20 May 2021
EMA/433036/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/II/0043

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

abbreviation	description of abbreviated term
ADCC	antibody-dependent cellular cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ADR	adverse drug reaction
AE	adverse event
AL amyloidosis	light chain amyloidosis
ALP	alkaline phosphatase
ALT	alanine transaminase
ASCT	autologous stem cell transplant
AST	aspartate transaminase
CHR	hematologic complete response (also referred to as HemCR)
CI	confidence interval
CR	complete response
CV	coefficient of variation
CyBorD	cyclophosphamide+bortezomib+dexamethasone (also referred to as VCd)
Dd	daratumumab + dexamethasone
dFLC	difference in involved and uninvolved free light chains
DIRA	daratumumab-specific IFE reflex assay
D-VCd	daratumumab+bortezomib+cyclophosphamide+dexamethasone
DVd	daratumumab + bortezomib + dexamethasone
EAIR	exposure-adjusted infusion reaction
ECOG	Eastern Cooperative Oncology Group
EFS	event-free survival
EU	European Union
FISH	fluorescent in-situ hybridization
FLC	free light chain
GCP	good clinical practice
HDM	high-dose melphalan
HemCR	hematologic complete response
HR	hazard ratio
HRQoL	health-related quality of life
IA	interim analysis
ICH	International Council for Harmonisation
IFE	immunofixation electrophoresis
iFLC	involved free light chains
IgG	immunoglobulin G
IMiD	immunomodulatory agents
IPCW	inverse probability of censoring weight
IRC	Independent Review Committee
IRR	infusion-related reaction (also referred to as systemic administration-related reactions)
ISR	injection site reaction
ITT	intent-to-treat
IV	intravenous
mAb	monoclonal antibody
MDSC	myeloid derived suppressor cells

MedDRA	Medical Dictionary for Regulatory Activities
MOD-EFS	major organ deterioration – event-free survival
MOD-PFS	major organ deterioration – progression-free survival
NAC	Naming and Approvals Committee
NCCN	National Comprehensive Cancer Network
NT-proBNP	N-terminal-pro hormone B-type natriuretic peptide
OrRR	organ response rate
OS	overall survival
PC	plasma cell
Pd	pomalidomide+dexamethasone
PD	progressive disease
PI	proteasome inhibitor
PK	pharmacokinetic
PR	partial response
Rd	lenalidomide+dexamethasone
rHuPH20	recombinant human hyaluronidase PH20
SC	subcutaneous
SD	standard deviation
sFLC	serum free light chain
SmPC	Summary of Medicinal Product Characteristics
SOC	system organ class
SPM	second primary malignancy
TEAE	treatment-emergent adverse event
uFLC	uninvolved free light chain
ULN	upper limit of normal
UK	United Kingdom
US	United States
VCd	cyclophosphamide+bortezomib+dexamethasone (also referred to as CyBorD)
Vd	bortezomib+dexamethasone
VGPR	very good partial response
VMP	bortezomib+melphalan+prednisone

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 5 November 2020 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with systemic light chain (AL) amyloidosis for Darzalex 1,800 mg solution for injection; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly. Version 8.4 of the RMP has also been submitted.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

Darzalex, was designated as an orphan medicinal product EU3/18/2020 on 25 May 2018. Darzalex was designated as an orphan medicinal product in the following indication: treatment of AL amyloidosis.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0116/2020 - EMEA-002152-PIP03-19 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

Scientific advice was obtained from the CHMP/SAWP in June 2016 regarding the proposed clinical development program for daratumumab in the treatment of AL Amyloidosis (EMEA/H/SA/2456/6/2016/II). The SAWP provided input on the proposed design of study AMY3001 including the primary endpoint, patient population, comparator and statistical considerations.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Blanca Garcia-Ochoa

Timetable	Actual dates
Submission date	5 November 2020
Start of procedure:	28 November 2020
CHMP Co-Rapporteur Assessment Report	8 February 2021

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CHMP Rapporteur Assessment Report	25 January 2021
PRAC Rapporteur Assessment Report	29 January 2021
PRAC Outcome	11 February 2021
CHMP members comments	15 February 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 February 2021
Request for supplementary information (RSI)	25 February 2021
CHMP Rapporteur Assessment Report	20 April 2021
PRAC Rapporteur Assessment Report	20 April 2021
PRAC members comments	28 April 2021
Updated PRAC Rapporteur Assessment Report	29 April 2021
PRAC Outcome	6 May 2021
CHMP members comments	07 May 2021
Updated CHMP Rapporteur Assessment Report	12 May 2021
Opinion	20 May 2021

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Systemic AL amyloidosis is a rare and incurable malignant plasma cell disorder characterised by clonal expansion of CD38+ plasma cells and an overproduction of immunoglobulin light chains that misfold into insoluble amyloid.

State the claimed therapeutic indication

The proposed addition to the existing indication statement in section 4.1 of the Summary of Product Characteristics (SmPC) is as follows:

"DARZALEZX is indicated for the treatment of adult patients with systemic light chain (AL) amyloidosis."

Epidemiology and risk factors, screening tools/prevention

The epidemiology of AL amyloidosis has not been well characterised. AL amyloidosis is rare, the incidence is approximately 3 - 12 cases per million persons per year, and an estimated prevalence of 30 000 to 45 000 AL amyloidosis patients in the United States and the European Union (Quock et al. 2018). There is a slight male predominance with nearly 60% of patients being male. The median age at diagnosis is 64 years, the majority of patients being over the age of 65 years and fewer than 5% of patients with AL are younger than 40 years (Nienhuis et al 2016, Quock et al. 2018).

AL amyloidosis typically develops from the background of a plasma cell neoplasm but can be associated with other lymphoproliferative disorders in which there is excess secretion of κ-or λ-free light chains, including WM or chronic lymphocytic leukaemia. Symptomatic multiple myeloma (MM), as defined by CRAB criteria, is diagnosed simultaneously in approximately 10% of patients with AL amyloidosis. In addition, up to 40% of patients with AL have 10% or more bone-marrow plasma cells at diagnosis but do not meet CRAB criteria. Later progression to overt myeloma in patients with isolated AL amyloidosis is rare.

Amyloidosis has a poor prognosis, the median survival without treatment is 13 months from diagnosis (Sanchorawala 2007, Chaulagain 2013). Cardiac involvement has the worst prognosis and results in death in about 6 months after onset of congestive heart failure. Only 5% of the patients with primary amyloidosis survive beyond 10 years.

Biologic features, aetiology and pathogenesis

The major systemic types of amyloidosis are AL (associated with a light chain-producing plasma cell dyscrasia), which is the most common, AA (associated with longstanding inflammation), wild-type ATTR (associated with normal transthyretin and old age), and hereditary ATTR (associated with a transthyretin mutation) amyloidosis.

Light chain amyloidosis (AL amyloidosis) is caused by extracellular deposition of insoluble fibrils in tissues and organs. These fibrils are derived from CD38+ clonal plasma cells that secrete light chains that misfold

into insoluble amyloid. Deposition of amyloid in vital organs results in serious and life-threatening organ dysfunction. The spectrum of morbidity and risk of mortality are determined by the pattern and extent of organ involvement (Gertz 2005; Gertz 2010).

Amyloid fibrils are identified by their characteristic appearance on electron microscopy and their affinity for Congo red.

The plasma cell (PC) proliferation in AL amyloidosis is typically low-burden, with <10% PCs in over half of the patients.

Serum and/or urine protein electrophoresis with immunofixation can identify a monoclonal protein in nearly 90% of AL patients. Addition of the serum-free light-chain assay to the diagnostic work-up increases the yield to over 98% of the patients. Most patients with AL amyloidosis have little or no intact monoclonal immunoglobulin but are characterized by the presence of monoclonal-free light chain. The monoclonal light-chain type is λ in approximately 70% of cases, κ in 25%, and biclonal in 5%.

Clinical presentation, diagnosis and stage/prognosis

The clinical presentation is dictated by the spectrum and severity of the organ involvement.

Amyloidosis has a poor prognosis, depending on the number and extent of organ involvement. The median survival without treatment is 13 months (Sanchorawala 2007, Chaulagain 2013). Approximately one-third of patients die largely due to cardiac involvement within the first year of diagnosis. Cardiac involvement has the worst prognosis and results in death in about 6 months after onset of congestive heart failure. Only 5% of the patients with primary amyloidosis survive beyond 10 years. Among patients with renal involvement, about one-third progress to dialysis. The involvement of other organs, e.g., liver, gastrointestinal tract and peripheral and autonomic nerves, contributes to significant chronic morbidity and mortality, such that the OS rate at 2 years is only 60% (Muchtar 2017; Wechalekar 2015). Achieving less than a CR or VGPR in AL amyloidosis is suboptimal, as a sufficient reduction of light chains is required to reduce both the acute proteotoxicity of the amyloid as well as the continuous organ damage due to amyloid deposits.

Though multiple prognostic models have been proposed for patients with amyloidosis, models that incorporate markers of cardiac damage have high predictive value for early death in AL amyloidosis. The revised Mayo Clinic Amyloid Staging system classifies patients as having stage I, II, III, or IV disease based upon the identification of zero, 1, 2, or 3 of the following risk factors: NT-pro- BNP ≥1,800 ng/L, cardiac troponin T ≥0.025 µg/L, and a difference between involved and uninvolved serum-free light chains ≥18 mg/ dL. Median overall survivals from diagnosis for stages I-IV were 94, 40, 14, and 6 months, respectively.

Management

No regimen has been approved for amyloidosis (Wechalekar 2015) and no optimal treatment has been identified (Anderson 2014, NCCN).

As both AL amyloidosis and multiple myeloma are clonal plasma cell disorders, the treatment approach is to use MM regimens to achieve rapid, deep, and durable hematologic responses (Wechalekar 2015; Mayo SMART Amyloidosis guidelines, Anderson 2014). Eradicating the clonal plasma cell in AL amyloidosis eliminates the production of the light chain that is both amyloidogenic and proteotoxic leading to organ failure. Despite this, there are key differences in the efficacy and safety between these 2 populations. The achievement of a rapid and deep hematologic response is the essential goal of therapy in AL amyloidosis and an indicator for clinical outcome. The depth of hematologic response is associated with organ improvement and survival (Palladini 2012, Kastritis 2020). Thus, the goal of therapy for patients with AL

amyloidosis is to achieve "complete hematologic response (CHR) or at a minimum very good partial response (VGPR) in order to prevent further end-organ damage, reverse existing organ dysfunction, and prolong OS (Chaulagain 2013, Merlini 2018). In AL amyloidosis, achieving a partial hematologic response or stable disease may not offer a clinical benefit, because ongoing light chain production may result in further organ damage. Therefore, partial response (PR) should always be viewed in conjunction with organ response in the evaluation of treatment outcomes (Comenzo 2012).

The entire armamentarium of multiple myeloma regimens has been used in AL amyloidosis. The use of cyclophosphamide+bortezomib+dexamethasone (CyBorD also referred to as VCd) is recommended by the NCCN, British Society of Haematology, and consensus guidelines (Comenzo 2012, Anderson 2014; Mahmood 2014, Wechalekar 2008). It is the preferred regimen for patients with newly diagnosed and relapsed AL amyloidosis due to the limited feasibility and high mortality rate of HDM/ASCT, and the cardiac and renal toxicities associated with IMiDs (D'Souza 2015).

The overall response rate (OrRR, PR or better) for CyBorD in the largest retrospective cohort of newly diagnosed patients with AL amyloidosis was 62% (125/201) patients with measurable disease compared with 100% in newly diagnosed patients with multiple myeloma, and with HemCR in 42 subjects (21%) and VGPR in 45 (22%). Cardiac response was achieved in 17% of patients, while renal response was observed in 25% of patients (Kumar 2012; Palladini 2015). High-dose melphalan and ASCT demonstrate a high efficacy profile; however, only a minority of patients are candidates (~20%) and it is associated with much higher treatment-related mortality than in multiple myeloma (5% to 24%, compared with 1%) (Jaccard 2007; D'Souza 2015). In long-term data on 701 patients evaluated at the Boston Amyloidosis Center of whom 394 (56%) were deemed eligible for transplant and 312 patients were treated with HDM/ASCT (Skinner 2004), the CHR rate was 40% and the transplant-related mortality was 13%. The organ response rate at 1-year post-transplant among those who achieved a CHR was 27% for cardiac and 63% for renal (NCCN 2019).

Thalidomide and lenalidomide-based regimens are associated with severe toxicities including bradycardia, syncope, and renal failure (Merlini 2018). Carfilzomib is known to be associated with severe cardiac toxicity in multiple myeloma and is prohibitively toxic in AL amyloidosis (Waxman 2018; Cohen 2016). Lenalidomide-containing regimens have been used in AL amyloidosis with similar results as thalidomide-containing regimens. The overall hematologic response rate for lenalidomide-based regimens has been 46% with a CHR of 25% (Cibeira 2015). Although lenalidomide is associated with lower rates of peripheral neuropathy than thalidomide, it is also a challenging drug in AL amyloidosis.

Although CyBorD is currently considered the standard of care, certain subgroups like cardiac Stage III, high dFLC (>180 mg/L), and t(11;14) continue to have dismal outcomes (Dispenzieri 2018; Palladini 2018).

In conclusion, the MM regimens demonstrate similar or lower hematologic responses in AL amyloidosis but are associated with higher rates of toxicity. Thus, a substantial unmet medical need exists for therapies in AL amyloidosis, that can provide clinical efficacy translating into survival benefits at a lower toxicity.

2.1.2. About the product

Daratumumab is a human CD38-targeted, IgG1 kappa monoclonal antibody (mAb) that binds with high affinity to a unique epitope on cluster of differentiation (CD) 38, a transmembrane glycoprotein expressed on the cell surface of a variety of hematologic malignancies. It is a targeted immunotherapy directed toward tumor cells that express high levels of CD38, such as the clonal plasma cells in multiple myeloma.

Multiple mechanisms of action have been observed for daratumumab, including complement dependent cytotoxicity, ADCC, ADCP, and induction of apoptosis by Fc gamma receptor-mediated crosslinking of tumor-bound mAbs. Complement dependent cytotoxicity occurs rapidly and maximal cell killing by

daratumumab is demonstrated within 1 hour of antibody mediated activation of the complement proteins *ex vivo*. Daratumumab induced ADCC is slower in its action *in vitro* (de Weers 2011), and daratumumab has also been shown to induce ADCP in the presence of macrophages (Overdijk 2012; Overdijk 2015).

Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ Tregs, CD38+ MDSCs, and CD38+ regulatory B cells (Chiu 2016). The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity, and destruction of the malignant myeloma cells is thought to lead to the clonal expansion of CD8+ and CD4+ T cells (Chiu 2016; Van De Donk 2017). Altogether, daratumumab's converging mechanisms of action are hypothesized to synergistically lead to the responses observed in patients with clonal plasma cell disorders, regardless of setting.

Recently, the daratumumab SC formulation was approved in the US and EU. The SC formulation reduces the incidence of IRRs and the risk for volume overload that may be anticipated in patients with AL amyloidosis with cardiac and renal involvement.

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

The current submission of daratumumab for the treatment of subjects with AL amyloidosis is based on data from the Phase 3 study, AMY3001, comparing daratumumab SC 1800 mg administered in combination with VCd to VCd alone.

Daratumumab IV received an initial marketing authorization for the treatment of adult patients with relapsed and refractory multiple myeloma (US: November 2015; EU: May 2016). Since the initial marketing authorisation, several indications have been approved for multiple myeloma in both the relapsed/refractory and newly diagnosed settings. More recently, the SC formulation of DARZALEX has been approved, and is currently pending approval in other countries.

During the design and conduct of Study AMY3001, the MAH sought advice from Regulatory Authorities (Table 1).

Table 1: Summary of Scientific Advice from Key Health Authorities

Date	Correspondence
FDA Consultations	
08 April 2016	Type B EOP 2 Meeting to discuss the proposed clinical development program for daratumumab in the treatment of AL amyloidosis. The Agency provided input on the proposed design of the Phase 3 study (AMY3001) including the primary endpoint, patient population, comparator, daratumumab dose regimen.
14 January 2020	Type B Pre-sBLA Meeting to discuss the proposed content, format, and planned efficacy and safety analyses for the sBLA for daratumumab SC administration focus on Study AMY3001.
CHMP Consultation	
23 June 2016	Scientific Advice was obtained from the CHMP SAWP to discuss the proposed clinical development program for daratumumab in the treatment of AL Amyloidosis. The SAWP provided input on the proposed design of Study AMY3001 including the primary endpoint, patient population, comparator and statistical considerations.

Key: AL amyloidosis=light chain amyloidosis; CHMP=Committee for Medicinal Products for Human Use; EOP=end-of-phase; FDA=Food and Drug Administration; sBLA=supplementary biologics license application; SAWP=Scientific Advisory Working Party; SC=subcutaneous

2.1.4. General comments on compliance with GLP, GCP

The MAH states, that the studies included in this submission were conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH GCP guidelines, applicable regulatory requirements, and in compliance with the protocol.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity/environmental risk assessment

Daratumumab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for daratumumab is required.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Overview of Study 54767414AMY3001 Supporting Efficacy of Dara SC+CyBorD in AL Amyloidosis

Study ID / EudraCT Number FPFV/Completion Study Status	Phase / Study Design / Study Population / Primary and/or Major Endpoints	Dose Regimen and Duration of Treatment	Number of Subjects Included in SCE Analyses (by Treatment Group)
54767414AMY3001 2016-001737-27 10 Oct 2017/ 14 Feb 2020 (cutoff) Ongoing	Phase 3 Randomized, open-label, active-controlled, multicenter study Subjects with newly diagnosed immunoglobulin light chain (AL) amyloidosis To evaluate the efficacy of Dara SC+CyBorD compared with CyBorD alone in the treatment of subjects with newly diagnosed AL amyloidosis Primary efficacy endpoint: overall HemCR rate Major secondary efficacy endpoints: • MOD-PFS • OS Other efficacy endpoints: • HemCR at 6 months • Hematologic VGPR or better rate • Time to hematologic response • Duration of hematologic response • Hematologic PFS • MOD-EFS • TtNT • Time to iFLC <ULN, time to iFLC ≤20 mg/L and Time to dFLC <10 mg/L Response • Organ response o Cardiac/renal/liver response rate at 6 months o Time to cardiac/renal/liver response • Organ progression o Cardiac/renal/liver progression at 6 months o Time to cardiac/renal/liver progression • Patient-reported outcomes (EORTC QLQ-C30, EQ-5D-5L, and SF-36v2)	Treatment Arm A: CyBorD alone Treatment Arm B: Daratumumab SC 1800 mg co-formulated with rHuPH20 2000 U/mL + CyBorD once every week for 8 weeks (Cycles 1-2), then, every other week for 16 weeks (Cycles 3-6), then every 4 weeks until progression of disease or subsequent therapy for a maximum of 24 cycles In both treatment groups, all cycles were 28 days, and CyBorD was administered as follows: Cyclophosphamide: 300 mg/m^2 (oral or IV) (maximum 500 mg) weekly on Days 1, 8, 15, and 22 for a maximum of 6 28 day cycles Bortezomib: 1.3 mg/m^2 (SC) weekly on Days 1, 8, 15, and 22 for a maximum of 6 28 day cycles Dexamethasone: PO or IV (investigator discretion) 40 mg weekly on Days 1, 8, 15, and 22 for a maximum of 6 28 day cycles • Subjects with protocol-specified comorbidities (ie, >70 years, BMI <18.5, hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy) may be treated with 20 mg dexamethasone	CyBorD: 193 Dara SC+CyBorD: 195

Key: AE=adverse event; AL=immunoglobulin light chain; BMI=body mass index; CyBorD=cyclophosphamide, bortezomib, and dexamethasone; Dara SC=daratumumab administered subcutaneously; dFLC=difference between involved and uninvolved free light chains; EQ-5D-5L= European Quality of Life Five Dimensions Questionnaire; EORTC QLQ C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; FPFV=first patient/first visit; HemCR=hematologic complete response; iFLC=involved free light chain; IV=intravenous; MOD-PFS=major organ deterioration progression-free survival; OrRR=organ response rate; OS=overall survival; PO=oral; PFS=progression-free survival; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous; SCE=Summary of Clinical Efficacy; SF-36v2=Item Short Form Survey; TtNT=time to next treatment; ULN=upper limit of normal; VGPR=very good partial response

2.3.2. Pharmacokinetics

The PK analyses in Study AMY3001 were based on the serum concentration of daratumumab in samples collected from subjects in the Safety Run-in Phase and in the daratumumab SC+CyBorD arm in the randomized phase of the study. Serum daratumumab concentrations at planned timepoints were summarized using descriptive statistics.

Table 3 Overview of Studies Contributing to the Summary of Clinical Pharmacology

Study Number	Phase	Study Population	Treatment/Dose Regimen (Number of Treated Subjects)	Number of Subjects in the PK Evaluable Analysis Set; PK Sampling Scheme
AMY3001	3	Subjects with AL amyloidosis	Safety Run-in Part: daratumumab SC+CyBorD (fixed dose of 1800 mg of daratumumab and 30,000 U of rHuPH20)+CyBorD (N=28). Randomized Part: Arm A: CyBorD (N=188); Arm B: daratumumab SC+CyBorD: (fixed dose of 1800 mg of daratumumab and 30,000 U of rHuPH20)+CyBorD (N=193). Daratumumab was administered weekly for the first 8 weeks (C1-2), every 2 weeks for the next 4 cycles (C3-6), and then every 4 weeks.	N=211; PK samples were collected in Safety Run-in (N=28) and Treatment Arm B (N=183) at C1D1 predose, on C1D4 (±1 day), at C1D8 predose, C2D1 predose, C3D1 predose, on C3D4 (±1 day), at C7D1 predose, C12D1 predose, EOT (±3 days), and 8 weeks after the last dose of daratumumab SC (±1 week); Predose samples included those collected before (up to 6 hours but not after the start of injection) daratumumab SC administration.

C=cycle; CyBorD=cyclophosphamide, bortezomib, and dexamethasone; D=Day; EOT=end of treatment; PK=pharmacokinetics; rHuPH20=recombinant human hyaluronidase PH20; SC=subcutaneous(ly).
PK-evaluable: includes subjects who received at least 1 administration of daratumumab and have at least 1 pharmacokinetic sample concentration value after the first administration.
Source: Mod5.3.5.1/AMY3001

Bioanalysis

Validated electro chemiluminescent immunoassay (ECLIA)-based methods were used to determine daratumumab concentrations and anti-daratumumab antibodies in human serum samples. In addition to a previous less drug tolerant ADA method, a newer enhanced drug tolerant PandA ECLIA method was used for detection of anti-daratumumab antibodies in human serum. For NAbs a validated target tolerant cell-based binding assay was available. For Study AMY3001, no ADA-positive subjects were detected; therefore, this NAb assay was not applied.

Daratumumab SC is a co-formulation of daratumumab and rHuPH20. A validated ECLIA method was used for assessment of anti-rHuPH20 antibodies in human plasma after SC administration. A validated *in vitro* hyaluronidase activity assay with a chromogenic readout was used to test for neutralising capacity. Interference testing of JNJ-64007957 was performed. JNJ-64007957 is a bi-specific IgG antibody, which is not used in Study AMY3001.

In Study AMY3001, daratumumab is given in combination with cyclophosphamide, bortezomib and dexamethasone. No assay interference is expected since these small molecules do not bind to assay reagents nor to CD38. Interference by light chains were not evaluated. A parallelism study showed that AL amyloidosis matrix could be diluted without influence on daratumumab quantification.

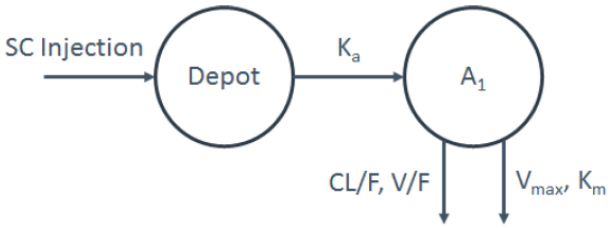
Population PK analysis

Serum daratumumab concentration-time data from Phase 3 Study AMY3001 were used for nonlinear mixed-effects modelling using NONMEM (Version 7.4) and the first-order conditional method with interaction (FOCEI). R (Version 3.6.0 or higher) was used for simulations to derive exposure metrics for subsequent exposure-response analysis. Perl Speaks NONMEM (PsN) (Version 4.8.1) and R package Xpose4 (Version 4.7.0) were used for model diagnostics and facilitation of NONMEM tasks, such as covariate testing.

The population PK analysis was based on 1,224 PK samples (sparse sampling) above the limit of quantitation from 211 subjects with AL amyloidosis (28 subjects from Safety Run-in Phase and 183 from daratumumab SC+CyBorD treatment arm of randomized phase in Study AMY3001) who received 1800 mg daratumumab SC. Eight observations were below the limit of quantification and excluded prior to model development. No visible outlier was identified.

The daratumumab SC modelling was based on a previously developed 2-compartment population PK model for describing the PK characteristics in subjects with multiple myeloma. However, the previous model became highly unstable when fitted to the sparse PK samples from AMY3001. The observed concentration-time data in subjects with AL amyloidosis were best described by a 1-compartment population PK model with first-order absorption and parallel linear and nonlinear Michaelis-Menten elimination pathways. The base model was parameterised in terms of Ka, nonspecific linear CL/F, apparent volume of distribution (V/F), Vmax, and daratumumab concentrations associated with half Vmax, Km, fixed to the value estimated in multiple myeloma patients. The residual error model was additive on log scale.

Figure 1 **Schematic Description of One-Compartment Population Pharmacokinetic Model with First-order Absorption and Parallel Linear and Nonlinear Michaelis-Menten Elimination Pathways for Daratumumab**



Abbreviations: A_1=daratumumab amount in the central compartment; CL/F=apparent clearance; Depot=K_a=first-order absorption rate constant; K_m=Michaelis-Menten constant; SC=subcutaneous; V/F=apparent volume of distribution; V_{max}=maximum velocity of the saturable clearance process, which decreases over time through a first-order rate (K_{DES})
Source: Mod5.3.3.5/PPK/Fig2

Body weight, sex, cardiac stage, proteinuria, renal stage, alkaline phosphatase, renal function (creatinine clearance [CrCL]), and hepatic function were the intrinsic factors explored as covariates in the population PK analysis. Immunogenicity responses against daratumumab and rHuPH20 were not formally evaluated as covariates. A formal covariate analysis was conducted using the likelihood ratio test with significance levels of 0.05 and 0.01 for forward addition and backward elimination, respectively.

