2. SYNOPSIS

Name of Sponsor/Company: Celladon Corporation	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Finished Product: MYDICAR®		
Name of Active Ingredient: Capsercagene ledaparvovec, AAV1/SERCA2a		

Title of Study:

A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicenter, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure

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Sites shown in gray font did not infuse any subjects in the study. Investigator / site shown in strikeout Dr. Miller was removed from the study by the study sponsor; Dr. Videback was withdrawn from the study at the investigator's request.

Publications (reference): Greenberg B, Yaroshinsky A, Zsebo K, et al. Design of a Phase 2b Trial of Intracoronary Administration of AAV1/SERCA2a in Patients With Advanced Heart Failure: The CUPID 2 Trial (Calcium Up-Regulation by Percutaneous Administration of Gene Therapy in Cardiac Disease Phase 2b). JACC: Heart Failure 2014;2:84-92.

Studied period (years): 2012 to 2016 Date first patient enrolled: 22 August 2012 Date last patient completed: 27 February 2015; Long-Term Follow-Up ongoing, last subject to complete in February 2016	**Phase of development:** Phase 2b

Objectives: The study primary objective was to investigate the efficacy of gene transfer therapy with MYDICAR added to an optimal HF regimen in improving outcomes in AAV1 neutralizing antibody (NAb) titer negative subjects with heart failure and reduced ejection fraction (HFrEF)

Primary Efficacy Endpoint: The primary efficacy endpoint was time to recurrent events, defined as hospitalizations or ambulatory treatment related to failure of the native heart that has not been implanted with a mechanical circulatory support device (MCSD).

Secondary Efficacy Endpoint: The secondary efficacy endpoint was time to first terminal event, defined as MCSD implant, heart transplant or death.

Exploratory Endpoints: Exploratory endpoints included change from baseline in New York Heart Association (NYHA) class, exercise ability as assessed by the 6-minute walk test (6MWT), quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ), and N-terminal pro–B-type natriuretic peptide (NT-proBNP).

Methodology: All subjects provided written informed consent and the study was conducted according to the principles of the International Conference on Harmonisation Guideline on Good Clinical Practice and the principles of the World Medical Association Declaration of Helsinki. All relevant Institutional Review Boards (IRB)/ Institutional Ethics Committees (IEC) and Bio-Safety Committees, or equivalent, approvals were obtained.

Following screening, 250 subjects were randomized in parallel in a 1:1 ratio to receive either 1 x 10^{13} DNase resistant

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particles (DRP) MYDICAR or placebo via an interactive web response system (IWRS) which triggered a just-in-time shipment of investigational medicinal product (IMP). Randomization was stratified by country and the ability to walk between 150 and 425 meters, inclusive, or outside these distances on the 6MWT. On Day 0 before infusion of the IMP, coronary angiography was performed, if it had not been performed within the two months prior to infusion, to determine the intracoronary (IC) administration strategy and to confirm that at least one coronary artery had Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

Infusion of the IMP was tailored to the subject's coronary anatomy and multiple infusion scenarios were possible depending on the extent and distribution of coronary artery stenoses, collateralization patterns and anatomic variations. Operators were instructed that in most cases it was expected that up to three infusions should be performed to capture the largest portion of left ventricular blood flow. An intravenous (IV) nitroglycerin infusion was started 10 to 25 minutes prior to infusion of IMP to enhance uptake of AAV1/SERCA2a in cardiomyocytes by increasing vasodilation of the capillary bed. All medical care and the need for overnight hospitalization conformed to institutional standards of care following routine cardiac catheterization. In Hungary, all subjects were hospitalized for 1 week following the IMP administration. All laboratory tests to assess safety were performed prior to discharge.

During the 12-Month Active Observation Period, subjects were seen in the clinic at Months 1, 3, 6, 9 and 12 for a battery of safety, efficacy and economic assessments. Subjects were then transitioned into the Long-Term Follow-Up Period (LT-FUP) for continued clinical event collection during quarterly in person clinic visits until the Primary Analysis Data Cutoff (PADC) was reached, which was when all subjects had completed the 12-Month Active Observation Period (or terminated early) and at least 186 adjudicated primary endpoints had occurred in the ITT population.

