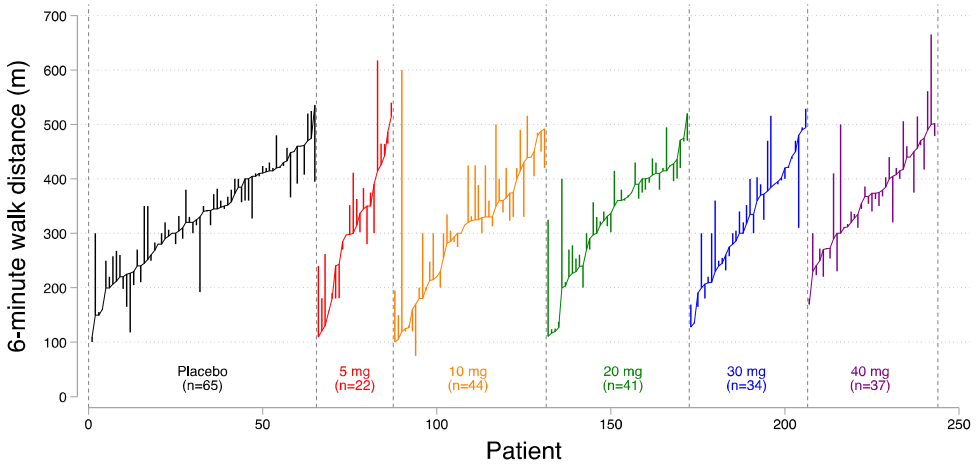


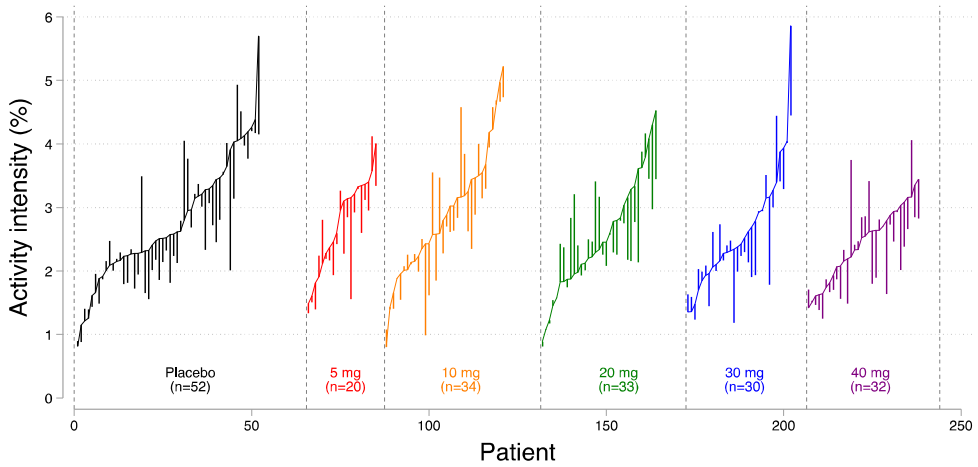


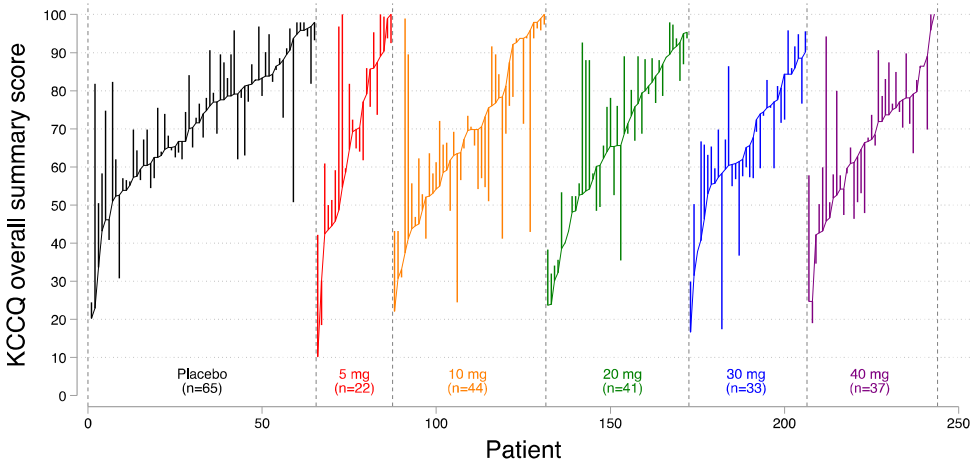


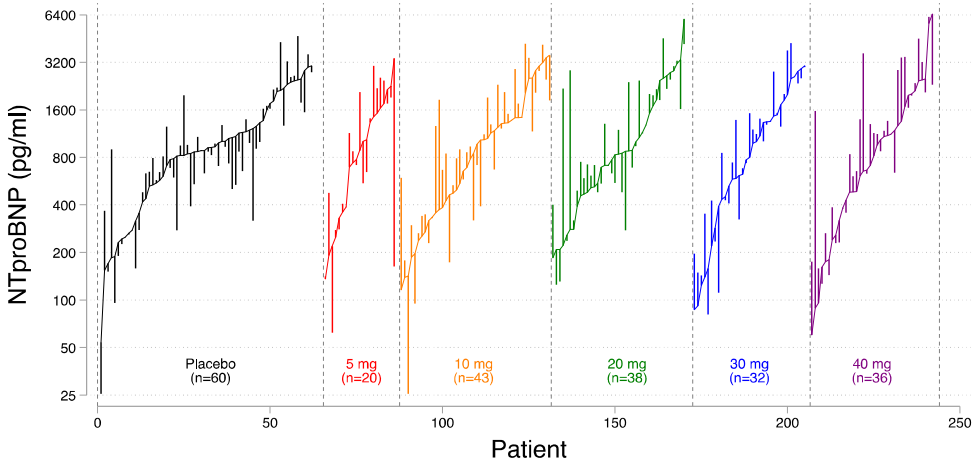


eFigure 6. Changes in Primary and Secondary Efficacy Endpoints From Baseline to 20 Weeks, Neladenoson vs. Placebo Treatment Groups: Parallel Line Plots (Per Protocol Set)