In the final covariate model, body weight and renal stage were identified as statistically significant covariates on apparent nonspecific linear CL (CL/F). The following covariates on apparent volume of distribution were identified as statistically significant: body weight, renal stage, and alkaline phosphatase.

Table 4 **Parameter Estimates of the Population PK Model of Daratumumab**

Parameter (unit)	Estimate	RSE (%)	IIV (%)	RSE (%)
CL/F (L/day)	0.210	4.12	41.8	11.3
Renal Stage II on CL/F	0.518	19.0		
Renal Stage III on CL/F	0.627	27.3		
WT on CL/F	0.926	16.0		
V/F (L)	10.8	3.09	28.1	12.6
Renal Stage II or III on V/F	-0.172	21.8		
WT on V/F	0.747	13.8		
Abnormal ALP on V/F	0.297	38.2		
V_{max} (mg/h)	1.07	11.2	146	Fixed
K_{des} (1/day)	0.0121	15.8	67.4	Fixed
K_m (µg/mL)	2.56	Fixed		
K_a (1/day)	0.773	8.31	61.2	20.4
Additive error (CV%)	17.8	5.56		

Abbreviations: ALP=alkaline phosphatase; CL/F=apparent clearance; CV%=coefficient of variation%; IIV=interindividual variability; K_a=first-order absorption rate constant; K_{des}=first-order rate for decrease in V_{max}; K_m=Michaelis-Menten constant; PK=pharmacokinetic; RSE=relative standard error; TVCL=typical value; V/F=apparent volume of distribution; V_{max}=maximum velocity of the saturable clearance process; WT=body weight.

Note: Objective function value=-1845.558. Conditional number=1.2. Conditional number was calculated as the ratio of the largest to smallest eigenvalue of correlation matrix of estimate. Additive error term was on log scale.

For IIV, RSE% is given for CV% and is an approximate value.

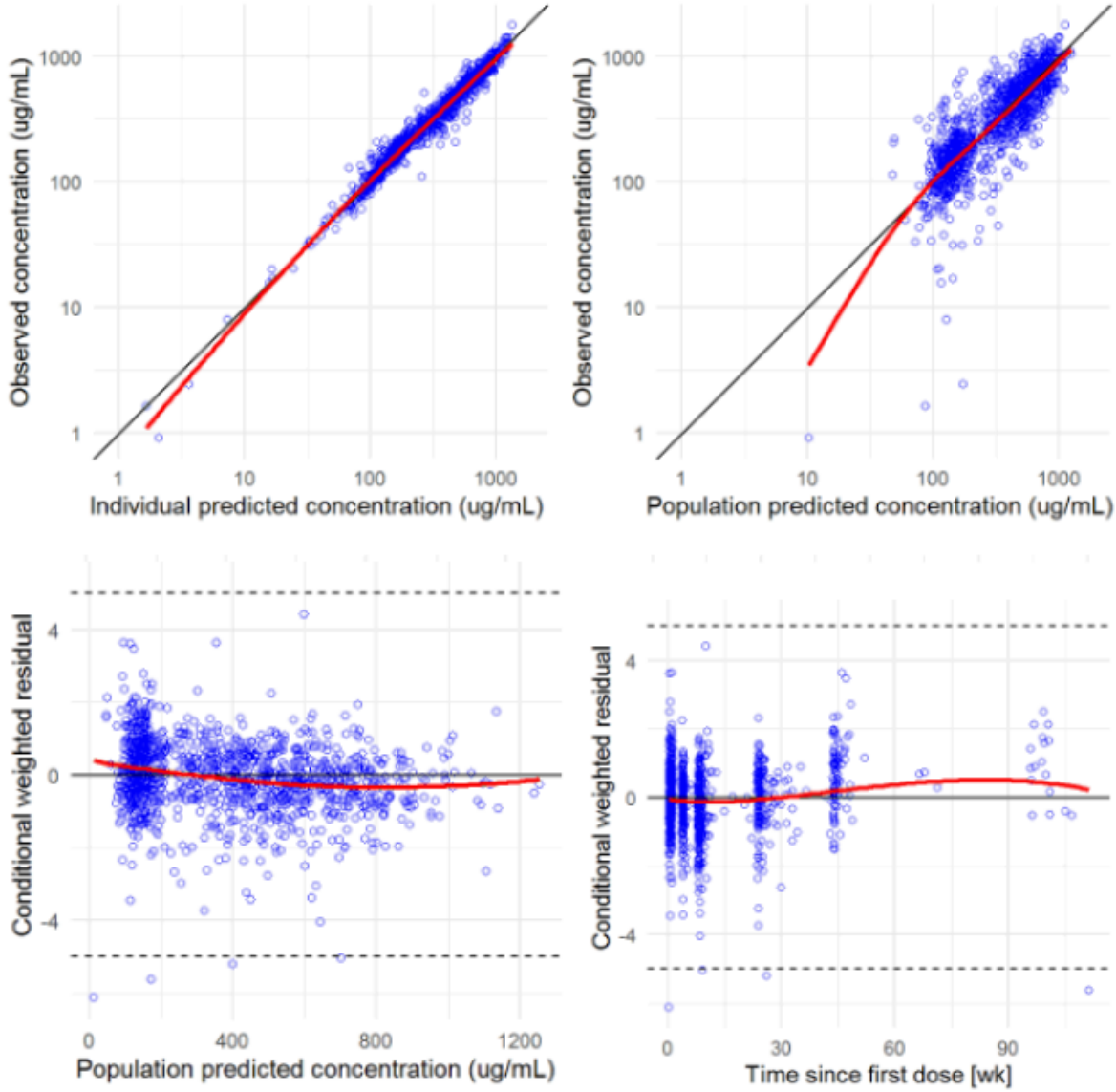
The typical values of PK parameters in Subject j,

$TVCL/Fj = 0.210 \bullet \left(\frac{BWj}{73.2}\right)^{0.926} \bullet$ (Renal Stage), where Renal Stage is a shift factor of 1 for subjects with renal Stage I, 1+0.518 for subjects with renal Stage II, and 1+0.627 for subjects with renal Stage III.

$TVV/Fj = 10.8 \bullet \left(\frac{BWj}{73.2}\right)^{0.747} \bullet ALPV \bullet$ (Renal Stage), where ALPV is a shift factor of 1 for normal ALP and 1+0.297 for abnormal ALP, and Renal Stage is a shift factor of 1 for subjects with renal Stage I and 1-0.172 for subjects with renal Stage II or Stage III.

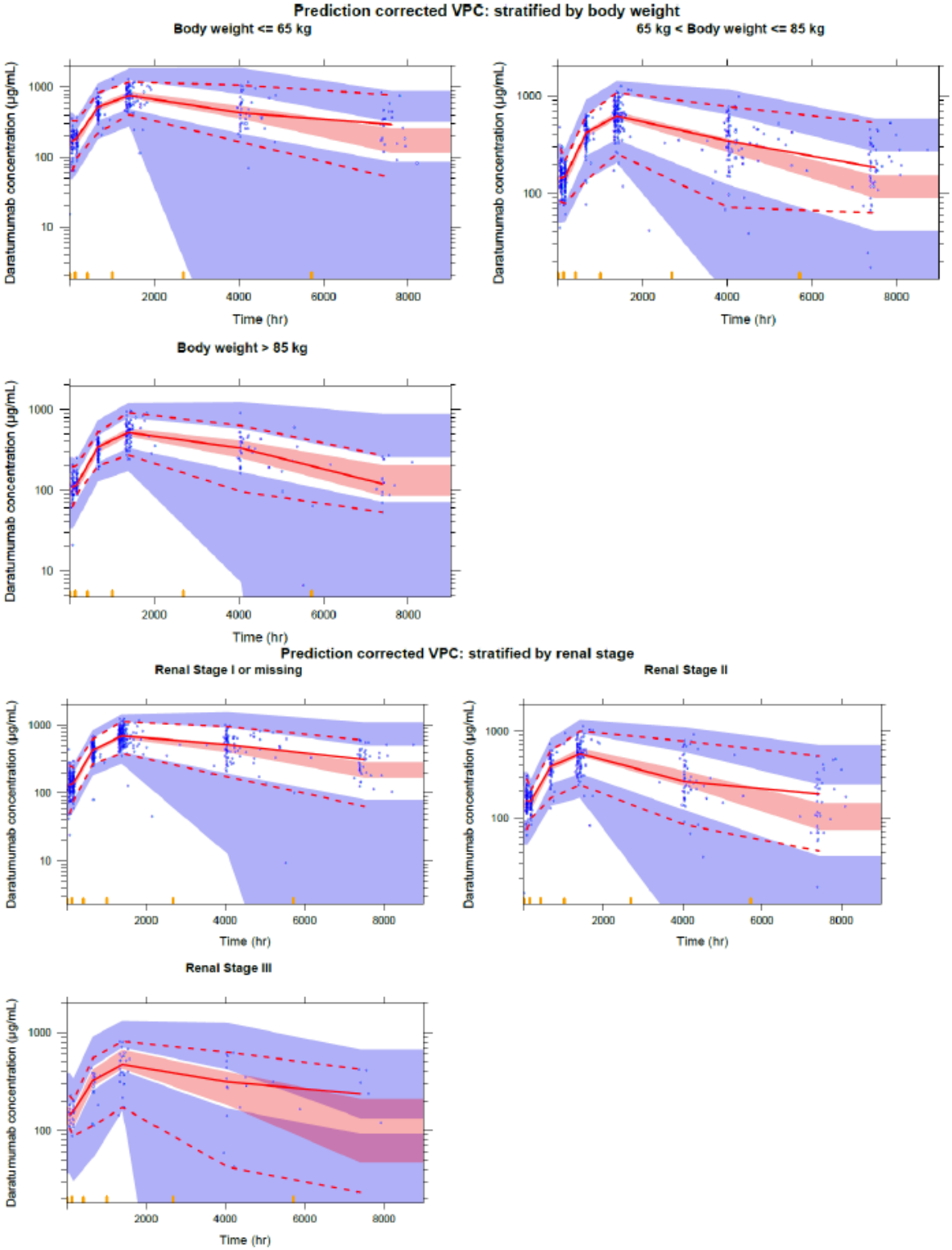
A nonparametric bootstrap analysis (N=1000) was conducted to evaluate the stability of the final model and to estimate confidence intervals (CIs) for the model parameters. Goodness-of-fit plots (GoF) and visual predictive checks (VPCs) with prediction correction were used to evaluate the predictive ability of the final model.

Figure 2 **Goodness-of-fit Plots for the Final population PK Model**



Abbreviations: Population PK=population pharmacokinetics.

Key: Red line represents the lowess smoother. Black line represents the line of identity for observed concentrations versus population prediction and individual prediction plots. For residual plots, black line represents horizontal line crossing the y axis at value of zero.



Abbreviations: Population PK=population pharmacokinetics; SC=subcutaneous; VPC=visual predictive check.
Key: Blue circle represents observation. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.
The x-axis was cut-off at 9000 hours to show the majority of the data.

Predicted Concentrations are summarized in the table below:

Table 5: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1,800 mg) in patients with AL amyloidosis

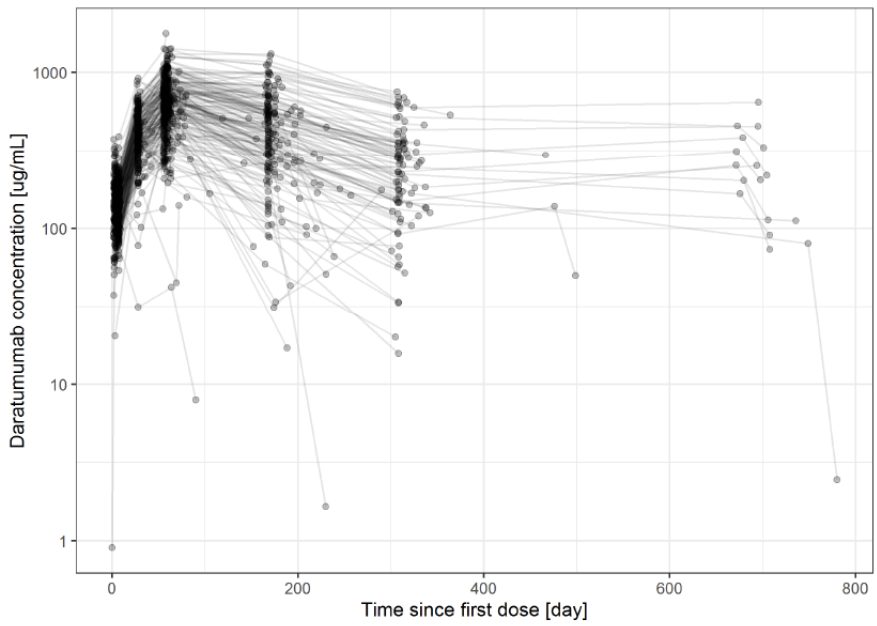
PK parameters	Cycles	subcutaneous daratumumab Median (5^{th}; 95^{th} percentile)
C_{trough} (µg/mL)	Cycle 1, 1^{st} weekly dose	138 (86; 195)
	Cycle 2, last weekly dose (Cycle 3 Day 1 C_{trough})	662 (315; 1037)
C_{max} (µg/mL)	Cycle 1, 1^{st} weekly dose	151 (88; 226)
	Cycle 2, last weekly dose	729 (390; 1105)
$AUC_{0\text{-}7\ days}$ (µg/mL•day)	Cycle 1, 1^{st} weekly dose	908 (482; 1365)
	Cycle 2, last weekly dose	4855 (2562; 7522)

Absorption

The population PK model estimated Ka (CV%) was 0.773 1/day (8.31%). The absolute bioavailability of daratumumab SC in AL amyloidosis was not estimated since daratumumab IV was not evaluated in Phase 3 Study AMY3001. The estimated Ka value based on the data from subjects with AL amyloidosis in Study AMY3001 was approximately 2.7-fold the estimated value based on the data from subjects with multiple myeloma. It is plausible that the difference in Ka values was due to the fact that there was no daratumumab IV data available from subjects with AL amyloidosis, and the 1-compartment model after daratumumab SC administration was employed for population PK analysis using data from AL amyloidosis subjects in Study AMY3001.

Daratumumab Serum Concentration versus time, is scheduled in figure below.

Figure 3 **Daratumumab Serum Concentrations Versus Time Profiles in Study AMY3001 on a Semi-logarithmic Scale**



Abbreviations: SC=subcutaneous.

Following daratumumab SC treatment with weekly dosing, serum daratumumab Ctrough increased to maximum in Cycle 3 Day 1 pre-dose with a mean ± SD of 597 ± 232 µg/mL.

The mean (SD) serum daratumumab peak concentration after the first dose (Cpeak,first) of 149 (58.7) µg/mL following the first daratumumab SC administration occurred on C1D4, and mean (SD) maximum peak concentration (Cpeak,max) of 708 (280) µg/mL following weekly daratumumab SC dosing occurred on C3D4. Mean Cpeak,max on C3D4 was 4.75-fold of the Cpeak, first on C1D4. At EOT, mean (SD) serum daratumumab concentrations was 225 (216) µg/mL, and then declined to 118 (123) µg/mL at post treatment Week 8.

Serum daratumumab concentrations were detectable at 8 weeks after last dose of study drug due to the long half-life of daratumumab.

Distribution

The population PK model-estimated apparent volume of distribution (CV%) after SC administration was 10.8 L (3.1%) in subjects with AL amyloidosis. The apparent volume of distribution approached the plasma volume. Body weight, baseline alkaline phosphatase, and renal stage were identified as statistically significant covariates that affect the apparent volume of distribution.

Elimination

Daratumumab undergoes parallel target-mediated (saturable) and linear clearance. The target-mediated clearance of daratumumab decreases with multiple dosing, as the target gets depleted.

The population PK model-estimated apparent nonspecific linear clearance (CV%) after SC administration was 0.210 L/day (4.1%) in subjects with AL amyloidosis. The estimated linear apparent clearance was very close to the clearance of nonspecific endogenous IgGs in the literature and was related to body weight as expected for mAbs.

The model-derived half-life associated with linear elimination was 27.5 days. The steady-state serum drug concentration appeared to have been reached approximately 5 months after the start of dosing at the recommended dosing regimen.

Dose proportionality and time dependencies

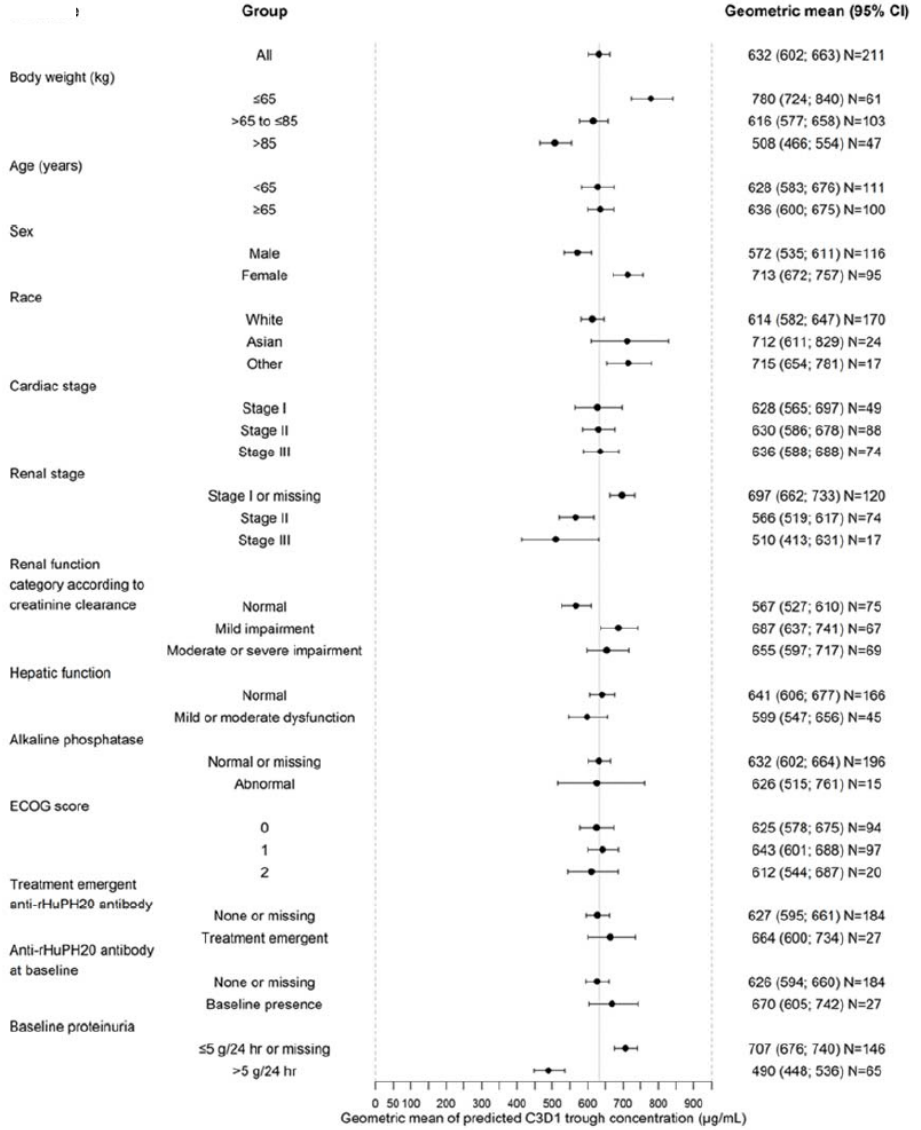
No dose proportionality study was performed to support this application for subjects with AL amyloidosis.

In the previous submission of daratumumab SC for multiple myeloma, dose proportionality was assessed in Study MMY1004, using the daratumumab mix-and-deliver intermediate SC formulation, where the first-dose Cmax increased 2-fold, and eighth-dose Cmax increased approximately 1.4-fold with a 1.5-fold increase in dose (from 1200 to 1800 mg). The area under the concentration-time curve from time 0 to Day 7 increased approximately 2-fold for first dose and 1.4-fold for the eighth weekly dose with a 1.5-fold increase in dose (from 1200 to 1800 mg).

Special populations

In the population PK model covariate analysis, intrinsic factors of interest (body weight, sex, cardiac stage, proteinuria, renal stage, alkaline phosphatase, renal function, and hepatic function) were investigated for their potential impact on the exposure to daratumumab SC in subjects with AL amyloidosis. A forest plot of subgroup analyses on simulated daratumumab pre-dose concentrations on C3D1 is presented in the figure below. The simulated daratumumab concentrations were generally consistent across different subgroups after the recommended dose and schedule, except for body weight, renal stage, and proteinuria.

Figure 4 Forest Plot of Subgroup Analyses on the Predicted Trough Concentrations on Cycle 3 Day 1

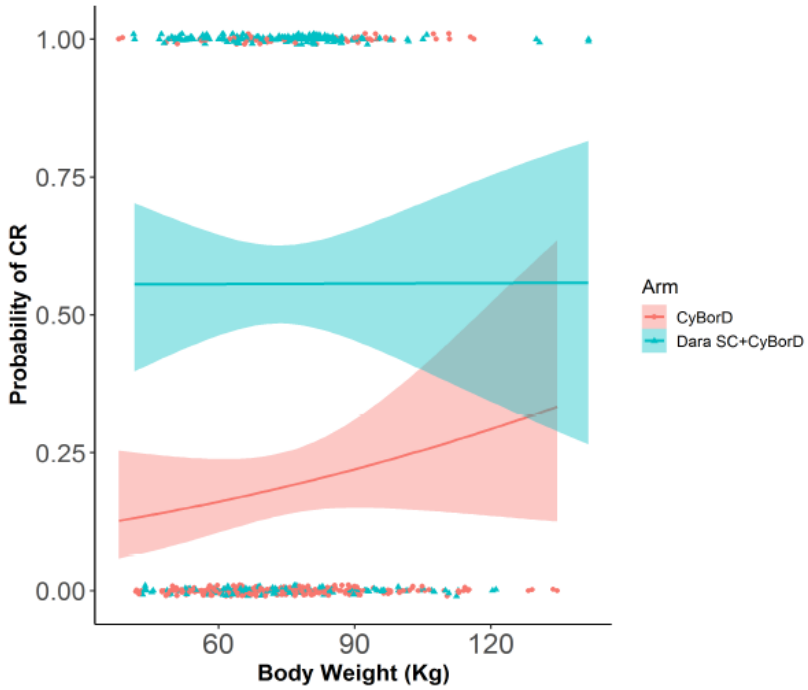


Abbreviations: C=Cycle; CI=confidence interval; D=Day; ECOG=Eastern Cooperative Oncology Group; rHuPH20=recombinant human hyaluronidase PH20.
Key: Solid black circles represent geometric means, and error bars represent 95% CI. Solid line represents reference value of the geometric mean of all subjects. Numbers represent geometric mean value, 95% CI, and the number of subjects in the comparison groups.
Note: The proteinuria cutoff point was 5 g/24 hr (Palladini 2014).
Source: Mod5.3.3.5/PPK/Fig3

Weight

As expected for a mAb administered SC by flat dose, higher serum daratumumab concentrations were observed in subjects with lower body weight and lower serum daratumumab concentrations were observed in subjects with higher body weight. For the lowest body weight subgroup (≤65 kg), the observed mean Ctrough, max of daratumumab on C3D1 was approximately 15% higher than that of the total PK evaluable analysis set. For the highest body weight subgroup (>85 kg), the observed mean Ctrough,max of daratumumab on C3D1 was approximately 17% lower than that of the total PK evaluable analysis set. For the middle body weight subgroup (>65 to 85 kg), the mean concentration of daratumumab on C3D1 was comparable to that of the total PK evaluable analysis set. Based on the exposure-response analyses for efficacy and safety, the administration of 1800 mg daratumumab SC flat-dose achieved adequate and consistent exposure for all body weight subgroups in the daratumumab SC+CyBorD arm of Study AMY3001. This is demonstrated in attachment 15, please see the figure below.

Figure 5 : **Incidence Rate of Hematologic complete response (HemCR) in Relation to Baseline Body Weight**

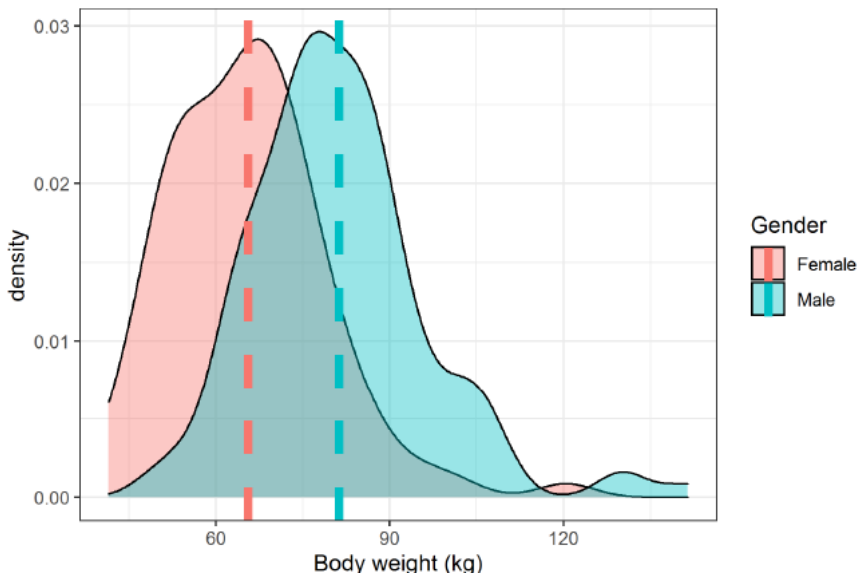


Abbreviations: CR=complete response, also called HemCR; CyBorD=cyclophosphamide, bortezomib, and dexamethasone; Dara=daratumumab; HemCR=hematologic complete response; SC=subcutaneous.
Key: The lines represent the predicted mean curves and the shaded regions are the 95% confidence intervals. Dots represent the observed rate of HemCR.

Sex

As sex was identified to be highly correlated with body weight, the slightly higher (25%) exposure following 1800 mg daratumumab SC administration in female subjects than in male subjects may be driven largely by body weight. In the final covariate analysis, sex was not identified to have a significant impact on daratumumab PK parameters in AL amyloidosis.