Number of patients (planned and analyzed): 250 planned/250 randomized (ITT population)/243 treated (mITT [modified ITT] and Safety Populations)

Diagnosis and main criteria for inclusion: Eligible subjects were between 18 and 80 years of age, inclusive, with a diagnosis of stable NYHA class II-IV chronic HF due to ischemic or non-ischemic cardiomyopathy and left ventricular ejection fraction ≤0.35 on optimal tolerated stable medical therapy for at least 30 days prior to randomization. A protocol amendment on study also required randomized subjects to have either elevated natriuretic peptides or a HF-related hospitalization or outpatient interventions within 6 months of screening. Subjects were required to have <1:2 or equivocal anti-AAV1 neutralizing antibody (NAb) titers within 90 days of screening.

Test product, dose and mode of administration, batch number: MYDICAR, 1 x 10^{13} DRP, IC, Lot Number B120166

Duration of treatment: Single IC infusion

Reference therapy, dose and mode of administration, batch number: Placebo containing the same excipients as MYDICAR with the absence of the active ingredient (300 mM NaCl, 10 mM L-histidine, 1 mM $MgCl_2$, 0.01% polysorbate 20 and Water for Injection at pH 7.0 as a sterile, preservative-free, clear colorless aqueous solution), IC, Lot Number B120163

Criteria for evaluation:

Efficacy: The primary analysis of the primary and secondary endpoints was done at the PADC using the modified intent-to-treat (mITT) population (randomized subjects who received IMP) to compare the differences between the MYDICAR and placebo groups; secondary analyses were done using the intent-to-treat (ITT) population (all randomized subjects) and additional pre-specified populations for comparisons.

Safety: Safety analyses were performed using the Safety Population of the 243 treated subjects. Safety endpoints included: subject disposition; time to CV-related death; treatment-emergent (TE) adverse events (AEs), including serious TEAEs (TESAEs) and adjudicated clinical events: AE incidence, severity, and relationship to IMP and procedure;

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changes from baseline in safety laboratory evaluations including hematologic, blood chemistries, hepatic, lipid profile, cardiac biomarker, and urinalysis evaluations; ELISpot assay to assess possible anti-AAV1 capsid cellular immune response; changes from baseline in HF-related medications; concomitant medical/surgical procedures; changes from baseline in vital signs; changes from baseline in physical examination findings; changes from baseline in 12-lead electrocardiogram (ECG) parameters, and; changes from baseline in implantable cardioverter defibrillator (ICD) interrogation parameters.

Statistical Methods: Treatment effects on the primary and secondary endpoints were estimated simultaneously by a semi-parametric joint frailty model (JFM) implemented using the NLMIXED procedure in SAS (SAS Institute, Inc., Cary, NC). This model accounts for correlated recurrent events within subjects and the correlation between recurrent and terminal events (i.e., informative censoring). The reference time point was randomization date for the ITT population and treatment date for all other analysis populations.

Monte Carlo simulation using background rates and correlations similar to those observed in CUPID-1, a pilot dose-finding study of MYDICAR, estimated that 186 recurrent events in 250 subjects with a median follow-up time of 18 months would provide 80% power at the 0.05 two-sided significance level to detect a recurrent event hazard ratio (HR) of 0.55 using a JFM.

SUMMARY – CONCLUSIONS

SAFETY RESULTS: There was no statistically significant difference between treatment groups in time to all-cause death or time to cardiovascular (CV)-related death. There were 11.2 deaths per 100 patient-years in the placebo group compared to 14.6 deaths per 100 patient-years in the MYDICAR group; the majority of deaths were adjudicated as CV-related. In a pre-specified subgroup analysis of the secondary endpoint (terminal events of MCSD, heart transplant or death), there was a significant interaction between treatment and geography with a higher HR in non-US subjects compared with US subjects. However, the number of first terminal events in the analysis of non-US subjects was too small (22 events in 85 subjects) to form any firm conclusions.

There were 10 subject deaths in the study that were adjudicated as sudden death, 7 in the MYDICAR group and 3 in the placebo group. There was one additional presumed sudden death in the placebo group. Although there were more sudden deaths in the MYDICAR group, the majority occurred late in the study with no apparent patterns observed and the number of events was too small to draw any conclusions. Of interest, the rate of sudden death was nearly 5 times higher in countries outside of the US (1.3 per 100 patient-years in the US, 6.3 per 100 patient-years ex-US). Given the small number of overall events, it is not clear whether this higher rate was due to chance, reflective of disease severity at baseline or was due to another unidentified difference.