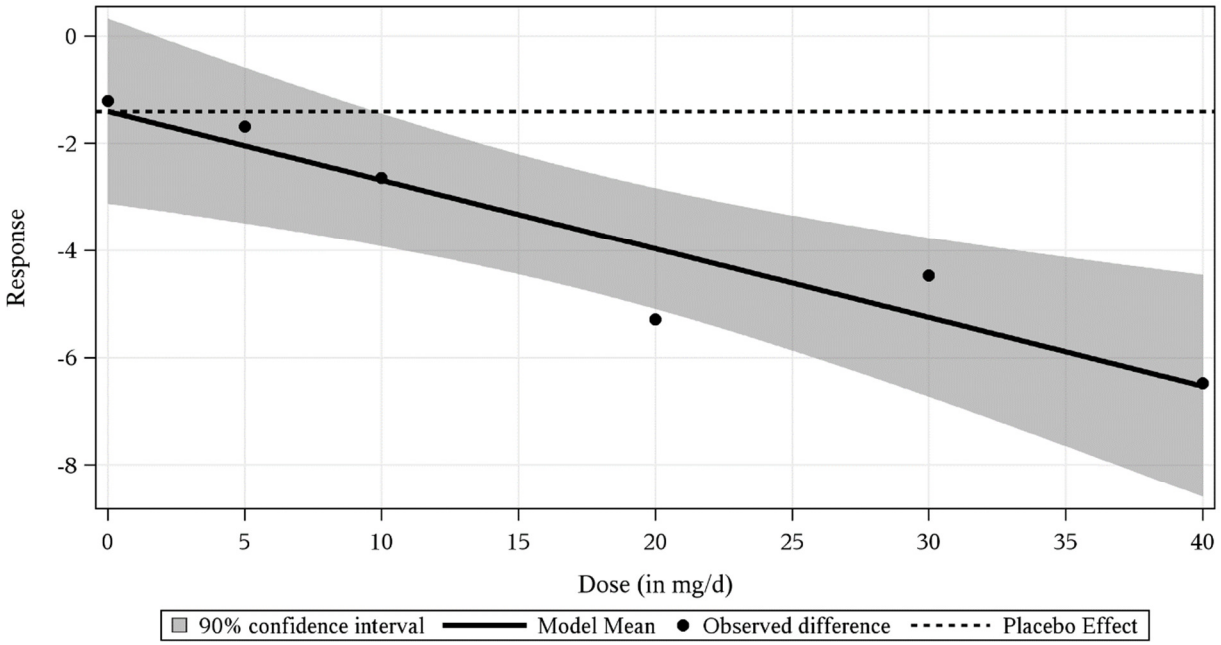








eFigure 7. Relationship between Neladenoson Bialanate Dose Groups and Change in Estimated Glomerular Filtration Rate Linear model, full analysis set:



For each patient without an observation at end of treatment the missing values were imputed according to a last observation carried forward (LOCF) approach, including the baseline values.

Candidate model shape	Estimate	Standard Error	t-Statistic	Degrees of Freedom	Adjusted p-value
Linear	4.5136	1.5408	2.9294	262	0.004
SigmoidalEmax1	4.4120	1.5171	2.9081	262	0.005
SigmoidalEmax2	4.5722	1.5742	2.9044	262	0.005
Emax	3.5819	1.4174	2.5271	262	0.01
Quadratic	4.2544	1.4742	2.8859	262	0.005

The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model.
For each patient without an observation at end of treatment the missing values were imputed according to a last observation carried forward approach (LOCF), including the baseline values.