Figure 6 : **Distribution of Body Weight Grouped by Sex (Male/Female)**



Impaired renal function

Extensive renal damage, measured by renal stage and the degree of proteinuria was identified to be a significant covariate on both the nonspecific linear apparent clearance and apparent volume of distribution, and was associated with increased elimination of daratumumab in the urine and consequent lower systemic exposure. Simulations, based on post hoc PK parameters, demonstrated that exposure to daratumumab SC was generally similar (19% lower) for subjects with renal Stage II (C3D1 Ctrough [95% CI]: 566 [519, 617] µg/mL) vs Stage I (C3D1 Ctrough [95% CI]: 697 [662, 733] µg/mL). Clinical efficacy analysis suggested that the HemCR rate does not appear to be related with daratumumab exposure (71.4% for subjects with renal Stage II, compared with 51.3% for subjects with renal Stage I). A lower (27%) daratumumab exposure was observed for subjects with renal Stage III (C3D1 Ctrough [95% CI]: 510 [413, 631] µg/mL) vs Stage I. However, this observation should be interpreted with caution due to the small sample size (N=17) and overlapping CI between renal Stages III and Stage II.

Pharmacokinetic interaction studies

No dedicated drug-drug interaction studies were performed with daratumumab SC in this submission for AL amyloidosis. The potential of drug interactions with small molecules typically used in AL amyloidosis were not assessed in this submission. However, the previous studies for multiple myeloma program have shown no drug-drug interaction between daratumumab and small-molecules drugs used in combination with daratumumab in multiple myeloma. In addition, the PK of daratumumab following the treatment of daratumumab SC+CyBorD in AL amyloidosis appeared to be similar to that in monotherapy and combination studies in multiple myeloma, suggesting no drug-drug interaction between daratumumab and cyclophosphamide, bortezomib, or dexamethasone.

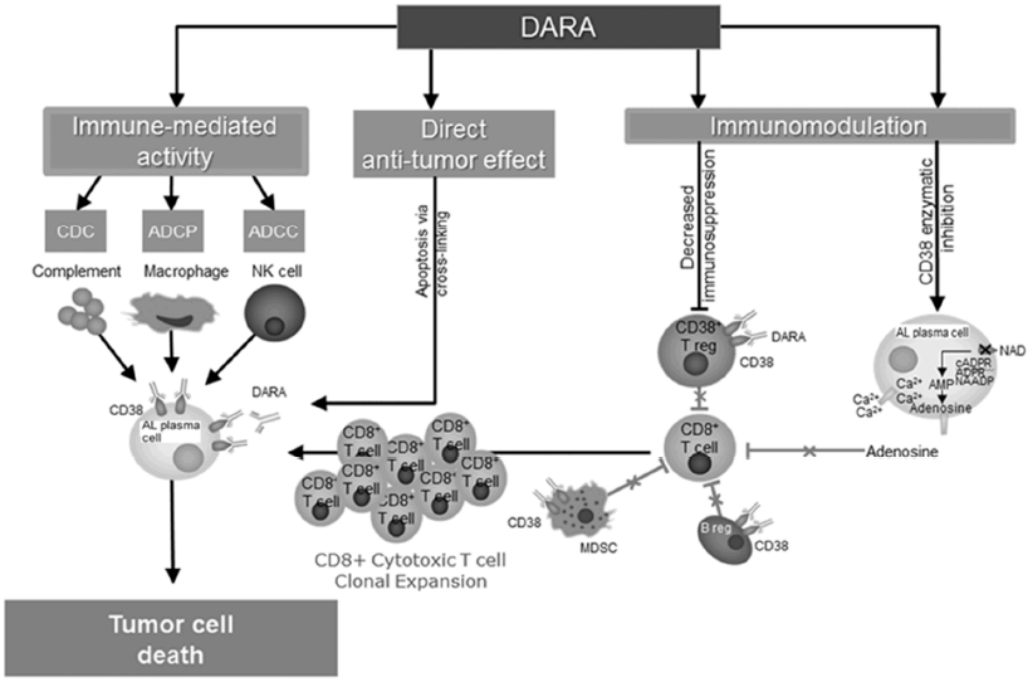
2.3.3. Pharmacodynamics

Mechanism of action

CD38 is a multifunctional glycoprotein enzyme that is highly expressed on the cell surface of diverse hematologic malignancies including multiple myeloma and clonal plasma cells that produce the amyloidogenic immunoglobulin light chain in AL amyloidosis. Daratumumab is a targeted immunotherapy directed toward tumor cells that express CD38 such as the clonal plasma cells in multiple myeloma and AL amyloidosis. Multiple mechanisms of action have been observed for daratumumab, including complement-dependent cytotoxicity, antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and induction of apoptosis by Fc gamma receptor-mediated crosslinking of tumor-bound mAbs. See figure below.

Daratumumab leads to the rapid and sustained elimination of highly immunosuppressive subsets of CD38+ Tregs, CD38+ myeloid-derived suppressor cells, and CD38+ regulatory B cells. The elimination of these immunosuppressive cells, modulation of CD38 enzymatic activity, and destruction of the malignant myeloma cells are thought to lead to the clonal expansion of CD8+ and CD4+ T cells. Altogether, daratumumab's converging mechanisms of action are hypothesized to synergistically lead to the deep responses observed in subjects.

Figure 7 **Daratumumab Mechanisms of Action in AL Amyloidosis**



Abbreviations: ADCC=antibody-dependent cellular cytotoxicity; ADCP=antibody-dependent cellular phagocytosis; ADPR=adenosine diphosphate ribose; AL=light chain amyloidosis; AMP=adenosine monophosphate; B reg=regulatory B cell; cADPR=cyclic ADPR; CD=cluster of differentiation; CDC=complement-dependent cytotoxicity; DARA=daratumumab; MDSC=myeloid-derived suppressor cell; NAADP=nicotinic acid adenine dinucleotide phosphate; NAD=nicotinamide adenine dinucleotide; NK=natural killer; T reg=regulatory T cell

2.3.4. PK/PD modelling

Exposure-response models

The relationships between exposure and the response endpoints were investigated using logistic regressions or survival analysis implemented in R (Version 3.6.0 or higher). The exposure-efficacy analyses were performed for the overall best confirmed hematologic response, including HemCR, VGPR, partial response (PR), and no response (NR). The exploratory exposure-safety analyses were conducted for selected adverse events, including organ disorders, infections, infusion-related reaction events and cytopenia events. The influence of body weight on efficacy and safety was also investigated.

For binary variables, linear logistic regression was used. The confirmed best overall hematologic response was analysed as an ordered categorical variable using an ordinal logistic regression model with sigmoid Emax.

Table 6 **: Parameter Estimate of E_{max} Model for HemCR**

Parameter	Estimate	RSE (%)
E_0	-1.47	13%
E_{max}	2.27	38%
Hill coefficient in log scale	0.68	148%
EC_{50}, µg/mL in log scale	5.76	8%

Abbreviation: E_0=baseline log odds when concentration=0; EC_{50}=half-maximal effect concentration; E_{max}=maximum efficacy; HemCR=hematologic complete response; RSE=relative standard error.

The time-to-event variable, major organ deterioration (MOD) PFS, was evaluated by K-M survival curves according to exposure quartiles. A Cox proportional hazard regression model relating daratumumab exposure to reduced hazard of death was also established (Table below).

Table 7 **Cox Proportional Hazard Estimates for MOD-PFS Using The Daratumumab Exposure Metrics, $C_{trough,max}$ and $C_{peak,first}$**

Parameter	Estimate	P-value	HR (95% CI)	AIC
$C_{peak,first}$	-0.00440	2.58e-03	0.9956 (0.9928-0.9985)	906
$C_{trough,max}$	-0.00152	6.43e-05	0.9985 (0.9977-0.9992)	898

Abbreviations: AIC=Akaike information criterion; CI=confidence interval; $C_{peak,first}$=peak concentration following the first dose; $C_{trough,max}$=maximal trough concentration; HR=hazard ratio; MOD-PFS=major organ deterioration progression-free survival.

If linear logistic regression trends were observed (on slope using a likelihood ratio test versus a constant relationship [p<0.05] or using the log-rank test [p<0.05]), further modelling was considered. Final model fits for categorical endpoints were evaluated by overlaying exposure-response predictions with observed response data with 95% CIs stratified by exposure quartiles, plotted at the median exposure per quartile. Final model fits for time-to-event variables were evaluated by overlaying Kaplan-Meier (K-M) time course predictions with observed K-M response data with 95% CIs stratified by exposure quartiles.

For simulations that were performed for exposure-response projections, the primary evaluation was the univariate exposure-response relationships. The modelled response with CIs was tabulated at the 5th, 25th, 50th (median), 75th, and 95th percentile exposure values. For time-to-event endpoints, the modelled response was calculated at landmark time points 6 and 12 months.

Ctrough,max was used as the exposure surrogate for daratumumab. Model fittings with all other exposure metrics, Ctrough,first, Cpeak,first, Ctrough,last, and Cpeak, last, showed a positive relationship between response probability and exposure (Table below).

Table 8 **Parameter Estimates of Ordinal Logistic Regression Model for Overall Best Confirmed Hematologic Response: Comparison of Different Exposure Metrics**

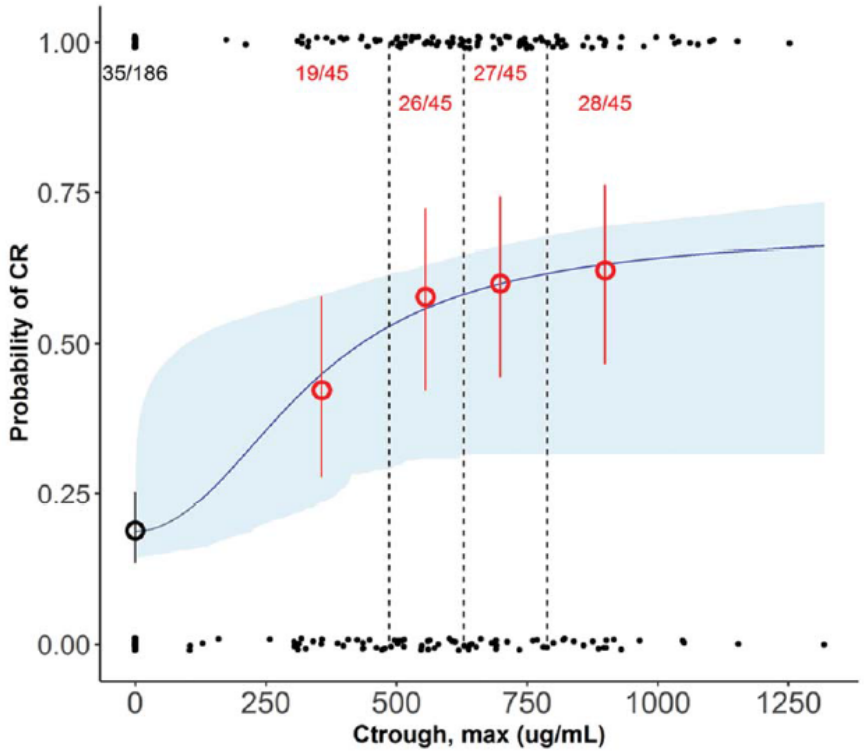
Parameter	$C_{trough,first}$	$C_{peak,first}$	$C_{trough,max}$	$C_{peak,max}$	$C_{trough,last}$	$C_{peak,last}$
Slope on exposure (%RSE)	-0.0104 (13)	-0.00977 (13)	-0.00245 (12)	-0.00217 (12)	-0.00216 (24)	-0.00248 (17)
Intercept for HemCR (%RSE)	-1.35 (12)	-1.37 (12)	-1.39 (11)	-1.42 (11)	-0.858 (16)	-1.09 (13)
Intercept for VGPR (%RSE)	0.0477 (287)	0.0344 (398)	0.0204 (669)	0.00250 (5496)	0.393 (33)	0.217 (62)
Intercept for PR (%RSE)	1.45 (12)	1.44 (12)	1.44 (12)	1.42 (12)	1.72 (10)	1.58 (11)
AIC	905	902	897	896	953	934

Abbreviations: AIC=Akaike information criterion; $C_{peak,first}$=peak concentration following the first dose; HemCR=hematologic complete response; $C_{trough,first}$=trough concentration following the first dose; $C_{peak,max}$=maximal peak concentration; $C_{trough,max}$=maximal trough concentration; $C_{peak,last}$=peak concentration following the last dose; $C_{trough,last}$=trough concentration following the last dose; PR=partial response; RSE=relative standard error; VGPR=very good partial response.

Exposure-response analyses

By using an Emax model, the exposure response analysis on the primary outcome HemCR rate, suggested that the Emax of daratumumab had been attained for the majority of the subjects at the studied 1800 mg daratumumab SC dosing regimen in AL amyloidosis (see Figure below).

Figure 8 Maximum Efficacy (E_{max}) Relationship between Predicted Daratumumab Maximum Trough Concentration and Complete Response



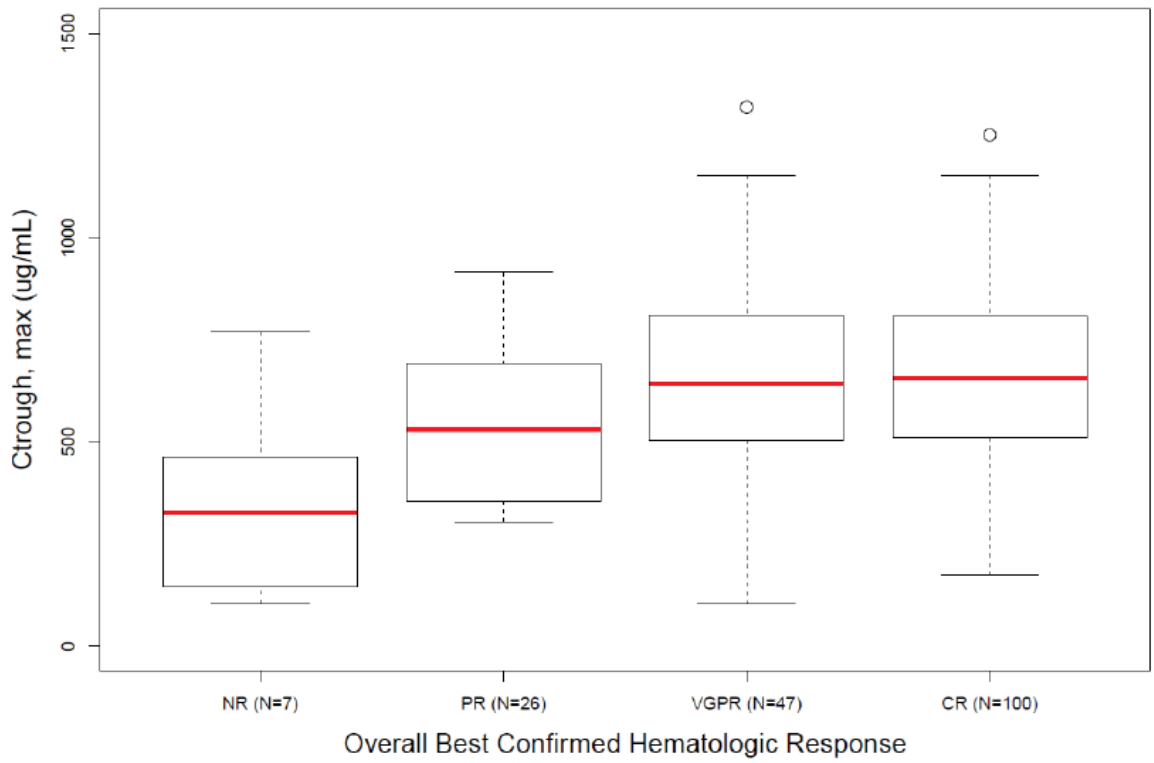
Abbreviations: CR=complete response (also called hematologic complete response [HemCR]); $C_{trough,max}$=maximum trough concentration; CyBorD=cyclophosphamide, bortezomib and dexamethasone; E_{max}=maximum efficacy.
Key: The solid blue line is the logistic regression fit using an E_{max} function. Light blue band represents the 95%confidence interval of the fit. Black dots at probabilities of 0 and 1 represent the observed HemCR. Subjects are stratified into exposure quartiles. The black vertical dashed lines separate the quartiles of $C_{trough,max}$. Red points are mean exposure and HemCR rate per quartile, and the black point is the HemCR rate from the CyBorD arm. Vertical red or black bars crossing the points are 95% confidence intervals of the HemCR rate.
Note: Subjects are stratified into daratumumab $C_{trough,max}$ quartiles. 1st quartile (≤486 µg/mL), 2nd quartile: (487 to 629 µg/mL), 3rd quartile (630 to 789 µg/mL), 4th quartile: (790 to 1320 µg/mL). The black vertical dashed lines separate the quartiles of maximal trough concentration. Red points are mean exposure and HemCR rate per quartile, and the black point is the HemCR rate from the CyBorD arm. Vertical red or black bars crossing the points are 95% confidence intervals of the HemCR rate.
Source: Mod5.3.3.5/PPK/Fig7

Exposure-efficacy analyses

Several PK metrics (trough concentration following the first dose [Ctrough,first], Cpeak,first, Ctrough,max, Cpeak,max, predicted trough daratumumab concentration following the last dose [Ctrough,last], and predicted peak daratumumab concentration following the last dose [Cpeak,last]) have been examined for their correlations with the efficacy endpoints. Among the tested exposure metrics, the 2 highly correlated exposure metrics Ctrough,max and Cpeak,max (r=0.99) had the strongest correlation with HemCR. Since both Ctrough,max and Cpeak,max were highly correlated, only Ctrough,max was selected as the exposure metric for the subsequent exposure-efficacy analyses.

The predicted daratumumab Ctrough,max for different categories of overall best confirmed hematologic response rate (including HemCR, VGPR, or PR) after 1800 mg daratumumab SC+CyBorD are shown in Figure below.

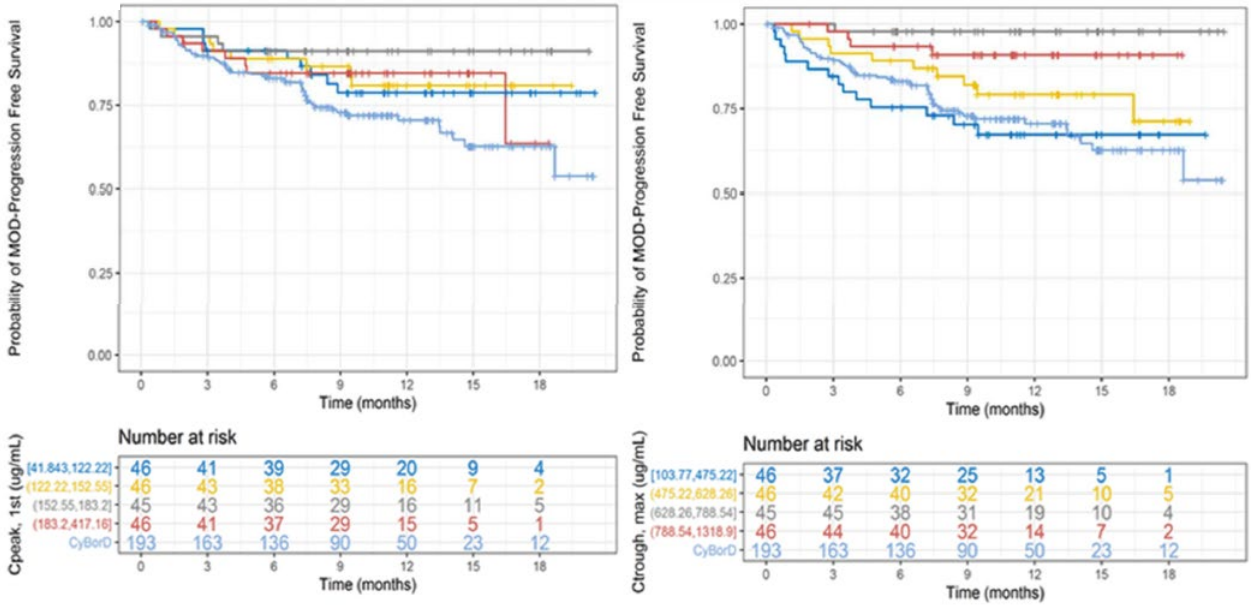
Figure 9 **Box Plot for Predicted Daratumumab Maximum Trough Concentrations for Different Categories of Overall Best Confirmed Hematologic Response after 1800 mg Daratumumab SC+CyBorD**



Abbreviations: CR=complete response (also called hematologic complete response [HemCR]); $C_{trough,max}$=maximum trough concentration; NR=no response; PR=partial response; SC=subcutaneous; VGPR=very good partial response.
Source: Mod5.3.3.5/PPK/Fig6

There was observed an improvement in MOD-PFS (major organ deterioration progression free survival) in the majority of subjects treated with daratumumab. See Figure below. There was no apparent improvement of MOD-PFS in the 1st exposure quartile using Ctrough,max as exposure metric, which may be due to the potential confounding effect as a result of time-varying clearance upon improvement of disease dynamics following drug treatment (i.e. clearance decreases when disease status improves. Consequently, subjects with less improvement of disease tend to have higher clearance and consequently lower Ctrough,max at later time points after treatment. This interaction between post-treatment effects and drug exposure may lead to a biased steep estimate of the exposure-efficacy response relationship for efficacy, which may be the reason to explain that the exposure-response analysis based on Ctrough,max showed similar or lower (for the first 7 months) MOD-PFS for the 1st quartile of subjects following the treatment of daratumumab SC+CyBorD compared with the 1st quartile of subjects following the treatment of CyBorD while a wider separation of remaining daratumumab SC+CyBorD exposure quartiles (2nd quartile to 4th quartile) versus CyBorD was observed using Ctrough,max as exposure parameter, compared with that when exposure metrics of Cpeak,first was used. These results were similar to those observed in daratumumab studies in multiple myeloma.

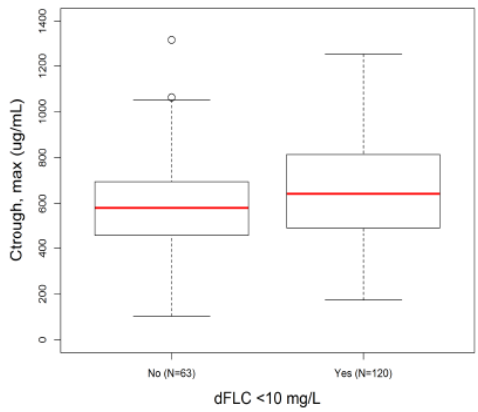
Figure 10 **Kaplan-Meier Survival Plots as an Estimate for MOD-PFS**



Abbreviations: $C_{peak,first}$=peak concentration following the first dose; $C_{trough,max}$=maximal trough concentration; MOD-PFS=major organ deterioration progression-free survival

The figure below shows the exposure-response relationship between the probability of dFLC and daratumumab Ctrough,max. Elevated daratumumab Ctrough,max was associated with an increased probability of achieving dFLC<10mg/L post-treatment, and the relationship is statistically significant (p<0.001). The probability of achieving dFLC<10mg/L post-treatment exhibited a statistically significant increase with increasing Ctrough,max values (p<0.0001). The observed incidence of achieving dFLC<10 mg/L posttreatment in the CyBorD alone arm was 30.6% and 60.9%, 63%, 57.8%, and 80.4% in the 1st to 4th exposure quartiles of Ctrough,max, respectively, in the daratumumab SC+CyBorD arm.

Figure 11 : **Exposure-Response Relationships for dFLC**



Abbreviations: $C_{trough,max}$=maximal trough concentration; dFLC=difference between involved and uninvolved free light chain.
Key: This box plot shows the exposure distributions, stratified by response.

Exposure-safety analyses

There was no clear exposure-response relationship between daratumumab exposure and safety endpoints (organ disorders, infections, IRR events, and cytopenia events) using Cpeak,first (for IRR) or Cpeak,max (for other endpoints), as shown in Table below.

Table 9 Incident Rates by Daratumumab Exposure Quartile for Safety Endpoints

Safety Endpoint	CyBorD % (95% CI) (N=188)	Daratumumab SC+CyBorD Exposure Quartiles, % (95% CI)			
		1st (N=46)	2nd (N=46)	3rd (N=45)	4th (N=46)
Infusion-related reaction	NA (NA-NA)	8.7 (2.4-20.8)	8.7 (2.4-20.8)	0 (0-7.9)	8.7 (2.4-20.8)
Grade ≥3	NA (NA-NA)	0 (0-7.7)	0 (0-7.7)	0 (0-7.9)	0 (0-7.7)
Neutropenia	6.4 (3.3-10.9)	8.7 (2.4-20.8)	10.9 (3.6-23.6)	8.9 (2.5-21.2)	13 (4.9-26.3)
Grade ≥3	2.7 (0.9-6.1)	4.3 (0.5-14.8)	4.3 (0.5-14.8)	4.4 (0.5-15.1)	6.5 (1.4-17.9)
Anemia	23.4 (17.6-30.1)	21.7 (10.9-36.4)	26.1 (14.3-41.1)	20 (9.6-34.6)	26.1 (14.3-41.1)
Grade ≥3	4.8 (2.2-8.9)	6.5 (1.4-17.9)	6.5 (1.4-17.9)	0 (0-7.9)	4.3 (0.5-14.8)
Thrombocytopenia	11.7 (7.5-17.2)	10.9 (3.6-23.6)	26.1 (14.3-41.1)	15.6 (6.5-29.5)	15.2 (6.3-28.9)
Grade ≥3	2.7 (0.9-6.1)	2.2 (0.1-11.5)	6.5 (1.4-17.9)	0 (0-7.9)	2.2 (0.1-11.5)
Lymphopenia	14.9 (10.1-20.8)	10.9 (3.6-23.6)	23.9 (12.6-38.8)	20 (9.6-34.6)	10.9 (3.6-23.6)
Grade ≥3	10.1 (6.2-15.3)	6.5 (1.4-17.9)	15.2 (6.3-28.9)	15.6 (6.5-29.5)	8.7 (2.4-20.8)
Infections and infestations	53.7 (46.3-61)	58.7 (43.2-73)	71.7 (56.5-84)	66.7 (51-80)	69.6 (54.2-82.3)
Grade ≥3	10.1 (6.2-15.3)	23.9 (12.6-38.8)	23.9 (12.6-38.8)	8.9 (2.5-21.2)	8.7 (2.4-20.8)
Cardiac disorder	21.8 (16.1-28.4)	34.8 (21.4-50.2)	26.1 (14.3-41.1)	22.2 (11.2-37.1)	37 (23.2-52.5)
Grade ≥3	9.6 (5.8-14.7)	13 (4.9-26.3)	10.9 (3.6-23.6)	6.7 (1.4-18.3)	13 (4.9-26.3)
Renal and urinary disorder	18.1 (12.9-24.3)	21.7 (10.9-36.4)	17.4 (7.8-31.4)	24.4 (12.9-39.5)	21.7 (10.9-36.4)
Grade ≥3	6.4 (3.3-10.9)	10.9 (3.6-23.6)	0 (0-7.7)	8.9 (2.5-21.2)	2.2 (0.1-11.5)

Abbreviations: CI=confidence interval; $C_{peak,first}$=peak concentration following the first dose; $C_{peak,max}$=maximal peak concentration; CyBorD=cyclophosphamide, bortezomib and dexamethasone; SC=subcutaneous.
Notes: $C_{peak,first}$ was used as the exposure measure for analyses on infusion-related reactions, while $C_{peak,max}$ was used as the exposure measure for analyses on other adverse events.
The quartiles for $C_{peak,first}$ were as follows: 1st quartile (≤122 µg/mL), 2nd quartile (123 to 153 µg/mL), 3rd quartile (154 to 183 µg/mL), and 4th quartile (184 to 417 µg/mL).
The quartiles for $C_{peak,max}$ were as follows: 1st quartile (≤570 µg/mL), 2nd quartile (571 to 722 µg/mL), 3rd quartile (723 to 898 µg/mL), and 4th quartile (899 to 1450 µg/mL).
Source: Mod5.3.3.5/PPK/Tab8

Other

In general, PK parameter estimates from the population PK model of 1800 mg daratumumab SC in subjects with AL amyloidosis were similar to estimates from the population PK model of 1800 mg daratumumab SC in subjects with multiple myeloma. Based on the population PK simulations, the recommended 1800 mg daratumumab SC dose in subjects with AL amyloidosis provided slightly higher Ctrough and Cpeak, but the observed daratumumab concentrations in subjects with AL amyloidosis were generally within the same range in comparison with observed PK data in subjects with multiple myeloma.