There were a total of 452 adjudicated clinical events in the safety population up to the PADC. Clinical events included all-cause death, all-cause hospitalization, hospitalization for HF, ambulatory worsening HF (or urgent HF visit), heart transplant, insertion of a MCSD, non-fatal myocardial infarction and non-fatal stroke. Over a total of approximately 350 patient-years of follow-up, 262 events occurred in placebo subjects for a rate of 1.470 clinical events per patient-year and 190 events occurred in MYDICAR subjects for a rate of 1.108 clinical events per patient-year. Most adjudicated clinical events were hospitalizations, followed by HF hospitalizations. For each type of clinical event, the difference between treatment groups was not statistically significant.

Ninety-one percent of subjects in both the MYDICAR and the placebo groups experienced at least one TEAE during the 12-month reporting period. There were no significant differences in the rates of TEAEs between MYDICAR and placebo subjects with the exception of ICD insertion (more placebo, $p = 0.01$) and upper abdominal pain (more MYDICAR, $p = 0.03$); cardiac arrest was borderline significant (more MYDICAR, $p = 0.06$). The higher rate of ICD insertion on study was probably reflective of the lower rate of ICDs at baseline in the placebo group (73%) compared to the MYDICAR group (81%) and the natural progression of disease. There was no apparent pattern of upper abdominal pain etiology,

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onset or duration with which to draw any conclusions on causality or relatedness to investigational intervention, and in light of the relatively small sample size, difference in upper abdominal pain events between treatment groups could well be due to chance. Since there were so few cardiac arrests in total, it is not possible to draw any conclusions regarding the relatedness to MYDICAR as opposed to chance. In light of the known association between cardiac arrest and sudden death in advanced HF, it is reasonable to conclude that the fatal cardiac arrests were related, directly or indirectly, to the subjects' underlying disease.

There were no meaningful differences in procedure-related complications from cardiac catheterization and diagnostic angiography between treatment groups. Complication rates were consistent with rates published in the literature with the most common being vascular disorders, administration site conditions and known adverse reactions to contrast media.

No clinically significant differences between treatment groups were noted in changes in exams of major organ systems over time, nor were any consistent clinically meaningful changes in blood pressure, heart rate or body temperature observed over time. No trends or significant changes, with the exception of blood urea nitrogen (BUN) levels, were noted in hematology, blood chemistries, electrolytes, cardiac enzymes, liver and kidney function tests, or ECG intervals, rhythm, waveform or morphology. Compared to placebo, significantly more MYDICAR subjects who had normal baseline BUN had elevated BUN above the upper limits of normal at 3 months post-treatment. A similar but non-significant result was also seen at 1 month post-treatment. No differences were detected between MYDICAR and placebo groups in electrocardiographic abnormalities or arrhythmias. There was no meaningful difference between treatment groups in subject disposition. Overall, the majority of subjects continued on a stable regimen of HF medications that was unchanged during the first 12 months: angiotensin converting enzyme inhibitor (ACEI) 53.5%, angiotensin-receptor blocker (ARB) 23.9%, beta blocker (BB) 89.3%, anti-mineralocorticoid), 54.7%; and any diuretic, 84%.

Of 11 subjects who were identified as clinically relevant to evaluate for T-cell response by ELISpot, results were negative for all MYDICAR-treated subjects. The only positive ELISpot result was for 1 placebo subject at one of two timepoints tested, indicating no discernable cellular immune response against the AAV1 capsid.

CONCLUSION: From 9 July 2012 through 5 February 2014, 1558 subjects at 67 centers in the US, Europe and Israel underwent AAV1 NAb pre-screening. Of these subjects, 921 (59.1%) were NAb positive and 284 (18.2%) were considered ineligible for other reasons, leaving 353 (22.7%) with a qualifying NAb titer (<1:2 or equivocal) who were eligible for further screening. Of these subjects, 103 (29.2%) were excluded and 250 subjects were enrolled into the study and randomized. Two of 123 subjects allocated to receive MYDICAR and 5 of 127 patients allocated to placebo were not treated. The remaining 121 subjects who received MYDICAR and 122 subjects who received placebo constituted the mITT population that was the pre-specified population for the primary efficacy analysis. Over the course of the study, 5 subjects (3 in mITT) withdrew consent and 1 (mITT) was lost to follow-up.