Stratification by ACE-inhibitor or angiotensin receptor blocker (ARB) use at baseline:

ACE-inhibitor/ARB use at baseline

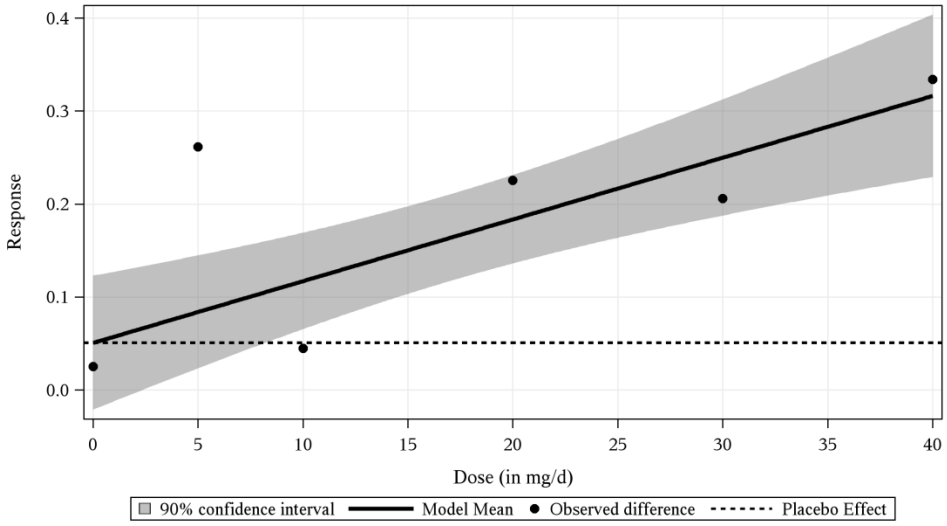
Candidate model shape	Estimate	Standard Error	t-Statistic	Degrees of Freedom	Adjusted p-value
Linear	5.4225	2.0185	2.6864	175	0.009
SigmoidalEmax1	5.2341	1.9749	2.6503	175	0.01
SigmoidalEmax2	5.5516	2.0540	2.7028	175	0.009
Emax	3.9871	1.8557	2.1486	175	0.03
Quadratic	4.9602	1.9128	2.5932	175	0.01

No ACE-inhibitor/ARB use at baseline

Candidate model shape	Estimate	Standard Error	t-Statistic	Degrees of Freedom	Adjusted p-value
Linear	2.9246	2.2089	1.3240	80	0.17
SigmoidalEmax1	2.7011	2.1862	1.2355	80	0.19
SigmoidalEmax2	2.8985	2.2715	1.2760	80	0.18
Emax	2.5799	2.0331	1.2690	80	0.18
Quadratic	2.7676	2.1450	1.2902	80	0.18