2.3.5. Immunogenicity

In the randomized part of the Phase 3 Study AMY3001, a total of 182 subjects were included in the daratumumab immune response evaluable population, and 181 subjects were included in the rHuPH20 immune response evaluable population in the daratumumab SC+CyBorD treatment arm.

None (0.0%) of the 182 randomized subjects in the daratumumab SC immune response-evaluable analysis set had treatment-emergent anti-daratumumab antibodies, indicating a low risk of immunogenicity to daratumumab SC when combined with CyBorD.

Eleven (6.1%) of the 181 randomized subjects in the rHuPH20 immune response-evaluable analysis set had treatment-emergent anti-rHuPH20 antibodies post the first daratumumab SC administration. Daratumumab exposure was comparable between subjects with treatment-emergent anti-rHuPH20 antibodies and those who were negative for anti-rHuPH20 antibodies. The incidence of treatment-emergent anti-rHuPH20 antibodies was consistent with observations in the Safety Run-in Phase of the study, and with the reported incidence of treatment-emergent anti-rHuPH20 antibodies in other daratumumab SC studies.

2.3.6. Discussion on clinical pharmacology

The main results of the performed PK analyses were consistent with those in previous monotherapy and combination studies in multiple myeloma. The bioanalytical methods were accepted in previous procedures. The in-study validation for sample analysis conducted in study AMY3001 indicated the methods performed well.

The characterisation of the pharmacokinetics in the target population lead to the development of a one-compartment population PK model with first-order absorption, and parallel and nonlinear elimination pathways. However, a previously developed population PK model in patients with multiple myeloma revealed that the PK properties of daratumumab were best described using a two-compartment PK model. The MAH justified the difference in the structural part of the population PK model due to the lack of experimental evidence gathered from the Phase 3 clinical trial (AMY3001). However, the MAH aimed to characterise the PK properties of daratumumab using only the experimental evidence from AMY3001, without considering a pooled analysis with other previous studies in order to increase the experimental evidence. A parameter comparison was conducted using the population PK model in MM and AL patients. In general, the main PK parameters are in agreement among both disease conditions (CL/F and Vc/F), showing the adequacy of the population PK model to serve as a tool to characterize the PK properties of daratumumab in AL amyloidosis patients. However, differences in Ka and covariate effects were found, indicating that additional factors are highly contributing to explain differences among both populations. Therefore, the current approach may be used only as descriptive purposes in AL amyloidosis patients and no dose selection/extrapolation exercises should be conducted. The popPK indicates the patients with body weight > 85kg and patients with renal stage II or III have decreased exposure, although a model-based analysis revealed that the exposure of these patients was within the exposure of the population with no clinically relevant effect in terms of efficacy. On the other hand, no definitive conclusions could be obtained in terms of hematologic response between patients in the daratumumab SC+CyBorD and CyBorD treatment arms given the small number of subjects in the combined subgroup of subjects with a baseline body weight of >85 kg and renal Stage III.

The observed PK results following 1800 mg daratumumab SC + VCd in subjects with AL amyloidosis from this phase 3 study AMY 3001, were consistent with those in previous monotherapy and combination studies in multiple myeloma. The observed volume of distribution of 10.8 L after SC administration in patients with AL amyloidosis was corresponding to the reported volume of distribution of 5.25 L (central compartment), and 3.78 L (peripheral compartment), in patients with multiple myeloma. The results suggest that daratumumab is primarily localised to the vascular system with limited extra vascular tissue distribution.

As an IgG1κ mAb, daratumumab is presumably biotransformed in the same manner as any other endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and undergoes to similar elimination. Renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are therefore unlikely to represent major elimination routes. The primary elimination pathways for daratumumab are clearance by the reticulo-endothelial system (degradation into small peptides and amino acids in the same way as that for an endogenous IgG) and target-mediated elimination. Values of clearance and half-live are similar to many other mAbs.

No dose proportionality study was performed to support this application for subjects with AL amyloidosis which is acceptable as this was assessed in Study MMY1004 (previous submission of daratumumab SC for multiple myeloma).

As expected for a mAb administered SC by flat dose, higher serum daratumumab concentrations were observed in subjects with lower body weight and lower serum daratumumab concentrations were observed in subjects with higher body weight. Consequently, this indicates that although weight has an influence on the achieved serum daratumumab concentrations, whatsoever it did not have any influence on the exposure-response analysis for efficacy and safety. This justifies the rationale for recommendation of a fixed dose of 1800 mg, for all individuals independently of weight group.
The totality of the data from the renal Stage III subgroup (which comprises proteinuria) and the moderate or severe renal impairment subgroup (categorized by CrCL) indicates that daratumumab exposures in subjects with renal damage generally overlap with those of the total PK-evaluable population, suggesting that dose adjustment is not needed for subjects in this subpopulation.

No dedicated drug-drug interaction studies were performed, and this is considered acceptable. As stated by the MAH, there are no overlapping elimination pathways between daratumumab and cyclophosphamide, bortezomib or dexamethasone, and therefore no interactions are expected between these agents.
The exposure-efficacy revealed a smooth and non-linear relationship between experimental Ctrough,max levels and probability of complete response (CR), showing that patients at Q1 will show a ~40% probability of CR and patients at Q4 a ~60% probability of CR. No exposure-safety relationship has been established among the safety variables considered.

No anti-daratumumab antibodies were detected in serum samples post-daratumumab SC administration. There were no apparent PK differences between subjects with positive anti-rHuPH20 antibodies in serum samples at baseline or subjects who developed treatment-emergent anti-rHuPH20 antibodies compared with subjects with negative anti-rHuPH20 antibodies at baseline or negative for treatment-emergent anti-rHuPH20 antibodies. These results reflect that the reported minor group of individuals (6.1%) who develop positive anti-rHuPH20, are consistent with the reported incidence of treatment-emergent anti-rHuPH20 antibodies in other daratumumab SC studies. Overall, the data indicate a low risk of immunogenicity of daratumumab when combined with cyclophosphamide, bortezomib, and dexamethasone in subjects with AL amyloidosis. The reported incidence of anti-daratumumab antibodies, and anti-rHuPH20 antibodies, in section 5.1 in the SmPC, is a pooled estimate including the incidence of both the MM and AL Amyloidosis population. The text has been updated in the SmPC to clarify this.

All the results from the overall analysis on PK data concerning ADME (absorption, distribution, metabolism, and excretion) and immunogenicity, were acceptable, and consistent with those from previous studies.

2.3.7. Conclusions on clinical pharmacology

The aim of the performed pharmacological analyses in the Phase 3 study AMY3001 was to assess PK, immunogenicity, PD, and exposure-response relationship of daratumumab SC in subjects with AL amyloidosis. These analyses are well performed and the results are sufficiently presented without causing any major concerns, regarding the implications of the findings.

The overall conclusion is that the proposed dosing regimen of subcutaneous daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone in patients with AL amyloidosis is considered adequate.

2.4. Clinical efficacy

2.4.1. Dose response study

No formal dose-response studies have been performed in AL-amyloidosis. Daratumumab administered at a dose of 16 mg/kg as IV infusion, is approved in the United States, European Union and other countries as monotherapy to patients with relapsed/refractory Multiple Myeloma (MM), as well as in combination with several anti MM therapies to patients with relapsed/refractory and newly diagnosed MM.

Recently a new SC formulation of daratumumab 1800 mg co-formulated with rHuPH20 has been approved by both the FDA and EMA in relapsed/refractory Multiple Myeloma (studies MMY3012, MMY2040 and MMY1004).

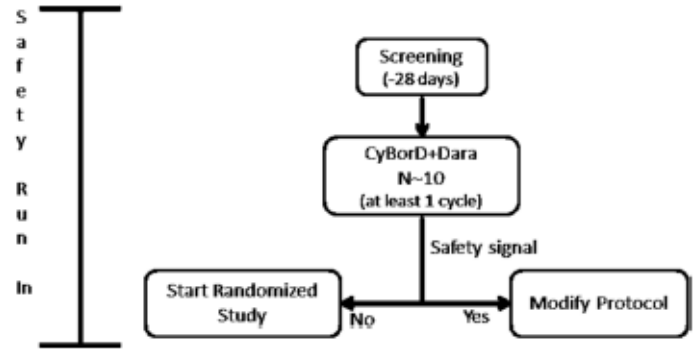
The majority of patients with amyloidosis have cardiac and renal co-morbidities. The IV infusion of daratumumab (1000 mL for the first infusion and 500 mL for the subsequent infusions) could have resulted in signs or symptoms of volume overload, particularly for the patients with cardiac or renal insufficiency. Given the potential advantages of SC-administration of daratumumab (e.g. small volume; fewer IRRs), this study will use a new, co-formulated drug product administered SC. The co-formulated daratumumab and rHuPH20 is a single, pre-mixed vial with daratumumab at a higher concentration of 120 mg/mL and rHuPH20 at a concentration of 2000 U/mL. The co-formulated drug product will reduce the time for drug preparation, reduce the SC-infusion volume to approximately 15 mL, and can be administered in 5 minutes by manual SC push.

2.4.2. Main study

Title of Study: AMY3001

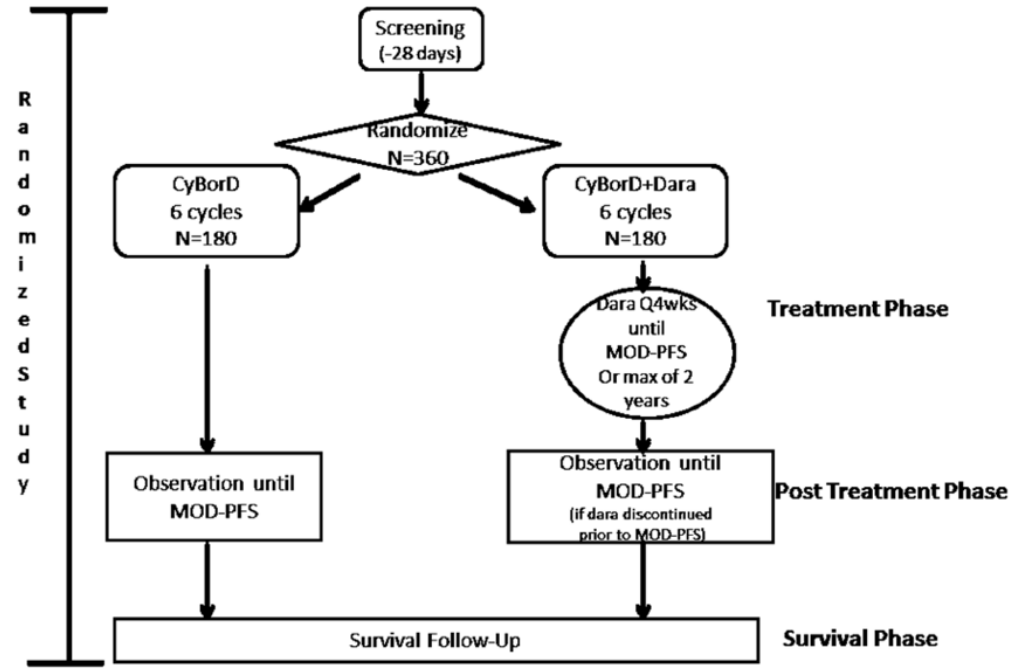
A randomized phase 3 Study to evaluate the efficacy and safety of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared with CyBorD alone in newly diagnosed systemic AL amyloidosis

Figure 12 Schematic Overview of the Safety Run-In



CyBorD+Dara=daratumumab SC + cyclophosphamide, bortezomib, and dexamethasone

Figure 13 : Schematic Overview of the Randomized AMY3001 Study



CyBorD=cyclophosphamide, bortezomib, and dexamethasone; Dara=daratumumab SC; MOD-PFS=major organ deterioration-progression-free survival

Methods

Study participants

Main Inclusion criteria

1. Males and females of 18 years or older.

2. Histopathological diagnosis of amyloidosis based on detection by IHC and polarizing light microscopy of green bi-refringent material in congo red-stained tissue specimens (in an organ other than bone marrow) or characteristic electron microscopy appearance.

Considerations for specific populations where other types of amyloidosis may be encountered:

- For male subjects 70 years of age or older who have cardiac involvement only, and subjects of African descent (black subjects), mass spectrometry typing of AL amyloid in a tissue biopsy is recommended to rule out other types of amyloidosis.

3. Measurable disease of amyloid light chain amyloidosis as defined by at least ONE of the following:

- serum M-protein ≥0.5 g/dL by protein electrophoresis (routine serum protein electrophoresis and immunofixation (IFE) performed at a central laboratory),
- serum free light chain ≥50 mg/L with an abnormal kappa:lambda ratio or the difference between involved and uninvolved free light chains (dFLC) ≥50 mg/ L.

Measurable disease by urine Bence-Jones proteinuria is not sufficient for study enrollment.

4. One or more organs impacted by AL amyloidosis according to consensus guidelines (Attachment 2).

5. Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) 0, 1 or 2.

6. Pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

a) Absolute neutrophil count ≥1.0 × 109/L;

b) Hemoglobin level ≥8.0 g/dL (≥5 mmol/L); transfusion allowed until 7 days before randomization;

c) Platelet count ≥50 × 109/L; transfusions are acceptable without restriction during the Screening period

d) Alanine aminotransferase level (ALT) ≤2.5 times the ULN;

e) Aspartate aminotransferase (AST) ≤2.5 times the ULN;

f) Total bilirubin level ≤1.5 × ULN except for subjects with Gilbert syndrome, in which case direct bilirubin ≤2 × ULN;

g) Estimated glomerular filtration rate (eGFR) ≥20 mL/min/1.73 m2, using the eGFR measured by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

Main Exclusion criteria

1. Prior therapy for AL amyloidosis or multiple myeloma including medications that target CD38, except from 160 mg dexamethasone (or equivalent corticosteroid) maximum exposure prior to randomization

2. Previous or current diagnosis of symptomatic multiple myeloma or plasmacytomas.

3. Clinically significant cardiovascular disease, including:

a) NT-ProBNP >8500 ng/L

b) NYHA classification IIIB or IV (Attachment 3). Cardiovascular-related hospitalizations within 4 weeks prior to randomization for subjects with congestive heart failure,

c) Heart failure that in the opinion of the investigator is on the basis of ischemic heart disease (eg prior myocardial infarction with documented history of cardiac enzyme elevation and ECG changes) or uncorrected valvular disease and not primarily due to AL amyloid cardiomyopathy

d) Inpatient admission to a hospital for unstable angina or myocardial infarction within the last 6 months prior to first dose or percutaneous cardiac intervention with recent stent within 6 months or coronary artery bypass grafting within 6 months.

e) History of prior sustained ventricular tachycardia or aborted ventricular fibrillation, history of atrioventricular nodal or sinoatrial (SA) nodal dysfunction for which a pacemaker/ICD is indicated but not placed (Subjects who do have a pacemaker/ICD are allowed on study)

f) Screening 12-lead ECG showing a baseline QT interval as corrected QTcF >500 msec. Subjects who have a pacemaker may be included regardless of calculated QTc interval.

g) Supine systolic blood pressure <90 mm Hg, or symptomatic orthostatic hypotension.

4. Planned stem cell transplant during C1-C6 of protocol therapy are excluded. Stem cell collection during C1-C6 of protocol therapy is permitted

5. History of malignancy (other than AL amyloidosis) within 3 years before the date of randomization (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast,

or other non-invasive lesion that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 3 years).

6. Chronic obstructive pulmonary disease (COPD) with a FEV1 <50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 <50% of predicted normal.

7. Moderate or severe persistent asthma within the past 2 years (see Attachment 6), or currently has uncontrolled asthma of any classification. (Note that subjects who currently have controlled intermittent asthma or controlled mild persistent asthma are allowed in the study).

8.Grade 2 sensory or Grade 1 painful peripheral neuropathy.

9. Any form of non-AL amyloidosis, including wild type or mutated (ATTR) amyloidosis.

Treatments

As this was the first study of daratumumab in treatment-naïve amyloidosis, the study was planned to start with a safety run-in of at least 10 subjects who will receive daratumumab plus CyBorD at the full dose for each regimen (Fig.1). The safety run-in was to confirm the safety of the new co-formulated drug product and the standard treatment regimen. A total of 10 subjects were considered appropriate for the initial phase of the study. Dosing of the subjects was staggered to allow for assessment of both, early or delayed IRRs. After at least 10 subjects have completed at least 1 cycle of treatment, there was an analysis of safety by the sponsor (and external academic hematologists) before proceeding to randomization.

In the randomized portion of the study, subjects randomized to Treatment Arm A were to receive study treatment with CyBorD (Figure 13). Subjects randomized to Treatment Arm B will receive CyBorD plus daratumumab subcutaneously, through a syringe by a manual push over approximately 5 minutes, at a fixed dose of 1800 mg.

Treatment was to be administered in the following order:

- **Treatment Arm A (CyBorD alone)**: dexamethasone first, then cyclophosphamide, and finally bortezomib.
- **Treatment Arm B (CyBorD plus daratumumab)**: premedication dexamethasone, followed by daratumumab, then cyclophosphamide, bortezomib and the remaining dose of dexamethasone.

All treatment cycles were 4 weeks (28-day cycles with a +/- 5-day window) in length. CyBorD was administered for a maximum of 6 cycles (24 weeks). Cycle 1 should begin within 72 hours of randomization. After Cycle 6, subjects may have received daratumumab monotherapy on Day 1 of subsequent 28-day cycles. Treatment with daratumumab was based on the approved daratumumab dosing regimen for multiple myeloma: weekly for the first 8 weeks (2 cycles), then every 2 weeks for 4 cycles (Cycles 3-6), and then every 4 weeks until progression of disease or subsequent therapy for a maximum of 24 cycles (~2 years) from the first dose of study treatment. Dosing schedule is presented in table below.

Table 10 Daratumumab SC+CyBorD Dosing Schedule

Weeks (Cycles)[a]	Schedule
Weeks 1 to 8 (Cycles 1-2)	Daratumumab SC+CyBorD, weekly (total of 8 doses)
Weeks 9 to 24 (Cycles 3-6)[b]	Daratumumab SC+CyBorD, every 2 weeks (total of 8 doses)
Week 25 onwards until disease progression[c]	Every 4 weeks

Abbreviations: CyBorD=cyclophosphamide, bortezomib, and dexamethasone; SC=subcutaneous

[a] All treatment cycles are 4 weeks (28 days) in length.

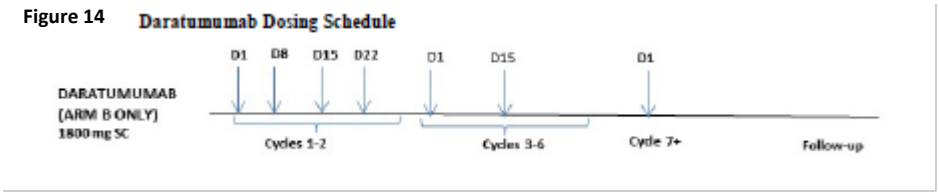
[b] First dose of the every-2-week dosing schedule is given at Week 9.

[c] First dose of the every-4-week dosing schedule is given at Week 25.

For subjects who were older than 70 years, underweight (BMI <18.5 kg), had hypervolemia, poorly controlled diabetes mellitus, or prior intolerance/AE to steroid therapy, the dexamethasone dose was administered at a dose of 20 mg weekly. For subjects receiving dexamethasone 20 mg weekly, it was recommended that dexamethasone 20 mg was administered as premedication on days of daratumumab treatment.

Subjects would receive pre-infusion and postinfusion medications in line with the SmPC. A schematic of the daratumumab dosing schedule is provided in Figure below.

Figure 14 Daratumumab Dosing Schedule



Subjects enrolled in the safety run-in phase of the study would be kept in the hospital for observation for at least 24 hours after the end of the Cycle 1 Day 1 SC-administration. Subjects enrolled in the randomized portion of the study and randomized to Treatment Arm B (CyBorD plus daratumumab) would be observed for at least 6 hours after the end of study drug administration during Cycle 1 Day 1 and, if deemed necessary by the investigator, after consecutive administrations.

Objectives

Primary Objective

- To evaluate the efficacy of daratumumab SC plus CyBorD (daratumumab SC+CyBorD) compared with CyBorD alone, in terms of **overall CHR**, in the treatment of newly diagnosed patients with AL amyloidosis.

The Secondary efficacy objectives are:

- To evaluate the clinically observable composite endpoints for major organ deterioration progression-free survival (MOD-PFS) in the two treatment arms.
- To evaluate the following efficacy measures following treatment with daratumumab in combination with CyBorD compared with CyBorD alone:
  - Organ response rate (OrRR)
  - Overall survival (OS)
  - Time to and duration of response
- To evaluate fatigue, mental functioning, and health-related quality of life in the two treatment arms.

- To assess the safety and tolerability of daratumumab when administered in combination with CyBorD
- To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPH20
- To explore minimal residual disease (MRD) status in amyloidosis patients as a surrogate for hematologic progression-free survival (HemPFS) and OS or as a biomarker for relapse

Exploratory Objectives

- To evaluate HemPFS
- To evaluate biomarkers of response following treatment in the two treatment arms.
- To evaluate physical functioning, symptom improvement, functional improvement and health utility following treatment in the two treatment arms.
- To evaluate diastolic function following treatment with daratumumab in combination with CyBorD compared with CyBorD alone
- To explore the pharmacokinetic/pharmacodynamic relationship of daratumumab, such as exposure response relationship for efficacy/safety endpoints or disease-related or mechanism-based biomarkers

Outcomes/endpoints

Primary Endpoint

The primary endpoint is overall CHR rate based on IRC assessment.

Secondary Endpoints

The secondary efficacy endpoints include:

- Major organ deterioration progression-free survival (MOD-PFS). This is a composite endpoint of clinically observable endpoints and will be defined from randomization to any one of the following events, whichever comes first:

  1. Death

  2. Clinical Manifestation of Cardiac Failure:

  Defined as development of dyspnea at rest (for at least 3 consecutive days) and due solely to amyloidosis cardiac deterioration, need for cardiac transplant, left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP)

  3. Clinical Manifestation of Renal Failure:

  Defined as the development of end-stage renal disease (need for hemodialysis or renal transplant)

  4. Development of hematologic PD as per consensus guidelines (Comenzo 2012). From CHR, abnormal free light chain ratio (light chain ratio must double) or from CHR/VGPR/PR, 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present)

  Free light chain increase of 50% to >100 mg/L

- Organ response rate (OrRR) for kidney, heart, liver, defined as the proportion of baseline organ involved subjects who achieve confirmed organ response in each corresponding organ.
- Overall survival (OS) measured from the date of randomization to the date of the subject's death. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive.
- CHR rate at 6 months, defined as the proportion of subjects who achieve a complete hematologic response at 6 months, according to the consensus guidelines for AL amyloidosis,[7] during or after the study treatment.
- Improvement in fatigue is defined as the change from baseline in the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30 Fatigue scale score, improvement in mental functioning is defined as the change from baseline in the 36-Item Short Form Survey version 2 (SF-36v2) Mental Component Summary (MCS), and improvement in health-related quality of life is defined as change from baseline in the EORTC QLQ-C30 Global Health Status scale score.
- Time to next treatment (TNT) defined as the time from the date of randomization to the start date of subsequent AL Amyloidosis (non-protocol) treatment. Death due to PD prior to subsequent therapy is considered as an event. Otherwise, TNT is censored at the date of death or the last date known to be alive.
- Hematologic VGPR or better rate is defined as the proportion of subjects who achieve hematologic CR or VGPR.
- Time to CHR (or VGPR or better) is defined as the time between the date of randomization and the first efficacy evaluation at which the subject has met all criteria for hematologic CR (or VGPR or better).
- Duration of CHR (or VGPR or better) is defined as the time between the date of initial documentation of CHR (or VGPR or better) to the date of first documented evidence of hematologic progressive disease. For subjects who have not progressed, data will be censored at the last disease assessment.
- Time to cardiac response, time to renal response, and time to liver response. Defined as the time between the date of randomization and the first efficacy evaluation at which the subject has each corresponding organ response.
- Duration of organ response is defined as the time between the date of initial documentation of each corresponding organ response to the date of first documented evidence of the corresponding organ progressive disease. For subjects who have not had organ progression, data will be censored at the last disease assessment.
- Time to cardiac progression, time to renal progression, and time to liver progression. Defined as the time from the date of randomization to the date of each corresponding organ progression per consensus guidelines.
- To evaluate fatigue, mental functioning, and health-related quality of life in the two treatment arms, using the EORTC QLQ-C30 Fatigue- and Global Health Status scale scores and the 36-Item Short Form Survey version 2 (SF-36v2) Mental Component Summary (MCS).
- To assess the safety and tolerability of daratumumab in the two treatment arms.
- To assess the pharmacokinetics of daratumumab and the immunogenicity of daratumumab and rHuPH20

- To explore minimal residual disease (MRD) status in amyloidosis patients as a surrogate for hematologic progression-free survival (HemPFS) and OS or as a biomarker for relapse

Exploratory objectives

- Hematologic progression-free survival (HemPFS) is defined as the time from the date of randomization to the date of first documentation of hematologic disease progression, according to central laboratory results and judged by international consensus guidelines, or death due to any cause, whichever occurs first. For those subjects who are still alive and have not yet progressed, the subject's data will be censored at the last disease assessment.
- Evaluation of MRD status in subjects who achieve CHR based on next generation sequencing or similar technologies.
- Assessment of physical functioning, symptom improvement, functional improvement, and health utility as measured by the SF-36v2, EORTC QLQ-C30 with supplemental symptom items, and the European Quality of Life Five Dimensions Questionnaire (EQ-5D-5L).
- Assessment of diastolic heart dysfunction based on analysis of transthoracic echocardiograms.