The subjects were predominantly white and male with approximately two-thirds from the US. A total of 56% of patients had coronary artery disease and HF was ascribed to an ischemic etiology in 51% of subjects. Subjects had moderate to severe HF as evidenced by NYHA Functional Class, EF, 6MWT distance, KCCQ score and NT-proBNP level. Baseline characteristics were balanced between treatment groups.

Median follow-up was 17.5 months since the study extended over 30 months in order to allow all randomized subjects to be followed for at least 12 months. When the last subject had been followed for 12 months, 232 recurrent and 65 terminal events had occurred in the mITT population. Of the 232 recurrent events that qualified as primary endpoints, 128 were in the placebo group and 104 were in the MYDICAR group; most were HF hospitalizations.

Treatment with MYDICAR failed to improve the rate of recurrent events (HR, 0.93; 95% confidence interval [CI] 0.53 to 1.65; p = 0.81). Of the 65 terminal events that qualified as secondary endpoints, 29 were in the placebo group and 36 were in the MYDICAR group; most were deaths. MYDICAR administration failed to improve time to first terminal event (HR, 1.27; 95% CI, 0.72 to 2.24; p = 0.40). MYDICAR treatment also did not improve time to all-cause death.

No differences between treatment groups were detected in subgroup analyses of the primary endpoint. In a pre-specified

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subgroup analysis of the secondary endpoint, there was a significant interaction between treatment and geography, with a higher HR in non-US subjects compared with US subjects. However, the number of events in the analysis of non-US subjects was small (22 events in 85 subjects), and baseline disease characteristics suggested that non-US MYDICAR subjects may have had more severe illness than non-US placebo subjects. There was no such interaction for the primary endpoint. No other significant interactions were detected for pre-specified subgroup analyses, although a significant interaction was observed for the non-pre-specified subgroup of subjects with diabetes.

There were no significant differences between treatment groups for any of the exploratory efficacy analyses (change from baseline in NYHA class, exercise ability as assessed by the 6MWT, quality of life as assessed by the KCCQ or levels of NT-proBNP) over 12 months of follow-up. No significant treatment group differences were observed in the ITT analyses or in analyses conducted in other pre-specified populations.

Overall, no major safety issues were identified in this study following the IC administration of MYDICAR at a dose of 1×10^{13} DRP. As far as clinical outcomes, which also served as an assessment of safety, there were no differences in the MYDICAR group compared to placebo. Discerning potential safety signals from the background of the underlying disease can be challenging and future studies should therefore seek to confirm that the increased incidence of abdominal pain, sudden death, cardiac arrest and elevated BUN levels at 3 months are not associated with MYDICAR.

Evaluation for the presence of AAV1/SERCA2a transgene was only possible in 8 MYDICAR-treated subjects, either from tissue collected when receiving a transplant or MCSD implantation due to deteriorating condition, or at autopsy. The transgene was present in myocardial tissue and other major organs collected from 7 of the 8 subjects at time points between 1.5 and 20 months after infusion, however levels were very low (approximate median of 43 copies/µg DNA; range < 10 to 192 copies/µg DNA), suggesting that future studies of MYDICAR in HF should consider a higher dose and/or a more efficient method of delivery.

A high degree of correlation was observed between treatment with MYDICAR and seroconversion (all but 2 MYDICAR-treated subjects became AAV1 NAb positive by Month 6), supporting accuracy of the clinical dose assignments.