The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model.
For each patient without an observation at end of treatment the missing values were imputed according to a last observation carried forward approach (LOCF), including the baseline values.

eFigure 8. Effect of Neladenoson Bialanate on Potassium
Linear model, full analysis set:

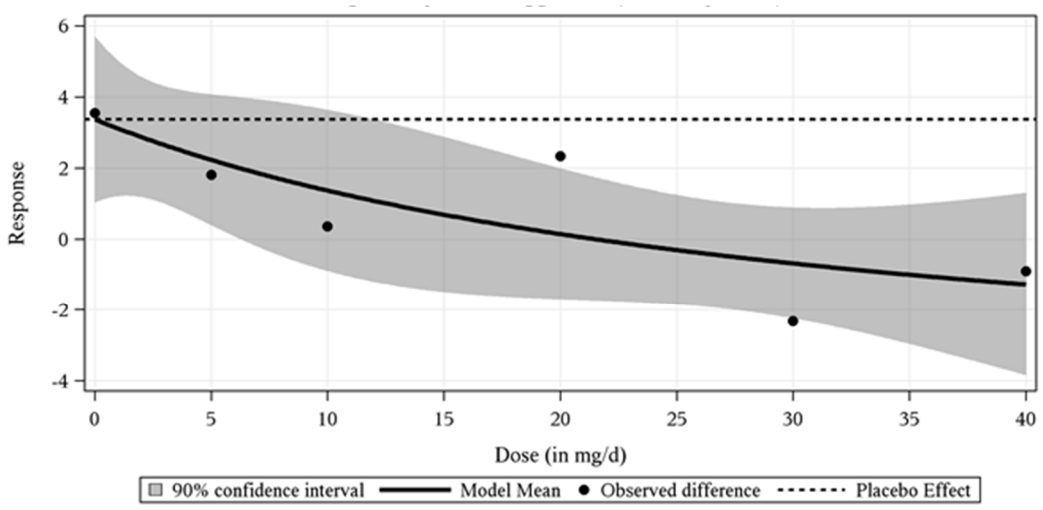


For each patient without an observation at end of treatment the missing values were imputed according to a last observation carried forward (LOCF) approach, including the baseline values.

Candidate model shape	Estimate	Standard Error	t-Statistic	Degrees of Freedom	Adjusted p-value
Linear	0.2382	0.0563	4.2297	294	<0.0001
SigmoidalEmax1	0.1913	0.0553	3.4568	294	0.0008
SigmoidalEmax2	0.2327	0.0575	4.0443	294	0.0001
Emax	0.1809	0.0515	3.5145	294	0.0007
Quadratic	0.1949	0.0537	3.6324	294	0.0005

The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model.
For each patient without an observation at end of treatment the missing values were imputed according to a last observation carried forward approach (LOCF), including the baseline values.