Sample size

The sample size for this study was based on the alternative hypothesis of a 15% improvement in overall CHR rate. Taking an overall CHR rate estimated to be 25% for the CyBorD arm (Palladini 2015), adding a 15% improvement translates to an overall CHR rate of 40% for the daratumumab SC+CyBorD arm. Approximately 360 subjects (180 subjects per arm) would provide more than 85% power to detect a 15% improvement in overall CHR rate using a likelihood ratio test with a 2-sided alpha of 0.05.

The post-treatment observation phase was to continue until approximately 200 MOD-PFS events had been observed. Therefore, this study was to achieve an approximately 80% power to detect a 33% reduction in the risk of hematologic progression, major organ deterioration, need for subsequent, non-cross resistant, anti-plasma cell therapy use for suboptimal hematologic response, and persistent amyloidosis-related organ dysfunction or death (HR [daratumumab SC+CyBorD vs CyBorD] of 0.67) with a log-rank test (2-sided alpha=0.05).

Randomisation

Central randomization was implemented in this study. Subjects were randomly assigned in a 1:1 ratio to receive either Treatment Arm A (CyBorD alone) or Treatment Arm B (daratumumab SC+CyBorD) based on a computer-generated randomization schedule. The randomization was balanced by using randomly permuted blocks and was stratified by cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min). Country List A contains the countries that typically offer stem cell transplant while country List B contains the countries that do not offer stem cell transplant for patients with AL amyloidosis.

Blinding (masking)

This is an open-label study, blinding procedures were not applicable. An Independent Data Monitoring Committee (IDMC) will assess the results of the interim analyses. The primary endpoint of overall CHR and secondary efficacy endpoints will be adjudicated by an IRC.

An IDMC, consisting of 2 clinicians and 1 statistician, will be established to review the interim results at the planned interim analyses. After the interim review, the IDMC will make recommendations regarding any required modification and provide guidance on the continuation of the study.

Statistical methods

Primary Efficacy Analysis Set

The primary efficacy analysis set will be the intent-to-treat (ITT) population, which is defined as subjects who have been randomly assigned to the Dara SC+CyBorD or CyBorD arm. Analyses of the primary endpoint overall CHR rate, secondary endpoints, including time-to-event variables (e.g., MOD-PFS, and OS), and demographic and baseline characteristic etc. will be based on this population.

Primary endpoint CHR

Estimand for the primary endpoint CHR

Treatment: Dara SC+CyBorD for up to 6 cycles followed by dara monotherapy until PD or start of subsequent non-cross resistant, anti-plasma cell therapy, or a maximum of 2 years from the start of the treatment or CyBorD for up to 6 cycles followed by observation.

Population: subjects with newly diagnosed AL amyloid

Endpoint: overall complete hematologic response (CHR)

Intercurrent event:

- Treatment discontinuation
- Start of subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis without hematologic progression

Measure of intervention: odds ratio of overall CHR rate

Two different strategies are used to account for the intercurrent events.

- Disease assessments after subsequent non-cross resistant, anti-plasma cell therapy will be ignored for a subject who started subsequent non-cross resistant, anti-plasma cell therapy for AL Amyloidosis (while on treatment strategy).
- Treatment discontinuation will be ignored (treatment policy strategy).

Stratified Cochran-Mantel-Haenszel (CMH) test will be used to test treatment difference in the proportion of subjects who achieved an overall CHR. The CMH estimate of odds ratio and its 95% CI and p-value for testing treatment difference will be reported. Stratification factors used in the analysis include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min).

A sensitivity analysis that target the primary estimand will be performed. The sensitivity analysis will be based on investigator assessed CR and computerized algorithm derived CR, respectively. Same analysis approach as for the main analysis will be implemented.

In addition, three planned supplementary analyses will be conducted:

a) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (i.e., negative serum and urine immunofixation and iFLC<ULN), the rest of the estimand remain the same

b) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (i.e., negative serum and urine immunofixation and iFLC<ULN and normalization of FLC ratio), the rest of the estimand remain the same

c) Changes which strategy is employed for the intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy. If there is a disease assessment that demonstrates CHR before PD after the start of subsequent non-cross resistant, anti-plasma cell therapy, the subject will be considered as a responder treatment policy strategy)

Major secondary endpoint MOD-PFS

The primary treatment comparison of the distribution of overall MOD-PFS will be based on inverse probability of censoring weighted (IPCW) log-rank test to adjust for potential dependent censoring due to switching to subsequent non-cross resistant, antiplasma cell therapy.

Due to expected small number of MOD-PFS events at the primary analysis, the distribution comparison of MOD-PFS for the 2 treatment groups will be based on unstratified IPCW log-rank test. Hazard ratio and its 95% confidence interval will be estimated using a unstratified weighted Cox proportional hazards model with treatment as the sole explanatory variable. Inverse probability of censoring weighted Kaplan-Meier curves will be plotted by treatment group.

At the final MOD-PFS analysis (i.e., when approximately 200 MOD-PFS events have been observed), a stratified MOD-PFS analysis including stratified IPCW log-rank test, stratified weighted Cox proportional hazards model with treatment as the sole explanatory variable will be performed.

Table 11 **MOD-PFS Event and Censoring Method**

Situation	Date of Progression or Censoring	Outcome
Hematologic PD or clinical manifestation of cardiac failure or clinical manifestation of renal failure prior to start of subsequent, non-cross resistant, anti-plasma cell therapy	Earliest date of any of these 3 events	MOD-PFS event
Death prior to start of subsequent, non-cross resistant, anti-plasma cell therapy	Date of death	MOD-PFS event
No post-baseline clinical evaluation of MOD-PFS	Randomization	Censored
No MOD-PFS events	Date of last clinical evaluation of MOD-PFS endpoint	Censored
Other (e.g., withdrawal of consent to study participation, lost to follow-up, start of subsequent, non-cross resistant, anti-plasma cell therapy etc.)	Date of last clinical evaluation of MOD-PFS endpoint prior to censoring situation	Censored

IPCW

Time-dependent stabilised weights will be calculated for each subject at time (t) by estimating the conditional probability of having remained uncensored (i.e., not switching to subsequent non-cross resistant, anti-plasma cell therapy) until time t given baseline covariates, divided by the estimated conditional probability of having remained uncensored until time t given baseline and time dependent covariates. The following baseline covariates and time-dependent prognostic factors for MOD-PFS and switching to subsequent non-cross resistant, anti-plasma cell therapy will be taken into consideration.

Baseline: Age (<65, >=65), Sex (Male, Female), Race (White, Others), ECOG Performance Score (0, >=1), Countries that typically offer transplant for patients with AL amyloidosis (List A: countries that typically offer transplant or List B: countries that typically not offer transplant), Baseline dFLC, Baseline iFLC. Type of FLC (kappa, lambda), Number of organ involvement (<2, vs >=2), Cardiac involvement (Y,

N), Cardiac stage (Stage I, II, and IIIa/IIIb), Renal involvement (Y, N), Renal function (CrCl ≥60 mL/min or CrCl <60 mL/min), Renal Stage (I, II, III)

Time varying covariates: dFLC, iFLC level, PR status, CR status, Worsening in hematologic response criterion from best achieved status, Alkaline Phosphate, eGFR, Proteinuria level, NT-proBNP, Progression of organ disease (Heart, Kidney and Liver) as defined in protocol Table 10 by laboratory values, Organ response (Heart, Kidney and Liver) as defined in protocol Table 10 by laboratory values, Interaction of organ function (protocol Table 10) and hematologic response (PR or better), Interaction of organ function (protocol Table 10), hematologic response (PR or better) and treatment cycle (<=6 vs >6), Exposure to study treatment (study drug discontinued or not).

Sensitivity Analysis of MOD-PFS

a. MOD-PFS based on investigator assessed hematologic PD. Same analysis approach as for the primary analysis (IPCW method) will be implemented

b. MOD-PFS based on IRC assessment by using naïve censoring method (i.e., censoring subjects at the last disease assessment before start of subsequent non-cross resistant, antiplasma cell therapy)

c. Unstratified analysis of MOD-PFS based on IRC assessment by using naïve censoring method

Supplementary Analysis of MOD-PFS

Supplementary analyses including other strategies for intercurrent events of subsequent non-cross resistant, anti-plasma cell therapy such as treatment policy strategy (no censoring at start subsequent non-cross resistant, anti-plasma cell therapy) and composite strategy (subsequent noncross resistant, anti-plasma cell therapy will be treated as a MOD-PFS event) will be performed.

A time-dependent Cox proportional-hazards model with subsequent non-cross resistant, antiplasma cell therapy as a time dependent covariate will be performed for MOD-PFS.

A supplementary analysis of MOD-PFS based on computer algorithm by censoring for death or hematologic progression after missing more than one consecutive disease evaluation will be performed.

A supplementary analysis of MOD-PFS with adjusted MOD-PFS definition excluding hematologic progression from MOD-PFS will be performed.

Major secondary endpoint OS

The Kaplan-Meier method will be used to estimate the distribution of OS for each treatment group. Median OS with 95% CI will be provided. Due to expected small number of death events at the planned final analysis, the distribution of OS for the 2 treatment groups will be compared based on an unstratified log-rank test. A p-value from an unstratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on an unstratified Cox's regression model with treatment as the sole explanatory variable.

At the final OS analysis, a stratified OS analysis will be performed. Stratification factors that are used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min).

Interim analysis and multiplicity considerations

Two interim analyses are planned for this study. The first interim will occur after the first 30 subjects are treated for at least 1 cycle in each arm. The purpose of the first interim analysis is to have a comprehensive evaluation of safety.

The second interim analysis will occur after at least 180 subjects in total have been treated for at least 6 cycles. The purpose of the second interim analysis is to evaluate cumulative interim safety and efficacy

data. Both futility and efficacy stopping rules are built in this interim analysis. The study may be stopped due to futility if the complete hematologic response rate in Dara SC+CyBorD arm is the same or worse than CyBorD arm. The study may be stopped due to efficacy if the significance level at this interim analysis to establish the superiority of Dara SC+CyBorD over CyBorD is less than or equal to 0.0001 (2- sided). The primary analysis will occur after all subjects are treated for at least 6 cycles and the alpha to be spent is 0.04999 (2-sided) by a user defined alpha spending function.

By the time of second interim analysis, it is estimated that there will be a very limited number of events for major secondary endpoints of MOD-PFS and OS. Therefore, only descriptive analysis will be conducted without formal hypothesis testing. Formal hypothesis testing of these major secondary endpoints will be conducted at the planned primary analysis and/or when approximately 200 MOD-PFS events are observed according to group-sequential rules.

If the testing of the primary endpoint of overall CHR rate is statistically significant, the following major secondary endpoints ordered below will be sequentially tested at the planned primary analysis, each with an overall two-sided alpha of 0.05, by utilising a hierarchical testing approach as proposed by Tang and Geller (1999) that strongly controls Type I error rate. The major secondary endpoints are ordered as follows:

1) MOD-PFS

2) OS

Changes in Planned Analyses

MOD-PFS

The protocol defined criteria for MOD-PFS included dyspnea at rest for at least 3 consecutive days as a clinical manifestation of cardiac failure. In the SAP, this component was removed due to the subjective nature of the event in accordance with HA request. After consultation with FDA and agreed upon by FDA, the primary analysis of MOD-PFS was changed from analysis without censoring subsequent non-cross resistant, anti-plasma cell therapy to IPCW analysis based on the ITT population.

Changes in the SAP

AMENDMENT HISTORY

SAP version	Issue Date
Original SAP	06Aug2018
Amendment 1	16Sep2019
Amendment 2	27Mar2020

Amendment -2

Based on FDA comments that dyspnea at rest for at least 3 consecutive days as a clinical manifestation of cardiac failure has subjective nature, it was requested to exclude from MOD-PFS definition. In addition, FDA has concern about patients who received subsequent treatment in the absence of hematologic progression or major organ deterioration

Summary of Changes:

- Dyspnea at rest for at least 3 consecutive days as a clinical manifestation of cardiac failure was excluded from MOD-PFS primary analysis

- The primary analysis of MOD-PFS will employ inverse probability of censoring weights (IPCW) method to adjust estimates of a treatment effect in the presence of subsequent non-cross resistant anti-plasma cell therapy
- Added sensitivity analysis and supplementary analysis for MOD-PFS
- Added time to iFLC≤ 20 mg/L response
- Minor edit changes for clarifications

Amendment -1 (16Sep2019)

The primary endpoint, complete hematological response (CHR) rate and key secondary endpoints of major organ deterioration free survival (MOD-PFS) and overall survival (OS) remain the same. In the original plan, a progression-free survival (PFS) endpoint (defined as hematologic progression, or cardiac, kidney or liver progression, or death, whichever comes first) was planned. Considering that there is no literature currently available to assess for clinical meaningfulness of aggregate PFS as an endpoint in AL amyloidosis treatment, separate analyses will be conducted for hematological PFS and organ-based progression. In the revised plan, the PFS analysis will be specific to hematologic PFS (defined as hematologic progression, or death, whichever comes first). Additional landmark analysis on organ response and progression has been added for appropriate interpretation of results and meaningful comparison to existing literature. In addition, supportive analysis has been added as appropriate (e.g., analysis on iFLC and dFLC, time to PR or better and additional subgroups). Further editorial changes were made throughout the document for clarification.

Summary of changes:

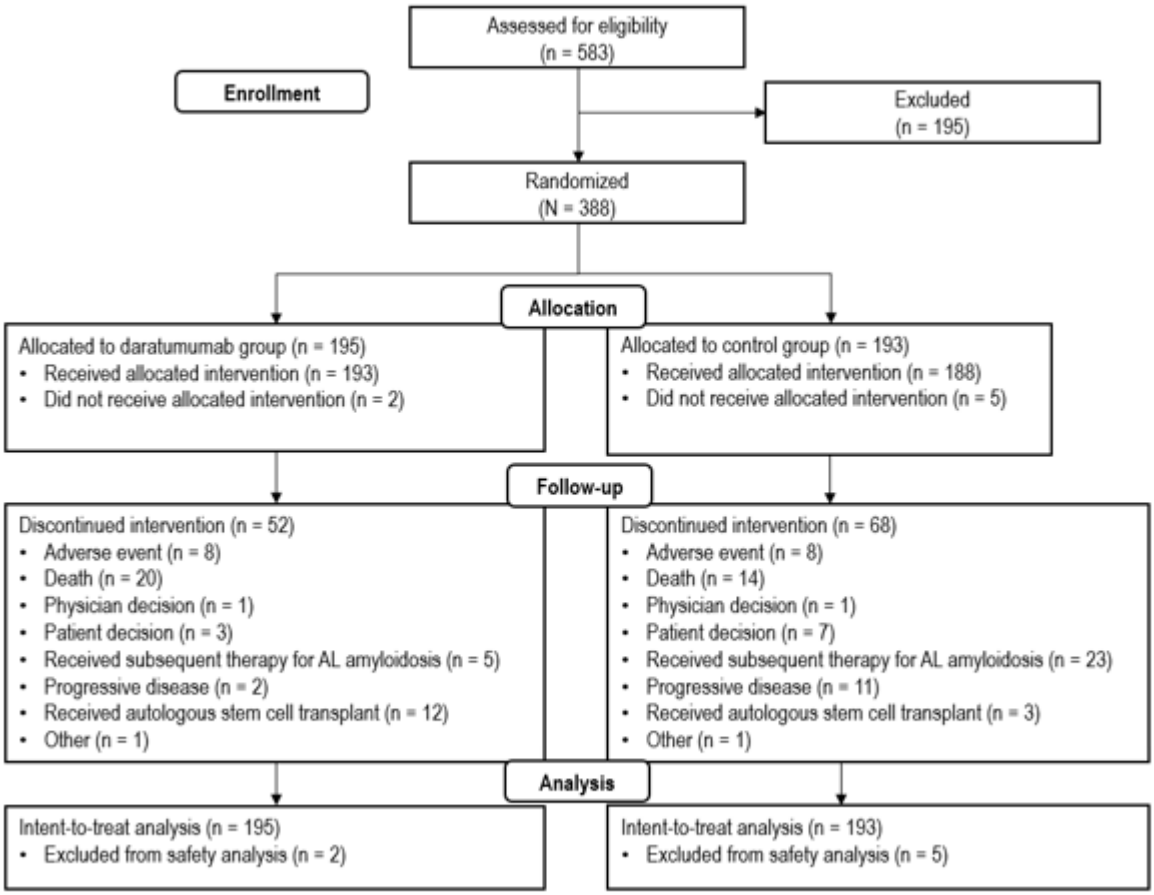
- PFS analysis will be specific to hematologic PFS and moved to exploratory endpoint. PFS endpoint was removed from statistical hierarchical testing
- Added organ response and progression 6-month landmark analysis for each involved organ
- Added t(11:14) and high risk of cytogenetic subgroup
- Added time to and duration of PR or better response
- Added Time to iFLC<ULN and Time to dFLC<10 mg/dL response
- Replaced time to organ progression with time to cardiac progression, time to renal progression and time to liver progression
- Added attachments of hematologic PD and response computerized algorithm and additional exploratory analysis to support HEMAR.
- Minor edit changes for clarifications

Results

Participant flow

At the time of clinical cut-off (14 February 2020), 388 subjects across 22 countries were enrolled in the randomized portion of the study to receive treatment with either daratumumab SC+CyBorD (195 subjects) or CyBorD (193 subjects). Two subjects in the daratumumab SC+CyBorD arm and 5 subjects in the CyBorD arm were randomized but never treated due to consent withdrawal.

Table 12 **Subject Disposition as of Clinical Cutoff Date (14 February 2020); Study 54767414AMY3001**



Source: Mod5.3.5.1/AMY3001/Tab3

Table 13 Summary of Subject Disposition; Intent-to-treat Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)	Total n (%)
Analysis set: intent-to-treat	193	195	388
Subjects randomized but not treated[a]	5 (2.6%)	2 (1.0%)	7 (1.8%)
Subjects treated[a]	188 (97.4%)	193 (99.0%)	381 (98.2%)
Subjects who discontinued treatment[b]	68 (36.2%)	52 (26.9%)	120 (31.5%)
Reason for discontinuation[b]			
Adverse event	8 (4.3%)	8 (4.1%)	16 (4.2%)
Death	14 (7.4%)	20 (10.4%)	34 (8.9%)
Physician decision	1 (0.5%)	1 (0.5%)	2 (0.5%)
Withdrawal by subject	7 (3.7%)	3 (1.6%)	10 (2.6%)
Received AL amyloidosis subsequent therapy	23 (12.2%)	5 (2.6%)	28 (7.3%)
Progression disease MOD-PFS	11 (5.9%)	2 (1.0%)	13 (3.4%)
Received ASCT	3 (1.6%)	12 (6.2%)	15 (3.9%)
Other	1 (0.5%)	1 (0.5%)	2 (0.5%)
Subjects who discontinued study[a]	41 (21.2%)	31 (15.9%)	72 (18.6%)
Reason for discontinuation[a]			
Death	27 (14.0%)	27 (13.8%)	54 (13.9%)
Lost to follow-up	1 (0.5%)	0	1 (0.3%)
Withdrawal by subject	13 (6.7%)	4 (2.1%)	17 (4.4%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[a] Percentages are based on number of subjects randomized.
[b] Percentages are based on number of subjects treated.
Note: Progression disease MOD-PFS includes hematologic progression or major organ deterioration.
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Recruitment

Study Initiation Date: 10 October 2017

Data cut off: 14 February 2020

The study is ongoing.

Study Center(s): Australia (4 sites), Belgium (4 sites), Brazil (8 sites), Canada (6 sites), China (5 sites), Denmark (3 sites), France (11 sites), Germany (7 sites), Greece (2 sites), Hungary (3 sites), Israel (5 sites), Italy (6 sites), Japan (12 sites), Mexico (2 sites), Netherlands (5 sites), Poland (3 sites), Spain (10 sites), South Korea (5 sites), Sweden (2 sites), Turkey (6 sites), United Kingdom (2 sites), United States of America (29 sites).

Conduct of the study

Protocol amendments

The original protocol was dated 6 April 2017. There were 3 amendments to the protocol, as summarized below.

Amendment 1 (03 April 2018): To revise the AL amyloidosis response consensus criteria. Key changes included: Clarification of the censoring of data for secondary endpoints of time to complete hematologic response and time to organ response. Stratification by cardiac stage will be based on the Mayo Clinic Cardiac Staging System. The renal organ response criteria updated as detailed in Palladini 2014. Subjects with

hypersensitivity or contraindications to cyclophosphamide or any of its metabolites were excluded. Clarification of the definition of hematologic progressive disease based on the recommendation of the AMY3001 Steering Committee that detectable monoclonal protein must be above a pre-defined quantitative level to qualify for progression.

Amendment 2 (23 January 2019): Identification of a new important risk (HBV reactivation), and how to manage subjects with the potential for HBV reactivation.

Amendment 3 (10 October 2019): To clarify that an aggregated (hematologic and organ) PFS was split into a specific HemPFS which was moved to an exploratory objective, while retaining organ-specific response rate and duration of response as secondary objectives; a CHR analysis at 6 months was added; Severity Criteria for adverse events were revised to align with NCI-CTCAE v4.03 severity definitions; and updated anticipated events in Attachment 12. To clarify, that normalisation of uFLC level and FLC ratio are not required when determining complete hematologic response.

Protocol deviations

All protocol deviations of eligibility criteria and those deviations that could impact subject safety or primary endpoints were considered MPDs.

Table 14 **Summary of Major Protocol Deviations; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)	Total n (%)
Analysis set: intent-to-treat	193	195	388
Total number of subjects with major protocol deviation	9 (4.7%)	8 (4.1%)	17 (4.4%)
Type of major protocol deviation			
Entered but did not satisfy criteria	3 (1.6%)	2 (1.0%)	5 (1.3%)
Received a disallowed concomitant treatment	1 (0.5%)	2 (1.0%)	3 (0.8%)
Other	6 (3.1%)	4 (2.1%)	10 (2.6%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).