Date of the report: 21 July 2015

ADDENDUM TO REPORT

MYDICAR® (CAPSERCAGENE LEDAPARVOVEC, AAV1/SERCA2A)

A PHASE 2B, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTINATIONAL, MULTICENTER, RANDOMIZED STUDY EVALUATING THE SAFETY AND EFFICACY OF INTRACORONARY ADMINISTRATION OF MYDICAR® (AAV1/SERCA2a) IN SUBJECTS WITH HEART FAILURE

CUPID-2

Protocol No. CELL-004

Indication studied:	Heart Failure with reduced ejection fraction (HFrEF) in AAV1 neutralizing antibody titer negative patients
Developmental phase of study:	2b
First subject enrolled:	22 August 2012
Last subject completed:	27 February 2015; Long-Term Follow-up February 2016
Release date of addendum to the report:	12 April 2016

1.1 Long-Term Follow-up

According to Global Amendment, Version 9, Amendment 8, 11 June 2015/UK Amendment, Version 9, Amendment 8, 16 June 2015 safety parameters had to be collected until the end of the Long-Term Follow-Up Period comprising a quarterly phone call designed to elicit information about hospitalizations, new medical conditions, HF status and long-term survival including subject status (death, lost to follow-up, withdrew consent, etc.); any new malignancy, new incident or exacerbation of a pre-existing condition (neurologic disorder, rheumatologic or autoimmune disorder, hematologic disorder, or new unexpected illness not otherwise captured.

The duration of Long-Term Follow-Up might have been variable for each subject; a subject should have been remained in Long-Term Follow-Up until Month 24 or until the Primary Analysis Data Cutoff had been declared, whichever had occurred later. For some subjects enrolled early in the study, Long-Term Follow-Up was continued past Month 24. This applied to any subject who completed or was discontinued from the 12-Month Active Observation Period; a subject who was terminated early from the Active Observation Period continued to be followed in the Long-Term Follow-Up until Month 24 or until the Primary Analysis Data Cutoff was declare d, whichever occurs later. AEs and SAEs were not collected in the Long-Term Follow-Up as it had been done up to Primary Analysis Data Cutoff.

Subject disposition in the mITT population during the reporting period is provided in **Table 1**.

Table 1**. Summary Subject Disposition, mITT Population**

Parameter	Placebo (N = 122)	MYDICAR (N = 121)	All Subjects (N = 243)
Completed 12-Month Active Observation Period [n (%)]			
No	21 (17.2)	23 (19.0)	44 (18.1)
Yes	101 (82.8)	98 (81.0)	199 (81.9)
Reason Did Not Complete 12-Month Active Observation Period [n (%)]			
N	21	23	44
Death	12 (57.1)	15 (65.2)	27 (61.4)
Heart transplant	2 (9.5)	3 (13.0)	5 (11.4)
Mechanical circulatory support device	5 (23.8)	2 (8.7)	7 (15.9)
Withdrew consent	0 (0.0)	1 (4.3)	1 (2.3)
Agreed to phone follow-up only	1 (4.8)	2 (8.7)	3 (6.8)
Other	1 (4.8)	0 (0.0)	1 (2.3)
Status at Primary Analysis Data Cutoff [n (%)]			
Completed Long-Term Follow-Up	0 (0.0)	1 (0.8)	1 (0.4)
In Long-Term Follow-Up	102 (83.6)	91 (75.2)	193 (79.4)
Terminated from the study	20 (16.4)	25 (20.7)	45 (18.5)
Withdrew consent	0 (0.0)	3 (2.5)	3 (1.2)
Unknown	0 (0.0)	1 (0.8)	1 (0.4)

Parameter	Placebo (N = 122)	MYDICAR (N = 121)	All Subjects (N = 243)
Duration of Follow-Up at Primary Analysis Data Cutoff (months)			
N	122	121	243
Mean (SD)	17.91 (5.363)	17.44 (5.744)	17.68 (5.549)
Median	17.91	17.54	17.81
IQR	13.80 , 22.01	13.80 , 21.59	13.80 , 21.72
Min, Max	3.5 , 29.2	1.8 , 29.4	1.8 , 29.4
Completed Long-Term Follow-Up [n (%)]			
N	110	105	215
No	24 (19.7)	23 (19.0)	47 (19.3)
Yes	86 (70.5)	82 (67.8)	168 (69.1)
Reason Did Not Complete Long-Term Follow-Up [n (%)]			
N Did not complete Long-Term Follow-Up [n (%)]	24	23	47
Death	16 (13.1)	16 (13.2)	32 (13.2)
Withdrew consent	4 (3.3)	5 (4.1)	9 (3.7)
Lost to follow-up	2 (1.6)	2 (1.7)	4 (1.6)
Other	2 (1.6)	0	2 (0.8)
Status at End of Study [n (%)]			
Completed Long-Term Follow-Up	86 (70.5)	82 (67.8)	168 (69.1)
Terminated from the study	27 (22.1)	28 (23.1)	55 (22.6)
Withdrew consent	4 (3.3)	6 (5.0)	10 (4.1)
Lost to follow-up	2 (1.6)	2 (1.7)	4 (1.6)
Duration of Follow-Up at End of Study (months)			
N	122	121	243
Mean (SD)	18.21 (5.365)	17.83 (5.753)	18.02 (5.554)
Median	18.38	18.68	18.55
IQR	13.95 , 22.11	14.80 , 21.94	14.64 , 22.11
Min, Max	3.5 , 29.3	1.8 , 29.5	1.8 , 29.5