eFigure 9. Relationship between Neladenoson Bialanate Dose Groups and Heart Rate

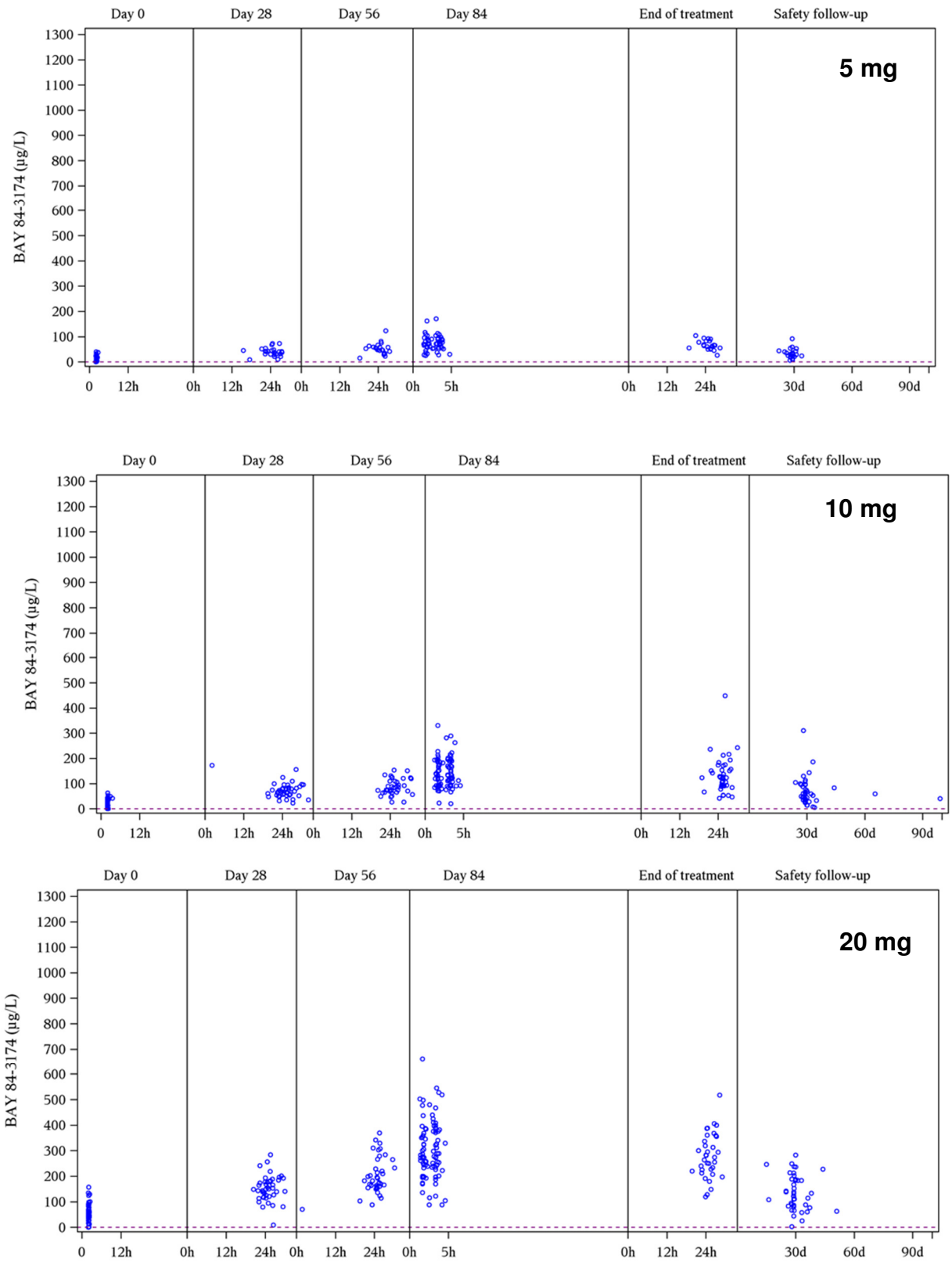


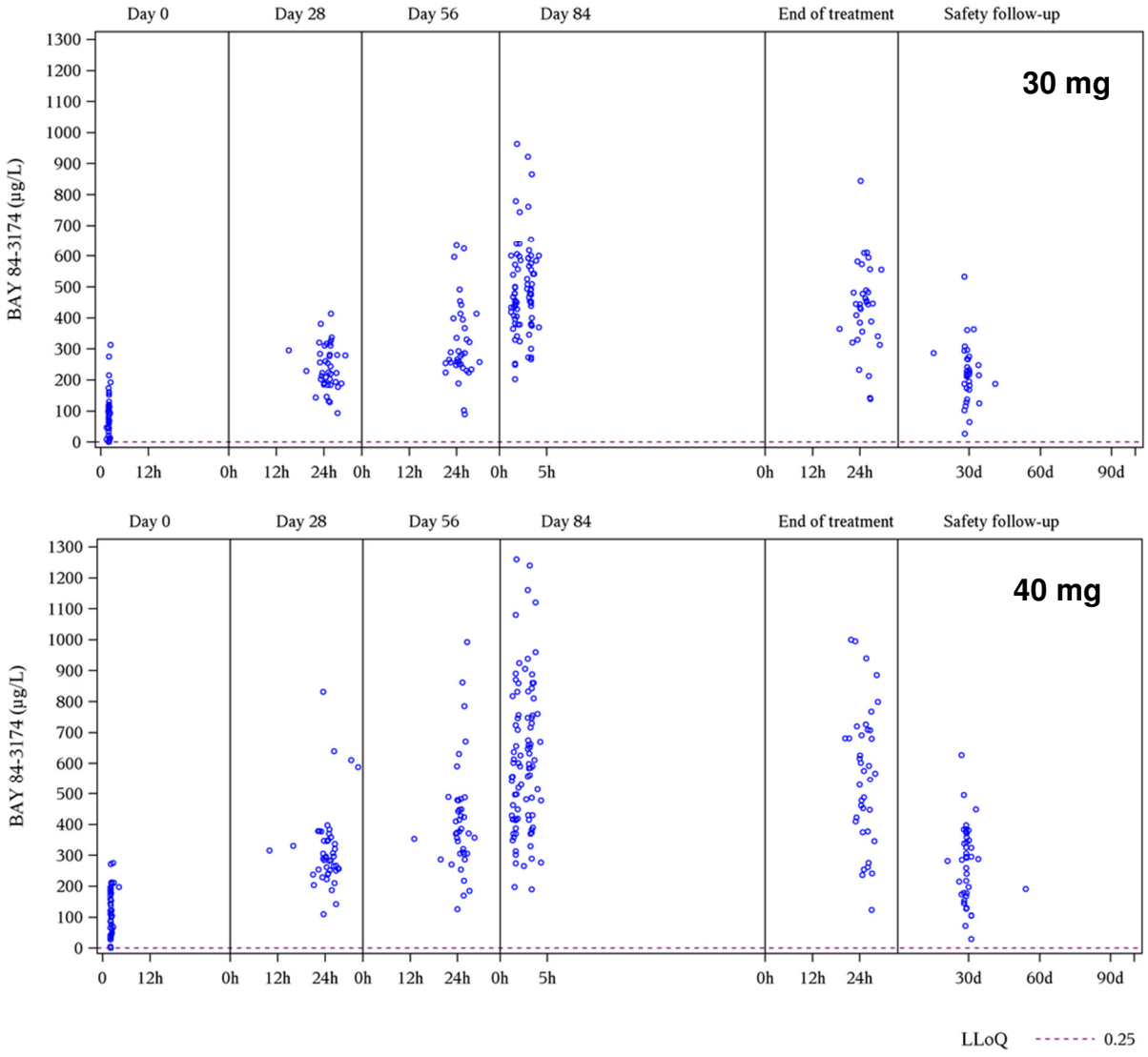
For each patient without an observation at maximum of day 142 and two days after last study drug intake the missing values were imputed according to a last observation carried forward (LOCF) approach, including the baseline values.

Candidate model shape	Estimate	Standard Error	t-Statistic	Degrees of Freedom	Adjusted p-value
Linear	2.9686	1.4716	2.0172	298	0.04
SigmoidalEmax1	2.7303	1.4476	1.8861	298	0.06
SigmoidalEmax2	2.8986	1.5047	1.9263	298	0.05
Emax	2.9143	1.3421	2.1715	298	0.03
Quadratic	2.9597	1.4028	2.1098	298	0.04

The Multiple Comparison Procedure-Modeling approach (MCP-Mod) was applied to calculate the adjusted p-values of the contrast tests for each candidate dose-response model.
For each patient without an observation at maximum of day 142 and two days after last study drug intake the missing values were imputed according to a last observation carried forward approach (LOCF), including the baseline values.

eFigure 10. Plasma Concentration of Neladenoson Bialanate by Extent of Exposure





LLOQ = lower limit of quantitation; BAY 84-3174 = neladenoson bialanate. Plasma concentration of the study drug was measured in all study participants during the following study visits and times: baseline, 2 hours post-dose; Week 4 [Day 28], pre-dose; Week 8 [Day 56], pre-dose; Week 12 [Day 84], 2 and 4 hours post-dose; Week 20 [end-of-treatment]; and Week 24 [safety follow-up], 28-days after end-of-treatment.