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Baseline data

The demographic and baseline disease characteristics are presented in the following tables:

Table 15 **Summary of Demographics and Baseline Characteristics; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
Analysis set: intent-to-treat	193	195	388
Age, years			
N	193	195	388
Mean (SD)	64.0 (9.66)	62.2 (10.16)	63.1 (9.94)
Median	64.0	62.0	64.0
Range	(35; 86)	(34; 87)	(34; 87)
Category, n (%)			
< 65	97 (50.3%)	108 (55.4%)	205 (52.8%)
>= 65	96 (49.7%)	87 (44.6%)	183 (47.2%)
Sex, n (%)			
N	193	195	388
Female	76 (39.4%)	87 (44.6%)	163 (42.0%)
Male	117 (60.6%)	108 (55.4%)	225 (58.0%)
Race, n (%)			
N	193	195	388
American Indian or Alaska Native	2 (1.0%)	1 (0.5%)	3 (0.8%)
Asian	34 (17.6%)	30 (15.4%)	64 (16.5%)
Black or African American	7 (3.6%)	6 (3.1%)	13 (3.4%)
Native Hawaiian or Other Pacific Islander	1 (0.5%)	0	1 (0.3%)
White	143 (74.1%)	151 (77.4%)	294 (75.8%)
Multiple	1 (0.5%)	0	1 (0.3%)
Unknown	5 (2.6%)	7 (3.6%)	12 (3.1%)
Ethnicity, n (%)			
N	193	195	388
Hispanic or Latino	13 (6.7%)	9 (4.6%)	22 (5.7%)
Not Hispanic or Latino	176 (91.2%)	179 (91.8%)	355 (91.5%)
Unknown	4 (2.1%)	7 (3.6%)	11 (2.8%)
Weight, kg			
N	193	195	388
Mean (SD)	73.41 (17.345)	73.38 (15.896)	73.40 (16.611)
Median	70.00	73.00	72.00
Range	(38.0; 134.6)	(41.5; 141.5)	(38.0; 141.5)
Category,n(%)			
<=65 kg	74 (38.3%)	62 (31.8%)	136 (35.1%)
>65 to 85 kg	74 (38.3%)	96 (49.2%)	170 (43.8%)
>85 kg	45 (23.3%)	37 (19.0%)	82 (21.1%)
Height, cm			
N	193	195	388
Mean (SD)	168.13 (10.231)	167.32 (10.449)	167.72 (10.336)
Median	168.10	167.20	168.00
Range	(139.1; 193.0)	(140.0; 190.5)	(139.1; 193.0)
Body surface area, m^2			
N	193	195	388
Mean (SD)	1.84 (0.255)	1.84 (0.237)	1.84 (0.246)
Median	1.81	1.83	1.81
Range	(1.2; 2.7)	(1.3; 2.5)	(1.2; 2.7)
Baseline ECOG score, n (%)			
N	193	195	388
0	71 (36.8%)	90 (46.2%)	161 (41.5%)
1	106 (54.9%)	86 (44.1%)	192 (49.5%)
2	16 (8.3%)	19 (9.7%)	35 (9.0%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: ECOG = eastern cooperative oncology group.
Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.
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Table 16 **Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
Analysis set: intent-to-treat	193	195	388
Time since initial AL Amyloidosis diagnosis, days			
N	193	195	388
Mean (SD)	62.4 (90.70)	101.5 (220.22)	82.1 (169.63)
Median	43.0	48.0	43.0
Range	(5; 1102)	(8; 1611)	(5; 1611)
Category, n(%)			
<=30	55 (28.5%)	51 (26.2%)	106 (27.3%)
>30-60	83 (43.0%)	74 (37.9%)	157 (40.5%)
>60	55 (28.5%)	70 (35.9%)	125 (32.2%)
Isotype of AL based on either immunofixation or light chain, n (%)			
N	193	195	388
Lambda	149 (77.2%)	158 (81.0%)	307 (79.1%)
Kappa	44 (22.8%)	37 (19.0%)	81 (20.9%)
Organ Involvement, n (%)			
N	193	195	388
Heart	137 (71.0%)	140 (71.8%)	277 (71.4%)
Kidney	114 (59.1%)	115 (59.0%)	229 (59.0%)
Liver	16 (8.3%)	15 (7.7%)	31 (8.0%)
Gastrointestinal tract	29 (15.0%)	30 (15.4%)	59 (15.2%)
Lung	5 (2.6%)	3 (1.5%)	8 (2.1%)
Nerve	33 (17.1%)	42 (21.5%)	75 (19.3%)
PNS	24 (12.4%)	32 (16.4%)	56 (14.4%)
ANS	11 (5.7%)	11 (5.6%)	22 (5.7%)
Soft tissue	55 (28.5%)	51 (26.2%)	106 (27.3%)
Number of organs involved			
N	193	195	388
Mean (SD)	2.0 (1.03)	2.0 (0.97)	2.0 (1.00)
Median	2.0	2.0	2.0
Range	(1; 6)	(1; 5)	(1; 6)
Category, n(%)			
1 organ	68 (35.2%)	66 (33.8%)	134 (34.5%)
2 organs	77 (39.9%)	76 (39.0%)	153 (39.4%)
>=3 organs	48 (24.9%)	53 (27.2%)	101 (26.0%)
Cardiac stage based on Mayo Clinic Cardiac Staging System[a], n (%)			
N	193	195	388
I	43 (22.3%)	47 (24.1%)	90 (23.2%)
II	80 (41.5%)	76 (39.0%)	156 (40.2%)
IIIa	64 (33.2%)	70 (35.9%)	134 (34.5%)
IIIb	6 (3.1%)	2 (1.0%)	8 (2.1%)
NYHA class, n (%)			
N	193	195	388
I	94 (48.7%)	101 (51.8%)	195 (50.3%)
II	89 (46.1%)	77 (39.5%)	166 (42.8%)
IIIA	10 (5.2%)	17 (8.7%)	27 (7.0%)
Renal function status - creatinine clearance, n (%)			

Table 16 **Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
N	193	195	388
<60 mL/min	62 (32.1%)	69 (35.4%)	131 (33.8%)
>=60 mL/min	131 (67.9%)	126 (64.6%)	257 (66.2%)
Chronic kidney disease stage[b], n (%)			
N	193	195	388
I	55 (28.5%)	60 (30.8%)	115 (29.6%)
II	76 (39.4%)	69 (35.4%)	145 (37.4%)
III	41 (21.2%)	51 (26.2%)	92 (23.7%)
IV	21 (10.9%)	15 (7.7%)	36 (9.3%)
V (End stage renal disease)	0	0	0
Cytogenetic risk at study entry[d], n (%)			
N	166	155	321
High risk	19 (11.4%)	17 (11.0%)	36 (11.2%)
Standard risk	147 (88.6%)	138 (89.0%)	285 (88.8%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: ANS = autonomic nerve system; dFLC = difference between involved and uninvolved free light chains; iFLC = involved free light chains; PNS = peripheral nerve system.

[a] Cardiac stage is derived based on the combination of NT-proBNP (N-terminal pro b-type natriuretic peptide) and hs-cTnT (high sensitivity cardiac troponin T). Subjects in IIIb category should be excluded from participation of the study per protocol. All subjects were known IIIa at screening, however progressed to IIIb at cycle 1 day 1.

[b] Chronic kidney disease stage is derived based on eGFR (estimated glomerular filtration rate).

[c] Renal stage is derived based on the combination of eGFR (estimated glomerular filtration rate) and proteinuria.

[d] Cytogenetic risk is based on FISH or karyotype testing. High risk is defined as: 1) by FISH testing: t (4; 14), t (14; 16), and 17p deletion; or 2) by Karyotype testing: t (4; 14), 17p deletion.

Note: Percentages are calculated with the number of subjects in each treatment group with available data as denominator.

Modified from Attachment TSIDEM02

Table 17 **Summary of Selected Biomarkers Related to AL Amyloidosis at Baseline; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
Analysis set: intent-to-treat	193	195	388
Abnormal kappa/lambda ratio, n/N (%)	151/193 (78.2%)	147/195 (75.4%)	298/388 (76.8%)
dFLC, mg/L			
N	193	195	388
Mean (SD)	487.9 (1192.63)	337.3 (474.38)	412.2 (907.83)
Median	185.7	200.3	187.1
Range	(1; 9983)	(2; 4749)	(1; 9983)
iFLC, mg/L			
N	193	195	388
Mean (SD)	510.8 (1191.55)	359.6 (471.83)	434.8 (906.49)
Median	210.0	214.0	211.0
Range	(20; 10000)	(11; 4757)	(11; 10000)
Bone marrow plasma cells, %			
N	193	195	388
Mean (SD)	12.0 (9.86)	13.3 (9.96)	12.7 (9.92)
Median	10.0	10.0	10.0
Range	(0; 55)	(1; 50)	(0; 55)
NT-proBNP, ng/L			
N	193	195	388
Mean (SD)	2433.0 (2565.88)	2219.5 (2260.39)	2325.7 (2416.41)
Median	1746.0	1388.6	1604.7
Range	(51; 12950)	(51; 10182)	(51; 12950)
NT-proBNP, ng/L - Cardiac involvement[a]			
N	137	140	277
Mean (SD)	3249.3 (2604.63)	2970.3 (2244.60)	3108.3 (2428.95)
Median	2434.8	2266.9	2307.9
Range	(217; 12950)	(51; 10182)	(51; 12950)
Hs-cTnT, ng/L			
N	193	195	388
Mean (SD)	54.5 (50.53)	55.3 (54.96)	54.9 (52.74)
Median	39.3	35.8	38.0
Range	(13; 291)	(13; 396)	(13; 396)
Hs-cTnT, ng/L - Cardiac involvement[a]			
N	137	140	277
Mean (SD)	66.4 (54.65)	70.3 (58.19)	68.4 (56.40)
Median	50.7	56.7	54.4
Range	(13; 291)	(13; 396)	(13; 396)
LVEF, %			
N	193	193	386
Mean (SD)	59.0 (8.85)	59.7 (10.20)	59.4 (9.54)
Median	60.0	61.0	60.0
Range	(32; 79)	(22; 77)	(22; 79)
Serum creatinine, umol/L			
N	193	195	388

Table 17 **Summary of Selected Biomarkers Related to AL Amyloidosis at Baseline; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
Mean (SD)	100.8 (45.28)	96.9 (42.76)	98.9 (44.02)
Median	88.0	85.0	87.0
Range	(37; 249)	(35; 256)	(35; 256)
eGFR, mL/min/1.73m^2			
N	193	195	388
Mean (SD)	70.7 (25.70)	72.5 (26.10)	71.6 (25.88)
Median	76.2	77.8	77.7
Range	(20; 121)	(21; 126)	(20; 126)
eGFR, mL/min/1.73m^2 – Renal involvement			
N	114	115	229
Mean (SD)	66.7 (27.17)	69.4 (27.15)	68.1 (27.13)
Median	70.4	76.3	71.1
Range	(20; 115)	(23; 123)	(20; 123)
Proteinuria, g/24hr			
N	193	193	386
Mean (SD)	4.1 (5.15)	3.8 (4.95)	4.0 (5.04)
Median	2.1	1.4	1.7
Range	(0; 21)	(0; 26)	(0; 26)
Proteinuria, g/24hr - Renal involvement			
N	114	114	228
Mean (SD)	6.8 (5.21)	6.3 (5.09)	6.6 (5.14)
Median	5.3	5.4	5.4
Range	(0; 21)[b]	(1; 26)	(0; 26)
Alkaline phosphatase, U/L			
N	193	195	388
Mean (SD)	109.5 (117.14)	104.9 (91.87)	107.2 (105.09)
Median	81.0	80.0	81.0
Range	(23; 1194)	(34; 633)	(23; 1194)
Alkaline phosphatase, U/L - Liver involvement			
N	16	15	31
Mean (SD)	375.1 (283.55)	345.2 (192.61)	360.6 (240.30)
Median	293.5	310.0	304.0
Range	(79; 1194)	(96; 633)	(79; 1194)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: dFLC = difference between involved and uninvolved free light chains; eGFR = estimated glomerular filtration rate; Hs-cTnT = high sensitivity cardiac troponin T; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-brain natriuretic peptide.
[a] Cardiac involvement is defined as echocardiogram: mean wall thickness >12mm, no other cardiac cause or an elevated NT-ProBNP (>332 ng/L) in the absence of renal failure or atrial fibrillation.
[b] Subjects were required to have proteinuria of at least 0.5g/24hr to qualify for renal involvement. Two subjects in the CyBorD arm met criteria at screening followed by proteinuria decreased to <0.5 g/day.
Note: Results are based on central lab data only.

Modified from Attachment TSIBMK01

Table 18 **Summary of Subsequent Non-cross Resistant Anti-plasma Cell Therapy by Therapeutic Class, Pharmacologic Class, and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)	Total n (%)
Analysis set: safety	188	193	381
Subjects with one or more subsequent non-cross resistant anti-plasma cell therapies	79 (42.0%)	19 (9.8%)	98 (25.7%)
Subjects with subsequent autologous stem cell transplant	20 (10.6%)	13 (6.7%)	33 (8.7%)
Therapeutic class			
Pharmacologic class			
Drug			
Antineoplastic agents	71 (37.8%)	15 (7.8%)	86 (22.6%)
Other antineoplastic agents	50 (26.6%)	1 (0.5%)	51 (13.4%)
Daratumumab	48 (25.5%)	0	48 (12.6%)
Ixazomib	2 (1.1%)	1 (0.5%)	3 (0.8%)
Isatuximab	1 (0.5%)	0	1 (0.3%)
Venetoclax	1 (0.5%)	0	1 (0.3%)
Alkylating agents	26 (13.8%)	14 (7.3%)	40 (10.5%)
Melphalan	26 (13.8%)	14 (7.3%)	40 (10.5%)
Immunosuppressants	30 (16.0%)	6 (3.1%)	36 (9.4%)
Immunosuppressants	30 (16.0%)	6 (3.1%)	36 (9.4%)
Lenalidomide	23 (12.2%)	4 (2.1%)	27 (7.1%)
Pomalidomide	8 (4.3%)	3 (1.6%)	11 (2.9%)
Macrolides, lincosamides and streptogramins	1 (0.5%)	0	1 (0.3%)
Clarithromycin	1 (0.5%)	0	1 (0.3%)
Corticosteroids for systemic use	1 (0.5%)	1 (0.5%)	2 (0.5%)
Corticosteroids for systemic use, plain	1 (0.5%)	1 (0.5%)	2 (0.5%)
Methylprednisolone	0	1 (0.5%)	1 (0.3%)
Prednisone	1 (0.5%)	0	1 (0.3%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: WHO drug dictionary, September 2016 version.
Modified from Attachment TSISAT01C

Numbers analysed

The primary analysis population was the intent-to-treat (ITT) population, which included all randomized subjects.

Table 19 : Summary of Subsequent Non-cross Resistant Anti-plasma Cell Therapy by Therapeutic Class, Pharmacologic Class, and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)	Total n (%)
Analysis set: safety	188	193	381
Subjects with one or more subsequent non-cross resistant anti-plasma cell therapies	79 (42.0%)	19 (9.8%)	98 (25.7%)
Subjects with subsequent autologous stem cell transplant	20 (10.6%)	13 (6.7%)	33 (8.7%)
Therapeutic class			
Pharmacologic class			
Drug			
Antineoplastic agents	71 (37.8%)	15 (7.8%)	86 (22.6%)
Other antineoplastic agents	50 (26.6%)	1 (0.5%)	51 (13.4%)
Daratumumab	48 (25.5%)	0	48 (12.6%)
Ixazomib	2 (1.1%)	1 (0.5%)	3 (0.8%)
Isatuximab	1 (0.5%)	0	1 (0.3%)
Venetoclax	1 (0.5%)	0	1 (0.3%)
Alkylating agents	26 (13.8%)	14 (7.3%)	40 (10.5%)
Melphalan	26 (13.8%)	14 (7.3%)	40 (10.5%)
Immunosuppressants	30 (16.0%)	6 (3.1%)	36 (9.4%)
Immunosuppressants	30 (16.0%)	6 (3.1%)	36 (9.4%)
Lenalidomide	23 (12.2%)	4 (2.1%)	27 (7.1%)
Pomalidomide	8 (4.3%)	3 (1.6%)	11 (2.9%)
Macrolides, lincosamides and streptogramins	1 (0.5%)	0	1 (0.3%)
Clarithromycin	1 (0.5%)	0	1 (0.3%)
Corticosteroids for systemic use	1 (0.5%)	1 (0.5%)	2 (0.5%)
Corticosteroids for systemic use, plain	1 (0.5%)	1 (0.5%)	2 (0.5%)
Methylprednisolone	0	1 (0.5%)	1 (0.3%)
Prednisone	1 (0.5%)	0	1 (0.3%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: WHO drug dictionary, September 2016 version.
Modified from Attachment TSISAT01C

Outcomes and estimation

Updated results with an additional 9 months of follow-up (clinical cut-off: 13 November 2020), since the primary analysis (clinical cut-off: 14 February 2020), resulted in a HemCR of 59.0% vs. 19.2%, for D-VCd vs. VCd, respectively; odds ratio [95% CI]=5.90 (3.72, 9.37); p<0.0001).

The median duration of treatment was 9.6 months in the daratumumab SC+CyBorD arm and 5.3 months in the CyBorD arm.

Primary endpoint - Overall Complete Hematologic Response Rate

Table below represents data from the primary analysis, clinical cut-off: 14 February 2020.

Table 20 **Summary of Primary, Sensitivity and Supplementary Analysis of Overall Hematologic Complete Response (CHR)**

	CHR Rate % (95% CI)		Odds ratio (95% CI)	P-value
	CyBorD	Dara SC+CyBorD	[Dara SC+CyBorD vs CyBorD]	
Primary Analysis				
IRC assessment: confirmed by a subsequent assessment	18.1 (13.0, 24.3)	53.3 (46.1, 60.5)	5.13 (3.22, 8.16)	<0.0001
Sensitivity Analyses				
Investigator assessment: confirmed by a subsequent assessment	17.1 (12.1, 23.2)	53.3 (46.1, 60.5)	5.51 (3.44, 8.83)	<0.0001
Computerized algorithm: confirmed by a subsequent assessment[a]	16.6 (11.6, 22.6)	53.3 (46.1, 60.5)	5.75 (3.57, 9.25)	<0.0001
Supplementary Analyses				
Computerized algorithm: without confirmation	22.8 (17.1, 29.4)	60.0 (52.8, 66.9)	4.92 (3.17, 7.64)	<0.0001
Computerized algorithm (negative serum and urine immunofixation and iFLC<ULN and normalization of FLC ratio): without confirmation[b]	18.1 (13.0, 24.3)	46.2 (39.0, 53.4)	3.90 (2.45, 6.21)	<0.0001
IRC assessment: without censoring subsequent non-cross resistant anti-plasma cell therapy and confirmed by a subsequent assessment[c]	21.8 (16.2, 28.3)	55.4 (48.1, 62.5)	4.55 (2.90, 7.14)	<0.0001
IRC assessment: hematologic response-evaluable Analysis Set; confirmed by a subsequent assessment[d]	19.1 (13.7, 25.6)	55.4 (47.9, 62.7)	5.25 (3.27,8.43)	<0.0001

Abbreviations: CHR=hematologic complete response; CI=confidence interval; CR=complete response; CyBorD= cyclophosphamide, bortezomib and dexamethasone; Dara SC=subcutaneous daratumumab; FLC=free light chain; iFLC=involved free light chain; IRC=Independent Review Committee; PD=disease progression; ULN=upper limit of normal

a) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (ie, negative serum and urine immunofixation and iFLC<ULN), the rest of the estimand remain the same
b) Changes the target variable to CHR based on computer algorithm without confirmation by Comenzo (2012) with clarifications to CR criteria (ie, negative serum and urine immunofixation and iFLC<ULN and normalization of FLC ratio), the rest of the estimand remain the same
c) Changes which strategy is employed for the intercurrent event of subsequent non-cross resistant, anti-plasma cell therapy. If there is a disease assessment that demonstrates CHR before PD after the start of subsequent non-cross resistant, anti-plasma cell therapy, the subject will be considered as a responder (treatment policy strategy)
d) Hematologic response-evaluable set includes subjects who have a confirmed diagnosis of amyloidosis and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post- baseline disease assessment.

Source: Attachment TEFRESP01, Attachment TEFRESP01A, Attachment TEFRESP01C, Attachment TEFRESP01F, Attachment TEFRESP01G, Attachment TEFRESP01H, Attachment TEFRESP01I

Table 21 Summary of Overall Best Confirmed Hematologic Response Based on IRC Assessment; Intent-to-treat Analysis Set (Study 54767414AMY3001)

	CyBorD		Dara SC + CyBorD			
	n (%)	95% CI[a] for %	n (%)	95% CI[a] for %	Odds Ratio (95% CI)[b]	P-value[c]
Analysis set: intent-to-treat	193		195			
Best response category						
Complete response (CR)	35 (18.1%)	(13.0%, 24.3%)	104 (53.3%)	(46.1%, 60.5%)	5.13 (3.22, 8.16)	<0.0001
Very good partial response (VGPR)	60 (31.1%)	(24.6%, 38.1%)	49 (25.1%)	(19.2%, 31.8%)		
Partial response (PR)	53 (27.5%)	(21.3%, 34.3%)	26 (13.3%)	(8.9%, 18.9%)		
No response (NR)	38 (19.7%)	(14.3%, 26.0%)	8 (4.1%)	(1.8%, 7.9%)		
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)		
Not evaluable (NE)	7 (3.6%)	(1.5%, 7.3%)	8 (4.1%)	(1.8%, 7.9%)		
VGPR or better (CR + VGPR)	95 (49.2%)	(42.0%, 56.5%)	153 (78.5%)	(72.0%, 84.0%)	3.75 (2.40, 5.85)	<0.0001
Overall response (CR + VGPR + PR)	148 (76.7%)	(70.1%, 82.5%)	179 (91.8%)	(87.0%, 95.2%)		

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: CI = confidence interval; NE = not estimable.
[a] 95% CIs are based on Clopper-Pearson exact test.
[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl>=60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for Dara SC + CyBorD.
[c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.

[TEFRESP01.RTF] [\\WILBTIA\WILBTIA02\JNJ JJAMY3001_U\DBL\TLF\TEFRESP01.SAS] 16JUN2020, 14:42

The MAH has updated the results as of clinical cut-off 13 November 2020, (Table 25) with an additional 9 months of follow-up, resulting in a HemCR of 59.0% vs. 19.2%, for D-VCd vs. VCd, respectively; odds ratio [95% CI]=5.90 (3.72, 9.37); p<0.0001).

Table 22 Summary of Overall Best Confirmed Hematologic Response Based on IRC Assessment (Cutoff: 13Nov2020); Intent-to-treat Analysis Set (Study 54767414AMY3001)

	CyBorD		Dara SC+CyBorD			
	n (%)	95% CI for %	n (%)	95% CI[a] for %	Odds Ratio (95% CI)[b]	P-value[c]
Analysis set: intent-to-treat	193		195			
Best response category						
Complete response (CR)	37 (19.2%)	(13.9%, 25.4%)	115 (59.0%)	(51.7%, 66.0%)	5.90 (3.72, 9.37)	<0.0001
Very good partial response (VGPR)	60 (31.1%)	(24.6%, 38.1%)	39 (20.0%)	(14.6%, 26.3%)		
Partial response (PR)	51 (26.4%)	(20.4%, 33.2%)	25 (12.8%)	(8.5%, 18.3%)		
No Response (NR)	38 (19.7%)	(14.3%, 26.0%)	8 (4.1%)	(1.8%, 7.9%)		
Progressive disease (PD)	0	(NE, NE)	0	(NE, NE)		
Not evaluable (NE)	7 (3.6%)	(1.5%, 7.3%)	8 (4.1%)	(1.8%, 7.9%)		
VGPR or better (CR+VGPR)	97 (50.3%)	(43.0%, 57.5%)	154 (79.0%)	(72.6%, 84.5%)	3.74 (2.39, 5.86)	<0.0001
Overall response (CR+VGPR+PR)	148 (76.7%)	(70.1%, 82.5%)	179 (91.8%)	(87.0%, 95.2%)		

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: CI = confidence interval; NE = not estimable.
[a] 95% CIs are based on Clopper-Pearson exact test.
[b] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl>=60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for Dara SC + CyBorD.
[c] P-value from the Cochran Mantel-Haenszel Chi-Squared test.

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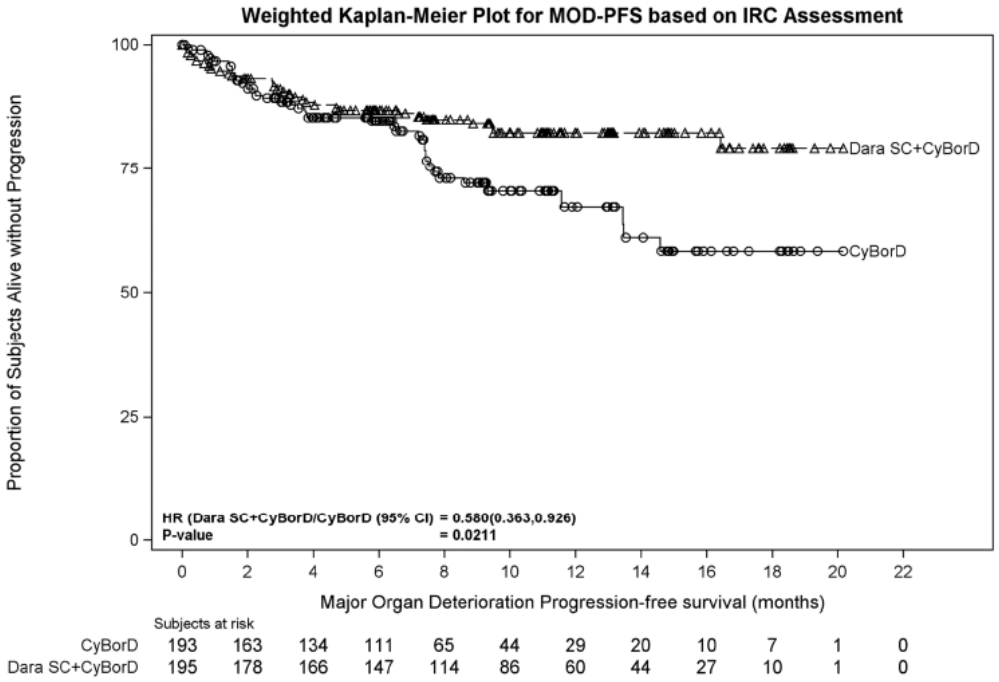
Secondary endpoints

Major Organ Deterioration Progression-free Survival

Figure 15 Inverse Probability Weighted Kaplan-Meier Plot for Major Organ Deterioration Progression-free Survival (MOD-PFS) Based on IRC Assessment; Intent-to-treat Analysis Set (Study 54767414AMY3001)



Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[GEFMODPFS_IPCW.RTF] [\\WILBTIA\WILBTIA02\JNJ JJAMY3001_U\DBL\TLF\TEFMODPFS_IPCW01.SAS.SAS] 04AUG2020, 14:43

Table 23 Summary of Primary, Sensitivity and Supplementary Analysis of MOD-PFS

	Hazard ratio (95% CI) [daratumumab SC+CyBorD vs CyBorD]	P-value
Primary Analysis		
IRC assessment- IPCW (stepwise procedure used to select baseline covariates and time-dependent covariates for weight calculation)	0.58 (0.36,0.93)	0.0211
Sensitivity Analyses		
IRC assessment – naïve censoring of subsequent therapy[a]	0.58 (0.37, 0.92)	0.0198
Investigator assessment– naïve censoring of subsequent therapy[a]	0.54 (0.34, 0.85)	0.0063
Supplementary Analyses		
IRC assessment– without censoring subsequent therapy[a, b]	0.57 (0.37, 0.87)	0.0094
IRC assessment- including subsequent therapy[a] as event determined by IRC (MOD-EFS)[b]	0.39 (0.27, 0.56)	<0.0001

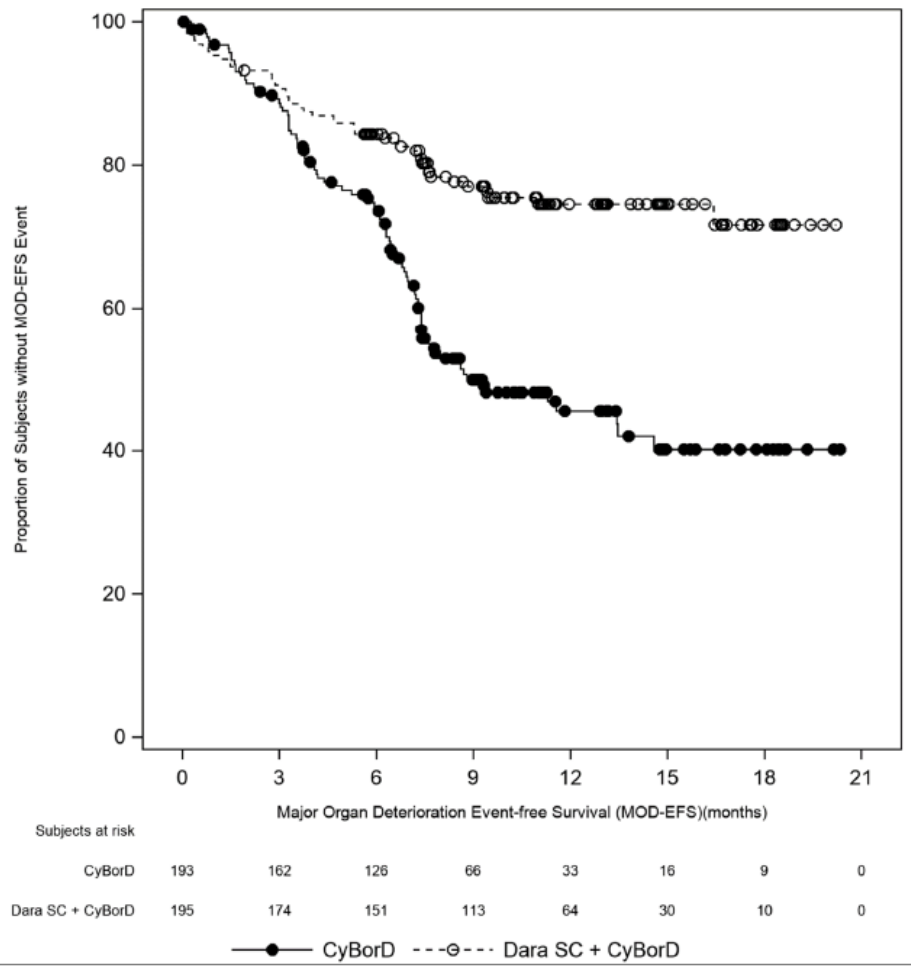
[a] refer to subsequent non-cross resistant, anti-plasma cell therapy.
[b] Based on stratified analysis. Analysis is stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl >=60 mL/min or CrCl <60 mL/min) as randomized.