Note: Percentages (%) are based on the numbers of Modified Intent-to-Treat subjects in the treatment dose group.

Note: Abbreviations: IQR = interquartile range (25th, 75th percentiles), SD = standard deviation.

Note: The end date for subject 231013 is considered as 10Feb2015

Table 2 provides information regarding the heart failure status at long-term follow-up until LPLV. There are no relevant differences regarding the heart failure status between the MYDICAR group and the placebo group. The rate of worsened heart failure status is slightly lower in the MYDICA group compared to the placebo group. Therefore no safety issues regarding heart failure status could be identified during the long-term follow-up period.

Table 2. Heart Failure Status at Final Long-Term Follow-Up Visit Modified Intent-to-Treat Population (until LPLV)

Parameter	Placebo (N = 122)	MYDICAR (N = 121)	All Subjects (N = 243)
Entered Long-Term Follow-Up [n (%)]			
No	12 (9.8)	16 (13.2)	28 (11.5)
Yes	110 (90.2)	105 (86.8)	215 (88.5)
Had At Least 1 Long-Term Follow-Up Visit [n (%)]			
N	110	105	215
No	2 (1.6)	3 (2.5)	5 (2.1)
Yes	108 (88.5)	102 (84.3)	210 (86.4)
Heart Failure Status at Final Long-Term Follow-Up Visit [n (%)]			
N	108	102	210
Worsened	15 (12.3)	10 (8.3)	25 (10.3)
No Change	78 (63.9)	75 (62.0)	153 (63.0)
Improved	15 (12.3)	17 (14.0)	32 (13.2)

Note: Percentages (%) are based on the numbers of Modified Intent-to-Treat subjects in the treatment dose group

Table 3 provides the results of the long-term follow-up questionnaire that was administered during CUPID-2 long-term follow-up until LPLV. The rates of hospitalizations reported for the long-term follow-up were comparable for the MYDICAR group and the placebo group.

Table 3. Regulatory Guidance on Gene Therapy Trial Questions During Long-Term Follow-Up Modified Intent-to-Treat Population (until LPLV)

Parameter	Placebo (N = 122)	MYDICAR (N = 121)	All Subjects (N = 243)
Entered Long-Term Follow-Up [n (%)]			
No	12 (9.8)	16 (13.2)	28 (11.5)
Yes	110 (90.2)	105 (86.8)	215 (88.5)
Had At Least 1 Long-Term Follow-Up Visit [n (%)]			
N	110	105	215
No	2 (1.6)	3 (2.5)	5 (2.1)
Yes	108 (88.5)	102 (84.3)	210 (86.4)
Hospitalization [n (%)]			
N	108	102	210
No	55 (45.1)	60 (49.6)	115 (47.3)
Yes	53 (43.4)	42 (34.7)	95 (39.1)
Malignancy [n (%)]			
N	108	102	210
No	107 (87.7)	98 (81.0)	205 (84.4)
Yes	1 (0.8)	4 (3.3)	5 (2.1)
New/Exacerbation of Hematologic Disorder [n (%)]			
N	108	102	210
No	108 (88.5)	100 (82.6)	208 (85.6)