Source: Attachment TEFMODPFS_IPCW01, Attachment TEFMPFS02, Attachment TEFMPFS02AZ, Attachment TEFMPFS01A, Attachment TEFMEFS02

Major Organ Deterioration Event-free Survival

The median MOD-EFS was 8.8 months for the CyBorD arm, but not reached in the dara SC+CyBorD arm (HR=0.39; 95% CI: 0.27, 0.56; nominal p-value <0.0001).

Figure 16 **Kaplan-Meier Plot for Major Organ Deterioration Event-free Survival (MOD-EFS) - Subsequent Non-cross Resistant Anti-Plasma Therapy Determined by IRC; Intent-to-treat Analysis Set (Study 54767414AMY3001)**



Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).

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Overall Survival

Table 24 **Summary of Overall Survival (OS); Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD
Analysis set: intent-to-treat	193	195
Overall survival (OS)		
Number of events (%)	29 (15.0%)	27 (13.8%)
Number of censored (%)	164 (85.0%)	168 (86.2%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	NE (15.44, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		0.7055
Hazard ratio (95% CI)[b]		0.90 (0.53, 1.53)
6-month survival rate % (95% CI)	88.8 (83.3, 92.5)	87.0 (81.4, 91.0)
12-month survival rate % (95% CI)	85.6 (79.3, 90.2)	85.6 (79.7, 89.9)
18-month survival rate % (95% CI)	76.9 (64.8, 85.3)	85.6 (79.7, 89.9)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on a log-rank test stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl >=60 mL/min or CrCl <60 mL/min) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl >=60 mL/min or CrCl <60 mL/min) as randomized. A hazard ratio <1 indicates an advantage for Dara SC + CyBorD.

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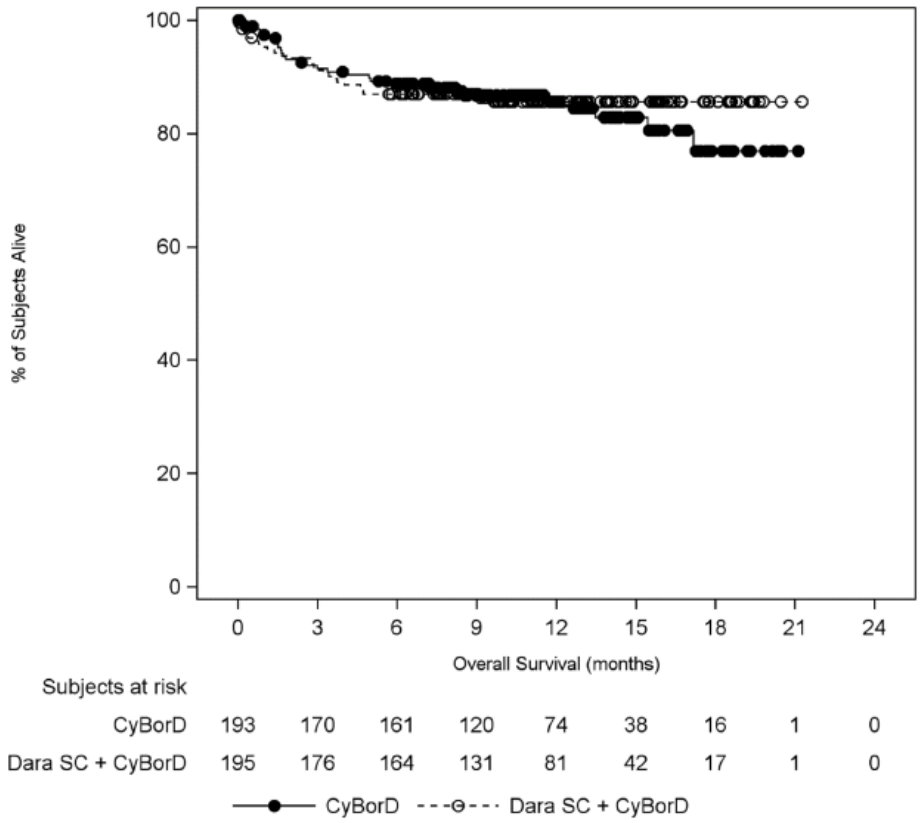
Figure 17 **Kaplan-Meier Plot for Overall Survival (OS); Intent-to-treat Analysis Set (Study 54767414AMY3001)**



Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).

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Other secondary endpoints

Hematologic CR at 6 and 12 Months

The CHR rate was higher in the dara SC + CyBorD group compared with the CyBorD at 6 months: 49.7% vs 14.0%, respectively, (odds ratio=6.09 with 95% CI: 3.70, 10.03; p<0.0001). At 12 months the CHR rate was: 28.2% vs 7.3%, respectively, (odds ratio=5.24 with 95% CI: 2.77, 9.90; p<0.0001).

Time to Hematologic Response

Table 25 **Summary of Time to Hematologic Response Based on IRC Assessment; Hematologic Response-evaluable Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD
Analysis set: Responders in Intent-to-treat	148	179
Time to complete hematologic response, days[a]		
N	35	104
Mean (SD)	96.37 (78.666)	82.92 (57.660)
Median	85.00	60.00
Range	(14.0; 340.0)	(8.0; 299.0)
Time to VGPR or better, days[b]		
N	95	153
Mean (SD)	47.13 (42.071)	36.54 (44.499)
Median	25.00	17.00
Range	(8.0; 171.0)	(5.0; 336.0)
Time to PR or better, days[c]		
N	148	179
Mean (SD)	32.52 (29.470)	19.63 (21.080)
Median	23.00	11.00
Range	(7.0; 170.0)	(5.0; 145.0)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: VGPR or better includes CR and VGPR. PR or better includes CR, VGPR and PR.
Hematologic response-evaluable set includes subjects who have a confirmed diagnosis of amyloidosis and measurable disease at baseline or screening visit. In addition, subjects must have received at least 1 administration of study treatment and have at least 1 post- baseline disease assessment.
[a] Time from randomization date up to the first response of complete hematologic response is summarized.
[b] Time from randomization date up to the first response of VGPR or better, whichever is the earliest, is summarized.
[c] Time from randomization date up to the first response of PR or better, whichever is the earliest, is summarized.
[d] Time from randomization date up to the first response of VGPR is summarized.
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Duration of Hematologic Response

With a median follow-up of 11.4 months, the median duration of CHR had not been reached in either treatment arm (range: 0.85+ to 17.5+ months for daratumumab SC+CyBorD; 0.03+ to 18.4+ months for CyBorD). Similarly, was the median duration of VGPR or better and duration of PR or better in both treatment arms not reached as the majority of responders continued to respond without hematologic progression.

Time to Subsequent Non-cross Resistant Anti-plasma Cell Therapy

More subjects in the CyBorD arm (43%) received subsequent non-cross resistant anti-plasma cell therapy compared with subjects in the daratumumab SC+CyBorD arm (10.8%). The median time to subsequent non-cross resistant anti-plasma cell therapy was not reached for subjects in the daratumumab SC+CyBorD arm and was 10.38 months in the CyBorD arm (HR=0.20, 95% CI: 0.12, 0.32; p<0.0001) (see table below).

Table 26 **Summary of Time to First Subsequent Non-cross Resistant Anti-plasma Cell Therapy; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD
Analysis set: intent-to-treat	193	195
Time to first subsequent non-cross resistant anti-plasma cell therapy		
Number of events (%)	83 (43.0%)	21 (10.8%)
Number of censored (%)	110 (57.0%)	174 (89.2%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	6.31 (4.67, 6.87)	NE (16.62, NE)
Median (95% CI)	10.38 (8.34, NE)	NE (NE, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)
P-value[a]		<0.0001
Hazard ratio (95% CI)[b]		0.20 (0.12,0.32)
6-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	78.4 (71.5, 83.9)	96.0 (91.7, 98.1)
12-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	46.1 (37.2, 54.4)	87.0 (80.4, 91.4)
18-month subsequent non-cross resistant anti-plasma cell therapy free rate % (95% CI)	40.3 (29.6, 50.7)	83.6 (73.2, 90.2)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: CI = confidence interval; NE = not estimable.
[a] p-value is based on a log-rank test stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl>=60 mL/min or CrCl <60 mL/min) as randomized.
[b] Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A or List B), and renal function (CrCl>=60 mL/min or CrCl <60 mL/min) as randomized. A hazard ratio <1 indicates an advantage for Dara SC + CyBorD.
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FLC Response and Time to iFLC <ULN and iFLC ≤20 mg/L and dFLC <10 mg/L

Serum free light chains were measured weekly during Cycle 1 and Day 1 only of Cycle 2 and beyond. Median iFLC (daratumumab SC+CyBorD: 214 mg/L; CyBorD: 210 mg/L) and median dFLC (daratumumab SC+CyBorD: 200.3 mg/L; CyBorD: 185.7 mg/L) were similar at baseline in both treatment arms (Table 17).

Table 27 **Summary of Subject FLC Response and Time to iFLC<ULN, Time to iFLC <=20mg/L and Time to dFLC<10 mg/L Response; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: intent-to-treat	193	195
Number of Subjects Reach to iFLC < ULN response	70 (36.3%)	149 (76.4%)
Number of Subjects Reach to iFLC <= 20 mg/L response	39 (20.2%)	138 (70.8%)
Number of Subjects Reach to dFLC < 10 mg/L response	59 (30.6%)	125 (64.1%)
Time to iFLC < ULN response, days[a]		
N	70	149
Mean (SD)	50.33 (50.027)	35.69 (43.009)
Median	30.50	17.00
Range	(8.0; 340.0)	(5.0; 247.0)
Time to iFLC <= 20 mg/L response, days[b]		
N	39	138
Mean (SD)	53.44 (40.359)	47.87 (44.095)
Median	32.00	24.00
Range	(8.0; 150.0)	(5.0; 205.0)
Time to dFLC < 10 mg/L response , days[c]		
N	59	125
Mean (SD)	56.54 (44.990)	48.40 (53.325)
Median	56.00	29.00
Range	(8.0; 225.0)	(5.0; 343.0)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: iFLC = involved free light chain; dFLC = difference between involved and uninvolved free light chains; ULN = upper limit normal.
[a] Time from randomization date up to the first disease evaluation that subject's iFLC level reduction to less than upper limit normal, confirmed by a subsequent assessment is summarized.
[b] Time from randomization date up to the first disease evaluation that subject's iFLC level reduction to less than or equal to 20 mg/L, confirmed by a subsequent assessment is summarized.
[c] Time from randomization date up to the first disease evaluation that subject's dFLC level reduction to less than 10 mg/L, confirmed by a subsequent assessment is summarized.
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At the time of clinical cut-off, more subjects in the daratumumab SC+CyBorD arm had iFLC <ULN, iFLC <20 mg/L, and dFLC <10 mg/L response compared with those in the CyBorD arm (daratumumab SC+CyBorD vs CyBorD: iFLC <ULN: 76.4% vs. 36.3%; iFLC <20 mg/L: 70.8% vs. 20.2%; dFLC <10 mg/L: 64.1% vs. 30.6%; see table above).

Fifty one percent (198/388) of subjects in the overall study population had dFLC >180 mg/L at baseline: 47.5% of subjects in the daratumumab SC+CyBorD arm and 12.4% of subjects in the CyBorD arm achieved CHR. The median time to iFLC <ULN response, iFLC <20 mg/L response, and dFLC <10 mg/L response was shorter in the daratumumab SC+CyBorD arm compared with the CyBorD arm (daratumumab SC+CyBorD vs CyBorD: iFLC <ULN response: 17 vs 30.5 days; iFLC $\leq$20 mg/L: 24 vs 32 days; and time to dFLC <10 mg/L: 29 vs 56 days; see table above).

Organ responses

Table 28 Cardiac and Renal Response Rates

	Dara SC+CyBorD vs CyBorD	
	6-month Response Rate	**Odds ratio (95% CI)**
Cardiac Response Rate[a] (n=235 subjects)		
IRC assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	41.5% vs 22.2%	2.44 (1.35, 4.42)
IRC assessment without censoring for subsequent non-cross resistant anti-plasma cell therapy	41.5% vs 22.2%	2.44 (1.35, 4.42)
Investigator assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	39.8% vs 18.8%	2.92 (1.58, 5.40)
Investigator assessment without censoring for subsequent non-cross resistant anti-plasma cell therapy	39.8% vs 18.8%	2.92 (1.58, 5.40)
Renal Response Rate[b] (n=230 subjects)		
IRC assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	53.0% vs 23.9%	3.88 (2.15, 6.99)
IRC assessment without censoring for subsequent non-cross resistant anti-plasma cell therapy	53.8% vs 27.4%	3.34 (1.88, 5.94)
Investigator assessment with censoring for subsequent non-cross resistant anti-plasma cell therapy	45.3% vs 18.6%	3.97 (2.13, 7.41)
Investigator without censoring for subsequent non-cross resistant anti-plasma cell therapy	46.2% vs 22.1%	3.29 (1.81, 5.99)

[a]Cardiac response was based on NT-proBNP response (>30% and >300 ng/L decrease in subjects with baseline NT-proBNP >650 ng/L) or NYHA class response (>2 class decrease in subjects with baseline NYHA class 3 or 4) per Comenzo 2012 consensus criteria (Appendix 1).
[b]Renal response was defined as ≥30% decrease in proteinuria or proteinuria decreased to <0.5 g/24 hours in the absence of renal progression.

Source: Attachment TEFCRR01AZ, Attachment TEFCRR01Z, Attachment TEFCRR02AZ, Attachment TEFCRR02Z, Attachment TEFRRR01AZ, Attachment TEFRRR01Z, Attachment TEFRRR02AZ, Attachment TEFRRR02Z

Patient-reported Outcomes were evaluated using 3 PRO measures, the EORTC QLQ-C30, EQ-5D-5L, and SF-36v2. No statistically significant difference was observed between Dara SC CyBorD and CyBorD arm change from baseline or median time to improvement or worsening.

Ancillary analyses

Results of the subgroup analyses of CHR for the pre-specified subgroups are presented below:

Figure 18 **Forest Plot of Subgroup Analysis of Confirmed Complete Hematologic Response Rate Based on IRC Assessment; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

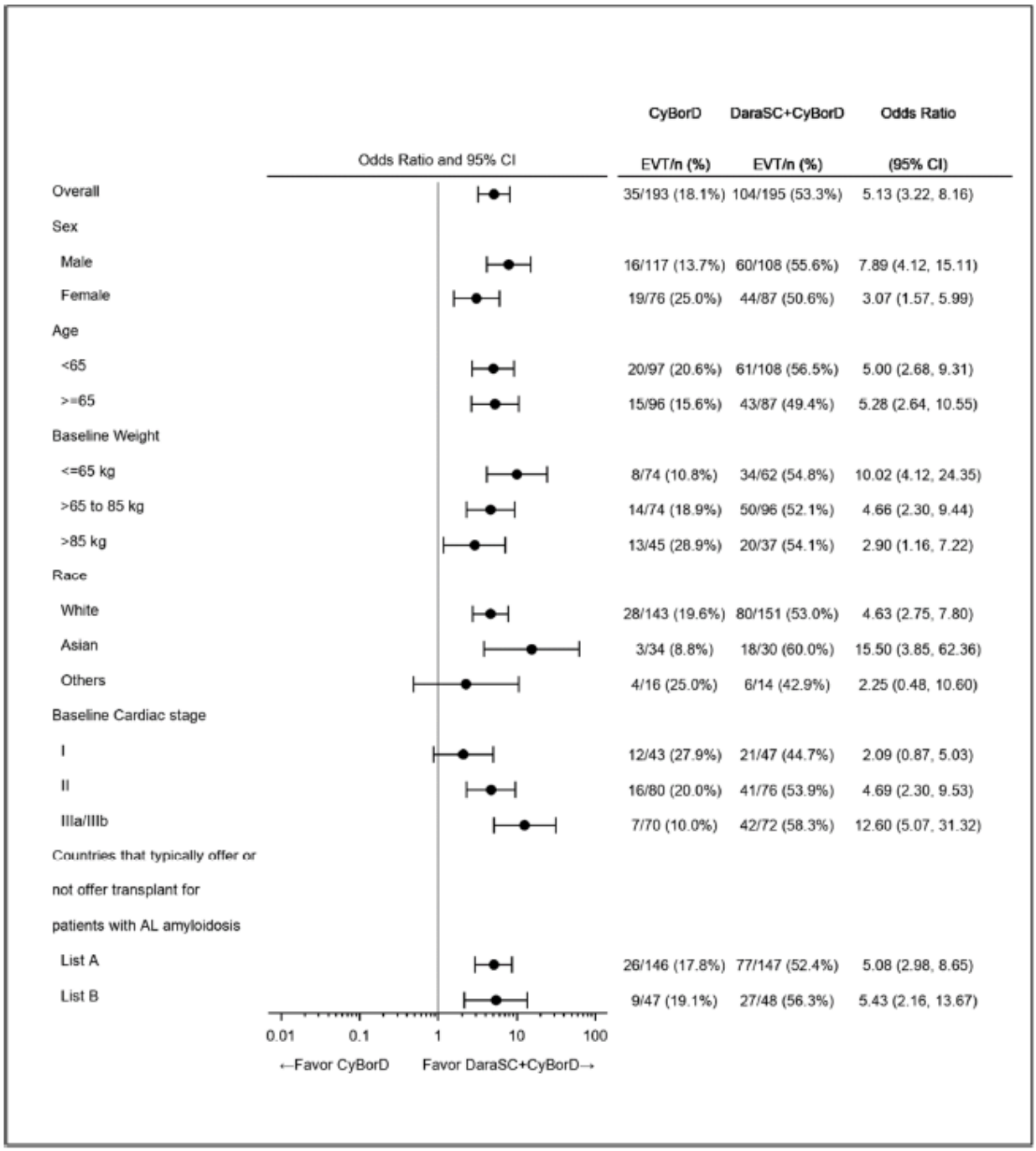
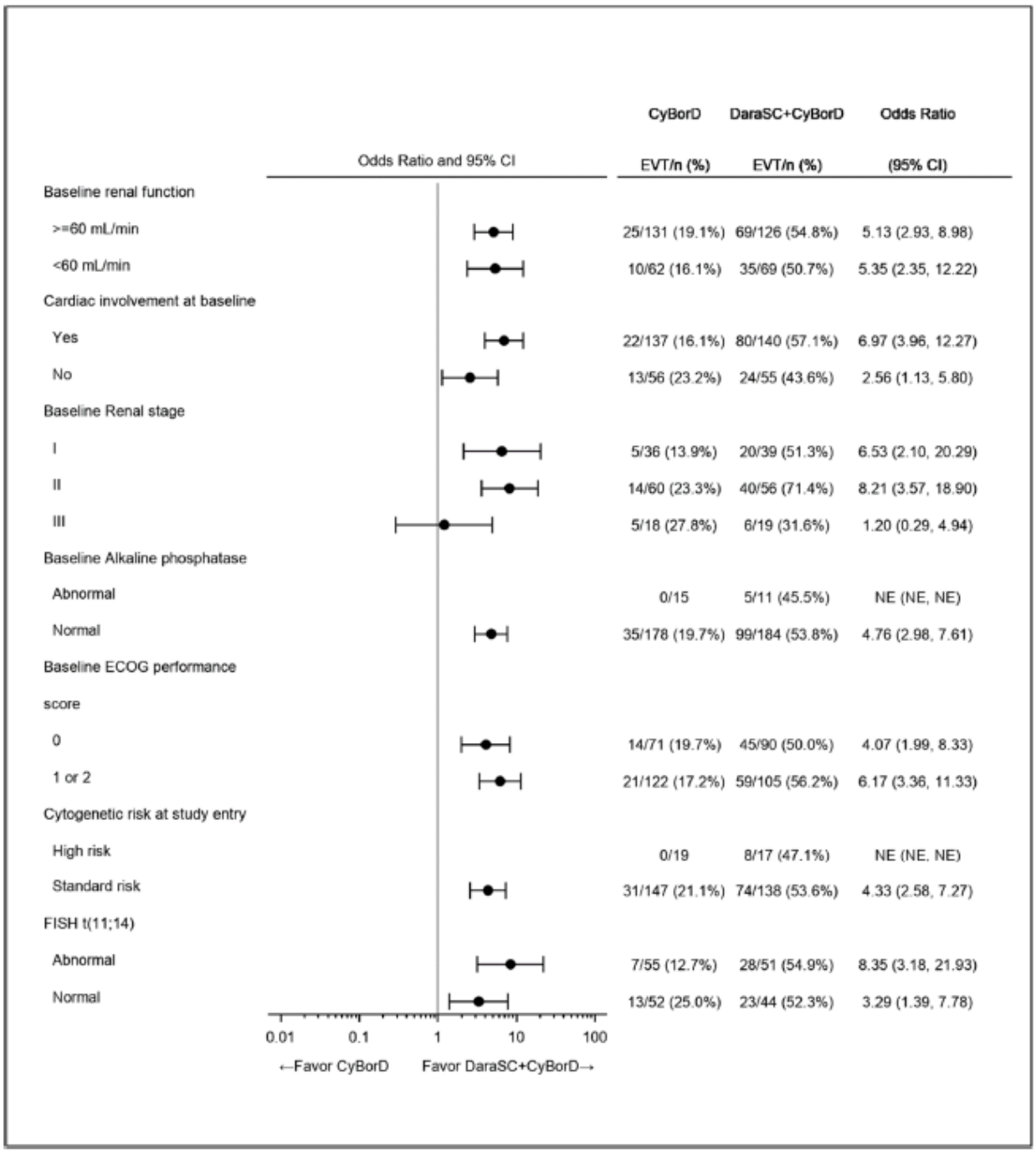


Figure 19 **Forest Plot of Subgroup Analysis of Confirmed Complete Hematologic Response Rate Based on IRC Assessment; Intent-to-treat Analysis Set (Study 54767414AMY3001)**



Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC=daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: CI = confidence interval; NE = not estimable.
Note: Cardiac stage IIIa/IIIb includes both IIIa subjects and subjects that are IIIa at randomization and progressed to IIIb at Cycle 1 Day 1. Details can be found in baseline disease characteristics table.
Note: Baseline renal stage is defined for subjects with baseline renal involvement.
List A - countries that typically offer autologous stem cell transplantation (ASCT); List B - countries that don't typically offer ASCT.
High risk is defined as: 1) by FISH testing: t (4; 14), t (14; 16), and 17p deletion; or 2) by Karyotype testing: t (4; 14), 17p deletion.
Overall: Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl>=60 mL/min or CrCl <60 mL/min)

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Efficacy in Poor Prognostic Groups

Table 29 Subgroup Analysis of Efficacy in Poor Prognostic Groups

	Complete Hematologic Response Rate Based on IRC Assessment			MOD-PFS Based on IRC Assessment Without Censoring Subsequent Non-cross Resistant Anti-plasma Cell Therapy		
	CyBorD	Daratumumab SC+CyBorD	Odds Ratio (95% CI)	CyBorD EVT/N Median (months)	Daratumumab SC+CyBorD EVT/N Median (months)	Hazard Ratio (daratumumab SC+CyBorD vs CyBorD) (95% CI)
FISH t(11;14)						
Absent	13/52 (25.0%)	23/44 (52.3%)	3.29 (1.39, 7.78)	18/52 14.59	5/44 NE	0.27 (0.10, 0.72)
Present	7/55 (12.7%)	28/51 (54.9%)	8.35 (3.18, 21.93)	12/55 NE	5/51 NE	0.41 (0.14, 1.17)
dFLC						
dFLC ≤180 mg/L	23/96 (24.0%)	56/94 (59.6%)	4.68 (2.51, 8.73)	21/96 NE	9/94 NE	0.39 (0.18, 0.86)
dFLC >180 mg/L	12/97 (12.4%)	48/101 (47.5%)	6.42 (3.12, 13.17)	32/97 (18.66, NE)	25/101 NE	0.67 (0.40, 1.13)
Baseline Cardiac Stage						
I	12/43 (27.9%)	21/47 (44.7%)	2.09 (0.87, 5.03)	7/43 NE	3/47 NE	0.33 (0.08, 1.28)
II	16/80 (20.0%)	41/76 (53.9%)	4.69 (2.30, 9.53)	21/80 NE	11/76 NE	0.55 (0.26, 1.14)
IIIa/IIIb	7/70 (10.0%)	42/72 (58.3%)	12.60 (5.07, 31.32)	25/70 NE	20/72 NE	0.66 (0.36, 1.19)

Source: Figure 6; Figure 7; Attachment TEFFLC03Z; Attachment TEFMPFS01F1; Attachment TEFMPFS01F2; Attachment TEFRESP01K1; Attachment TEFRESP01K2

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30 Summary of Efficacy for trial AMY3001

Title: A randomized phase 3 study to evaluate the efficacy and safety of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (Dara+CyBorD) Compared with CyBorD in newly diagnosed systemic AL Amyloidosis		
Study identifier	AMY3001	
Design	Open-label, multicenter phase 3 study to evaluate the effect of daratumumab in combination with CyBorD with CyBorD alone in newly diagnosed amyloid light chain amyloidosis.	
	Duration of main phase:	FPI 17 April 2018; data cut off 14-Febr-2020; ongoing Approximately 2.35 years
	Duration of Run-in phase:	FPI 10 October 2017, LPI 13 April 2018; ongoing.
	Duration of Extension phase:	NA
Hypothesis	Superiority	

Treatments groups	CyBorD		Cyclophosphamide 300 mg/m2, oral or IV weekly on Days 1, 8, 15, 22, per 28-day cycle for a maximum of 6 cycles. Bortezomib 1.3 mg/m2, SC weekly on Days 1, 8, 15, 22, per 28-day cycle for a maximum of 6 cycles. Dexamethasone 40 mg weekly on Days 1, 8, 15, 22.
	D + CyBorD		Daratumumab SC 1800 mg once weekly C1 +2, once every other week C3 to C6 in combination with CyBorD. From C7 and beyond daratumumab was given as monotherapy every 4 weeks until PD, start of subsequent therapy, or a maximum of 2 years from the start of the study.
Endpoints and definitions	Primary Endpoint	CHR rate	The proportion of subjects who achieve a complete hematologic response, ie.: negative serum and urine IFE, involved free light chain level decrease to less than the upper limit of normal, and normal free light chain ratio.
	Secondary Endpoint	MOD-PFS	The time from the date of randomization to either death, clinical manifestation of end stage cardiac failure, - renal failure or hematologic PD, whichever occurs first
	Secondary Endpoint	OS	The time from the date of randomization to death.
	Secondary Endpoint	Hematologic VGPR or better rate	The proportion of subjects who achieve a confirmed hem CR or VGPR.
	Secondary Endpoint	Time to CHR	The time between the date of randomization and the first efficacy evaluation that the subject has met all criteria for hematologic CR.
	Secondary Endpoint	Cardiac/renal response rate at 6 months	The proportion of cardiac/renal response-evaluable subjects who achieved cardiac response at 6 months (ie, initial or confirmation is within 6 +/- 1 months), per consensus guideline.
Database lock	15 May 2020, clinical cut-off date: 14 February 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	CyBorD	Dara SC+CyBorD
	Number of subjects	193	195
	Overall CHR (%)	18.1	53.3
	95% CI	13.0; 24.3	46.1; 60.5

	MOD-PFS (median)	Median not reached Number of events: 53 (27.5%)	Median not reached Number of events: 34 (17.4%)
	95% CI	NE	NE
	Overall Survival	Median not reached Number of events: 29 (15.0%)	Median not reached Number of events: 27 (13.8%)
	95% CI	NE	NE
	Median time to CHR (days)	85.0	60.0
	Range (days)	14.0 - 340.0	8.0 - 299.0
	Median time to hematologic VGPR or better (days)	25	17
	Range (days)	8 to 171	5 to 336
Effect estimate per comparison	Primary endpoint: Overall CHR	Comparison groups	Dara SC+CyBorD vs CyBorD
		Odds Ratio	5.13
		95% CI	3.22, 8.16
		P-value	<0.0001
	Secondary endpoint: MOD-PFS	Comparison groups	Dara SC+CyBorD vs CyBorD
		Hazard Ratio	0.580
		95% CI	0.363, 0.926
		P-value	0.0211
	Secondary endpoint: MOD-EFS	Comparison groups	Dara SC+CyBorD vs CyBorD
		Hazard Ratio	0.39
		95% CI	0.27, 0.56
		P-value	<0.0001
	Secondary endpoint: Overall Survival	Comparison groups	Dara SC+CyBorD vs CyBorD
		Hazard Ratio	0.91
		95% CI	0.54, 1.53
		P-value	0.7140
	Secondary endpoint: Cardiac Response Rate at 6 months	Comparison groups	Dara SC + CyBorD
		Odds Ratio	2.44
		95% CI	1.35, 4.42
		P-value	0.0029
	Secondary endpoint: Renal Response Rate at 6 months	Comparison groups	Dara SC + CyBorD
		Odds Ratio	3.34
		95% CI	1.88, 5.94
		P-value	0.0029

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The current marketing application includes one randomized, open-label, active controlled Phase 3 study AMY3001 for newly diagnosed AL amyloidosis:

- A Randomized Phase 3 Study to evaluate the efficacy and safety of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared with CyBorD in newly diagnosed systemic AL amyloidosis.