Parameter	Placebo (N = 122)	MYDICAR (N = 121)	All Subjects (N = 243)
Yes	0	2 (1.7)	3 (1.2)
New/Exacerbation of Neurologic Disorder [n (%)]			
N	108	102	210
No	104 (85.2)	101 (83.5)	205 (84.4)
Yes	4 (3.3)	1 (0.8)	5 (2.1)
New/Exacerbation of Autoimmune Disorder [n (%)]			
N	108	102	210
No	106 (86.9)	102 (84.3)	208 (85.6)
Yes	2 (1.6)	0	2 (0.8)
Any Other Unexpected Illness [n (%)]			
N	108	102	210
No	99 (81.1)	93 (76.9)	192 (79.0)
Yes	9 (7.4)	9 (7.4)	18 (7.4)

Note: Percentages (%) are based on the numbers of Modified Intent-to-treat subjects in the treatment dose group.

During long-term follow-up period malignancies were reported in 4 patients treated with MYDICAR (malignant melanoma, squamous cell carcinoma of head and neck, prostate adenocarcinoma and metastatic squamous cell carcinoma of the lung including hospitalization for resection of metastatic brain lesions causing hydrocephalus) and in 1 patient treated with placebo (colon carcinoma).

In the CUPID-2 trial up to the PADC (primary analysis data cut off) neoplasms were identified in six subjects: three in subjects treated with MYDICAR and three in subjects treated with placebo (see section 12.2.3 of CSR). All cases were newly diagnosed. In the MYDICAR arm, all three malignancies were disorders of the skin: one case of basal cell carcinoma in the upper right chest at Day 84 which was surgically excised, one case of malignant melanoma in the posterior thorax at Month 16 which was surgically excised, and one case of squamous cell carcinoma of the head and neck at Month 15. These subjects were all white males age 64, 71 and 54 years upon study entry. No disease pattern was observed in the placebo group: one case of benign tracheal neoplasm at Day 96 for which no treatment was recommended and was ongoing at the end of active observation (subject was an active smoker with COPD), one case of a possible stump neuroma of the left foot at Day 165 which was treated by injection and resolved within 22 days (subject had experienced an injury to the left foot at Day 21), and one case of skin papilloma at Day 26 which was removed. After PADC during the long term follow-up period two additional neoplasms were reported in two subjects treated with MYDICAR and one neoplasm in one subject treated with placebo. In the MYDICAR arm a prostate adenocarcinoma was reported at the month 21 in a 72-year old male patient with a history of benign prostate hyperplasia previously treated with transurethral resection and a metastatic squamous cell carcinoma of the lung requiring hospitalization for resection of metastatic brain lesion causing hydrocephalus was reported at Month 24 in a 59-year old male patient, a former smoker (38 pack-years) with no history of previous malignancy. In the placebo arm a colon carcinoma was reported at Month 15 in a 69-year-old male patient with no history of previous malignancy.

New/Exacerbation of Hematologic Disorder were reported in 2 patients treated with MYDICAR (chronic anemia and macrocytic anemia) and in none of the placebo treated patients.

New/Exacerbation of Neurologic Disorder were reported in 1 of the MYDICAR treated patients (cerebrovascular accident) and in 4 placebo treated patients (hemorrhagic stroke, status epilepticus, tremors, minor stroke).

New/Exacerbation of Autoimmune Disorder were reported in none of the MYDICAR treated patients and in 2 placebo treated patients (vitiligo and gout attack).

For other unexpected illnesses 9 patients treated with MYDICAR reported pulmonary nocardia infection, flu-like symptoms, back spasms, staphylococcus aureus infection of the ICD, basal cell carcinoma of the skin (rather to be classified as malignancy), mural thrombus, metabolic disorders (gout and diabetes), corneal micro deposits due to amiodarone and abdominal aortic aneurysm. Seven (7) placebo treated patients reported gastrointestinal complaints, renal and splenic infarcts secondary to sub-therapeutic INR from coumadin non-compliance in a patient with LV thrombus in medical history, splenic infarction, erysipelas, cytomegalovirus infection, diarrhea and cholecystectomy.

None of the events reported for hematological, neurological, autoimmune disorders and for unexpected illnesses or for other reasons of hospitalization raised safety concerns regarding the MYDICAR treatment. No final conclusion regarding occurrence of malignancies can be drawn from results obtained from long-term follow-up of this study. Occurrences of malignancies need to be carefully analysed in future studies.