The following indication was initially proposed:

- Daratumumab is indicated for the treatment of adult patients with systemic light chain (AL) amyloidosis.

Clinical data cut-off for the study was February 2020. An additional 9 months of data were requested and provided during the assessment procedure (cut-off 13 November 2020). Eligible patients were ≥ 18 years of age with a newly diagnosed AL (light chain) amyloidosis and with ECOG 0-2. Patients had to have measurable hematologic disease, at least one affected organ, cardiac Stage I-IIIA (based on the modified Mayo 2004 Cardiac Staging), and NYHA Class I-IIIA. Patients with NYHA Class IIIB and IV were excluded. The MAH has amended the wording of indication to reflect that all patients received CyBorD as backbone therapy (see below). The fact that all patients should have at least one organ impacted, and the exclusion of patients with NYHA classification IIIB and IV is adequately reflected in the SmPC, Section 5.1. Patients were randomised 1:1 to receive a standard regimen CyBorD (cyclophosphamide 300 mg/m^2 oral or IV, bortezomib 1.3 mg/m^2 SC, and dexamethasone 40 mg oral or IV) on Days 1, 8, 15, and 22 of each 28-day cycle with or without a fixed dose of daratumumab 1.800 mg SC once weekly from weeks 1 to 8 (Cycles 1-2), once every 2 weeks from weeks 9 to 24 (Cycles 3-6), then once every 4 weeks until disease progression or a maximum of two years. The daratumumab SC dose and schedule is based on previous data from Study MMY3012 and is approved in Multiple Myeloma. The CyBorD was given for a maximum of 6 cycles.

The study design was appropriate as was the primary endpoint, overall CHR rate and secondary endpoints. The overall CHR is regarded as an appropriate primary endpoint for phase III trials employing chemotherapeutic agents for newly diagnosed untreated AL amyloidosis patients without advanced cardiac involvement, according to international consensus recommendations (Comenzo 2012, Palladini 2012). Indeed, even if surrogacy for OS has not been demonstrated, there seems to be a clear association between CHR and long-term outcomes (MOD-PFS and OS), i.e. particularly significant decreases in the pathologic or involved FLC (iFLC) are associated with better survival. There were several secondary endpoints, such as MOD-PFS, OS, hematologic VGPR or better, time and duration of hematologic response. The protocol was amended twice, based on request from the FDA, dyspnoea was removed from the MOD-PFS definition and IPCW was applied as the primary method. With reference to Amendment 3 a new secondary endpoint was added: "Complete Haematologic Response at 6 months". The MAH has clarified that this endpoint was specified as one of the secondary endpoints in the original SAP and later added in the protocol, at Amendment 3, for appropriate interpretation of results and meaningful comparison to existing literature (as this endpoint is widely reported in the literature in subjects with newly diagnosed AL amyloidosis). In addition, the MAH noted that HemCR rate at 6 months was analysed, as a supportive endpoint, only after the analysis of the primary efficacy endpoint was conducted, to ensure the appropriate statistical interpretation of the results. Even if it relates to secondary endpoints and not the primary efficacy endpoint at amendment 3 (10 October 2019) the aggregated PFS (both haematological and organ) was split into a specific HemPFS which was moved to an exploratory objective. MOD-PFS was retained as a secondary endpoint which seems reasonable. According to the MAH, the split was aimed to an appropriate

interpretation of results and for meaningful indirect comparison to existing literature and had no impact on the final outcomes. Even if amendment 3 appears to have been implemented once all patients were recruited in the study bearing in mind that it did not affect the primary endpoint but only exploratory analyses of secondary/exploratory endpoints, it is acknowledged that this change had not compromised the study results.

The clinical response was evaluated based on International Consensus Criteria as determined by the Independent Review Committee (IRC) and validated by computerised algorithm with 3 stratification factors: cardiac stage (I, II, IIIa, European Modification of Mayo 2004 Cardiac Stage), countries that typically offer autologous stem cell transplant (ASCT) for patients with light chain (AL) amyloidosis (list A) and those who do not (list B), and renal function (CrCl ≥ 60 ml/min and < 60 ml/min).

Efficacy data and additional analyses

A total of 388 patients were randomized, 195 to dara SC + CyBorD and 193 to CyBorD. The median age was 62 and 64 years respectively with a similar range, and 44.6% and 49.7% respectively being ≥ 65 years. The median time since diagnosis was 43 days, with a wide range (5;1611). A total of 8 subjects had a diagnosis of AL amyloidosis for more than 2 years prior to study inclusion, 5 of these had AL amyloidosis for 1000 days and 1 subject had AL amyloidosis for 865 days. These subjects had more localised manifestations of the disease and did not receive any treatment. They also met the eligibility criteria for the study AMY 3001.

The majority of subjects (79.1%) had lambda free light chain disease and the median number of organs involved at baseline was 2 (range 1;6) in both treatment arms. The most common organs involved were cardiac (71.4%) and renal (59.0%), being similar in the dara SC + CyBorD and CyBorD groups. Patients had NYHA class I (50.3%), II (42.8%) and IIIA (7.0%), according to the revised Mayo cardiac stage, 23.2% had stage I, 40.2% had stage II and 34.5% had stage IIIA with a balanced allocation for the two treatment arms. In general baseline demographic – and disease characteristics were well balanced between the two treatment arms. However, the analysis by ECOG at baseline (i.e. ECOG PS 0 vs. ECOG PS 1 or 2) could be considered somewhat misleading, since the results in the group with the worst status (ECOG 2) might be diluted by the results in the higher represented group of patients with ECOG PS 1. Even if there are few patients enrolled with ECOG PS 2 (total of 35 patients) the MAH was invited to present data by ECOG status separately. These data have been presented and the reported percentages of response remain similar among all the groups, including the very small one of patients with ECOG PS 2 (n=16).

The MAH has narrowed the previous broad indication to: "DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis." This new indication reflects the study population of the AMY3001 study and is acceptable. The fact that all patients had one or more organ affected and that none of the included patients had NYHA IIIB or higher and very few Mayo cardiac stage IIIB has also been adequately reflected in the SmPC, Section 5.1. The SC formulation of daratumumab is endorsed.

With a median follow-up of 11.4 months, an overall CHR rate of 53.1% in the dara SC+CyBorD arm compared with 18.1% in the CyBorD arm (odds ratio=5.13; 95% CI: 3.22, 8.16; p<0.0001) is considered clinically relevant and meaningful in this group of newly diagnosed AL amyloidosis with organ involvement. Pre-planned sensitivity analysis of CHR based on investigator evaluation and computerised algorithm, showed consistent results. The CHR rates were consistent for the pre-planned stratification factors (cardiac stage, renal function and whether countries offer ASCT or not), in favour of the dara SC+CYBorD arm compared with the CyBorD arm. Analysing poor prognostic groups: the presence of t(11;14) analysed by FISH, Cardiac stage III and dFLC > 180 mg/L indicated a trend towards a beneficial effect of the Dara SC+CyBorD arm compared with CyBorD, however, the interpretation of the results in the subgroups are

hampered by the small sample size and no statistically significant difference could be demonstrated. However, the median duration of CHR has not been reached at the time of clinical cut-off in either treatment groups. Fewer patient in the daratumumab SC + CyBorD arm compared with the CyBorD alone arm received subsequently ASCT. Besides from geographical differences in the use of ASCT, one of the reasons to this difference could be the higher HemCR rate in the dara SC+CyBorD arm, and the fact that subjects in the dara SC+ CyBorD arm continued daratumumab beyond the 6 cycles of CyBorD. The VGPR or better rate, was significantly higher in the Dara SC + CyBorD group compared with CyBorD alone, 78.5% vs. 49.2%, (Odds ratio 3.75; 95% CI:2.40, 5.85; p< 0.0001). The median time to overall CHR was 60 days for the dara SC+CyBorD arm and 85 days for the CyBorD arm.

Time to response is an important variable, for subjects who achieved CHR, the median time to CHR was 60.0 days in the dara SC+CyBorD arm and 85.0 days in the CyBorD arm, respectively. For subjects who achieved ≥VGPR, the median time to ≥VGPR was 17 days in the dara SC+CyBorD arm and 25 days in the CyBorD arm.

Measures of and time to deep hematologic responses were superior for daratumumab SC+CyBorD compared with CyBorD alone when assessed by:

- iFLC <ULN (76.4% vs. 36.3%; time to iFLC <ULN: 17 vs. 30.5 days),
- iFLC ≤20 mg/L (70.8% vs. 20.2%; time to iFLC ≤20 mg/L: 24 vs. 32 days), and
- dFLC <10 mg/L (64.1% vs. 30.6%; time to dFLC <10 mg/L: 29 vs. 56 days)

This is considered relevant information since significant decreases in the pathologic or involved FLC (iFLC) are associated with better survival in this patient population (Comenzo et al., 2012). The depth and rapidity of hematologic responses to daratumumab SC plus CyBorD is noticed. Although the Kaplan-Meier curves for MOD-PFS separates after 6.5 months, MOD-PFS is not a standard acceptable endpoint in AL amyloidosis and the data are not mature with only 43% of the 200 planned events at the time of analysis. It could however be of value from a clinical point of view, but the IPW method used is regarded as hypothetical, indicating the results should be considered exploratory.

As a supplement to MOD-PFS, Major Organ Deterioration Event-free Survival (MOD-EFS) was introduced. Subjects may switch to subsequent non-cross resistant, anti-plasma cell therapy due to insufficient hematologic response or aggravating organ function. The median MOD-EFS was 8.8 months for the CyBorD arm, but not reached in the dara SC+CyBorD arm (HR=0.39; 95% CI: 0.27, 0.56; nominal p-value <0.0001). As of the clinical cut-off of 14 February 2020, OS data were not mature. The majority of early deaths were observed in subjects with baseline cardiac involvement. Even if CHR is a relevant primary endpoint and the observed effect likely to translate into clinically relevant benefit, OS data are also of noticeable importance. However according to published data (Palladini 2015) 55% of subjects with newly diagnosed AL amyloidosis and treated with CyBorD, are estimated to survive 5 years. The updated OS data of further 9 months of follow-up are still immature and the MAH should provide the primary and final analyses of OS as a post-authorisation efficacy study. A trend towards improvement of cardiac – and renal 6-month response was noted, from a clinical point of view it is interesting whether the beneficial effect of achieving complete hematologic response can affect the organ response and diminish the organ failure. The MAH has updated the results with a further period of 9 months of follow-up. The updated data are consistent with the primary analysis.

In summary, based on the data submitted daratumumab SC + CyBorD combination appears to be an adequate option for treatment of patients with newly diagnosed AL amyloidosis.

2.4.4. Conclusions on the clinical efficacy

Light chain (AL) amyloidosis is a rare, complex disease associated with significant morbidity and mortality. The prognosis for AL amyloidosis is associated with early diagnosis, treatment, and the extent of organ involvement. The achievement of a rapid and deep CHR is the essential goal of therapy in AL amyloidosis. It has been demonstrated that the depth of hematologic response is associated with organ improvement and better survival in patients with AL amyloidosis (Palladini 2012). However, there is no licensed therapy regimen for AL amyloidosis and several multiple myeloma regimens have been introduced. The CyBorD regimen is recommended by the NCCN and consensus guidelines and is the preferred regimen for newly diagnosed AL amyloidosis as it has less cardiac and renal toxicities than the IMiDs and other combinations.

Most studies using CyBorD in AL amyloidosis are retrospective, the largest in front line AL amyloidosis with HemCR of 21%, VGPR of 22%, cardiac response achieved in 17% of patients, while renal response was observed in 25% of the patients.

An overall CHR rate of 53.1% in the dara SC+CyBorD arm compared with 18.1% in the CyBorD arm (odds ratio=5.13; 95% CI: 3.22, 8.16; p<0.0001) is therefore considered clinically relevant and meaningful in this group of newly diagnosed AL amyloidosis with organ involvement. The MAH has amended the wording of indication to: "*DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis*" therefore adequately reflecting the patients included in the AMY3001 study (i.e. newly diagnosed AL amyloidosis patients) and also the CyBorD backbone treatment.

OS data are still immature and although thus far do not suggest a detrimental effect of dara SC + CyBorD on OS, which is reassuring, provision of final OS data is considered key to benefit risk. In this regard the MAH has committed to provide the primary and final analyses of OS from study AMY3001 as a post authorization commitment.

The following measures are considered necessary to address issues related to efficacy:

The MAH should provide the final overall survival analysis as a post-authorisation efficacy study by 31 July 2025. If a statistically significant difference in OS is demonstrated after adjusting for multiple data looks and multiplicity, the MAH will submit OS data for the agency's review. Otherwise, the MAH will share the interim OS results and the final OS data will be provided at the time of the final analysis as an Annex II condition.

2.5. Clinical safety

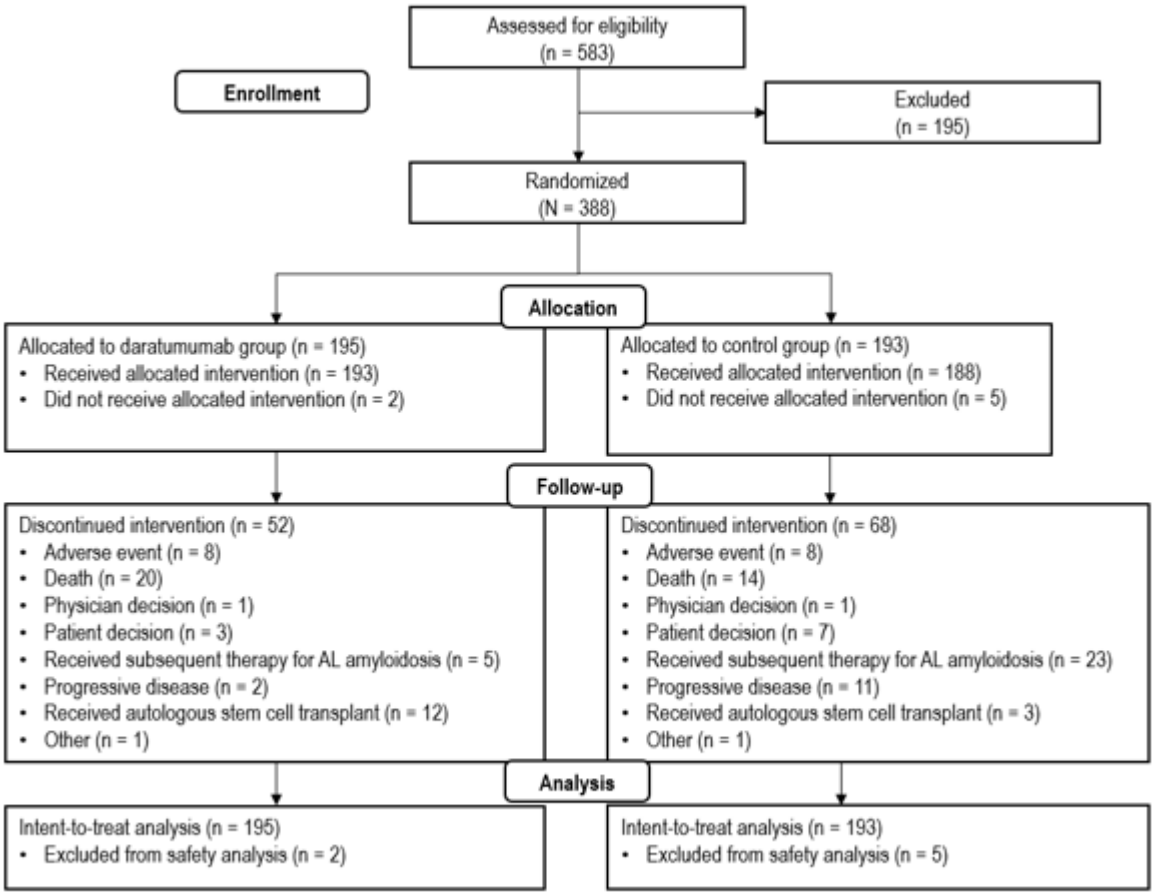
Introduction

For this application, the safety of daratumumab SC in combination with CyBorD (cyclophosmamide-bortezonib-dexamethasone) in subjects with newly diagnosed AL amyloidosis is based on results from the Phase 3 Study AMY3001. Safety data and exposure were evaluated in the Safety Analysis Set, which included all randomized subjects who received at least 1 administration of any study treatment (partial or complete). Safety analyses were based on the safety analysis population, which included subjects treated in the Safety Run-in and randomized parts of the study. At the time of the clinical cut-off (14 February 2020), 388 subjects across 22 countries were randomized to receive treatment with either daratumumab SC-CyBorD or CyBorD. There were 193 and 188 subjects treated with daratumumab SC-CyBorD or CyBorD, respectively.

Due to the study design, daratumumab was continued beyond the initial 6 cycles of CyBorD, resulting in a longer median duration of exposure for subjects in the daratumumab SC-CyBorD arm compared with the

CyBorD arm. TEAEs were to be reported up to 30 days after last dose of study treatment, thus TEAE rates should be interpreted in the context of the longer median exposure duration for subjects in the daratumumab SC-CyBorD arm compared with the CyBorD arm. To provide this perspective, AEs are summarized over the total duration of the study as well as by Cycles 1-2 (during which a similar number of subjects received treatment), Cycles 3-6 (during which more subjects discontinued treatment in the CyBorD arm) and beyond Cycle 7 (during which only subjects in the daratumumab SC-CyBorD arm received study treatment. Additionally, exposure adjusted evaluation of TEAEs was performed.

Table 31 **Subject Disposition as of Clinical Cutoff Date (14 February 2020); Study 54767414AMY3001**



Source: Mod5.3.5.1/AMY3001/Tab3

Safety Run-in phase: Given the potential safety concern with regards to the use of IV daratumumab in the amyloidosis population (i.e., volume overload), this study utilised the daratumumab SC formulation. Patients with newly diagnosed AL amyloidosis were still at risk of developing AEs attributable to hypervolemia (e.g., dyspnea, peripheral edema) secondary to amyloid-induced cardiac or renal insufficiency. Additionally, daratumumab had not been co-administered with CyBorD. Therefore, prior to the start of the randomized portion of the study to evaluate daratumumab SC in combination with CyBorD, a Safety Run-in was conducted and safety evaluation was planned to be assessed after at least 10 patients had received at least 1 cycle of treatment. Safety evaluation was performed by the sponsor and external haematologists after 15 patients had received at least 1 cycle of treatment.

All 28 patients in the Safety Run-in cohort had 1 or more TEAEs, and 75% had 1 or more Grade 3 or 4 TEAEs.

Table 32 Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; All Treated Safety Run-in Analysis Set (Study 54767414AMY3001)

	Dara SC + CyBorD Run-in n (%)
Analysis set: all treated safety run-in	28
Subjects with 1 or more serious TEAEs	12 (42.9%)
System organ class Preferred term	
General disorders and administration site conditions	4 (14.3%)
Fatigue	1 (3.6%)
Multiple organ dysfunction syndrome	1 (3.6%)
Oedema	1 (3.6%)
Oedema peripheral	1 (3.6%)
Peripheral swelling	1 (3.6%)
Infections and infestations	4 (14.3%)
Cellulitis	2 (7.1%)
Pneumonia	2 (7.1%)
Peritonitis	1 (3.6%)
Upper respiratory tract infection	1 (3.6%)
Injury, poisoning and procedural complications	3 (10.7%)
Fall	3 (10.7%)
Renal and urinary disorders	3 (10.7%)
Acute kidney injury	3 (10.7%)
Nephrolithiasis	1 (3.6%)
Gastrointestinal disorders	2 (7.1%)
Diarrhoea	1 (3.6%)
Gastric haemorrhage	1 (3.6%)
Metabolism and nutrition disorders	2 (7.1%)
Dehydration	1 (3.6%)
Hyponatraemia	1 (3.6%)
Hypovolaemia	1 (3.6%)
Psychiatric disorders	2 (7.1%)
Mental status changes	1 (3.6%)
Suicide attempt	1 (3.6%)
Blood and lymphatic system disorders	1 (3.6%)
Anaemia	1 (3.6%)
Cardiac disorders	1 (3.6%)
Cardiac failure congestive	1 (3.6%)
Musculoskeletal and connective tissue disorders	1 (3.6%)
Myopathy	1 (3.6%)
Nervous system disorders	1 (3.6%)
Syncope	1 (3.6%)
Respiratory, thoracic and mediastinal disorders	1 (3.6%)
Pulmonary oedema	1 (3.6%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.

Table 33 Listing of Deaths During the Study; All Treated Safety Run-in Analysis Set (Study 54767414AMY3001)

Treatment Group	Subject ID	Death Date (Study Day of Death[a])	Total No. of Dara[b] Injections	Study Day[c] of Last Dara[b] Injection	Total Cy[b] Dose (mg)	Study Day[c] of Last Cy[b] Dose	Total No. of Bor[b] Injections	Study Day[c] of Last Bor[b] Injection	Total Dex[b] Dose (mg)	Study Day[c] of Last Dex[b] Dose	Cause of Death	Adverse Event (MedDRA Preferred Term [Verbatim])
Dara SC + CyBorD Run-in	US10003-100015	24DEC2018 (370)	17	176	10420	169	24	169	960	169	PROGRESSIVE DISEASE	
	US10003-100029	10SEP2018 (200)	16	155	12000	162	24	162	960	162	OTHER - DEATH FOLLOWING TRANSPLANT, UNSPECIFIED	
	US10009-100032	23JUL2019 (508)	24	431	11500	203	13	112	480	203	ADVERSE EVENT	Chronic kidney disease [CHRONIC KIDNEY DISEASE]
	US10015-100033	19JAN2020 (685)	10	71	5500	78	10	78	240	78	OTHER - PUBLIC RECORDS ONLY INDICATE THAT PATIENT PASSED AWAY PEACEFULLY AT HOME.	
	US10033-100042	13SEP2018 (133)	10	74	6000	78	12	78	384	78	PROGRESSIVE DISEASE	
	US10036-100002	15SEP2018 (313)	19	281	9550	141	20	141	800	142	OTHER - TRANSPLANT-RELATED TOXICITIES.	

Patient exposure

The median total dose (exposure) of cyclophosphamide (mg/m2), bortezomib (mg/m2), and dexamethasone (mg) was well-balanced during Cycles 1-2 and slightly higher in the daratumumab SC+CyBorD arm during Cycles 3-6, which is likely reflective of more subjects in the CyBorD arm discontinuing study treatment starting from Cycle 3 onward. Comparatively, the extent of exposure of individual study agents, cyclophosphamide (mg/m2), bortezomib (mg/m2), and dexamethasone (mg); as measured during each respective cycle for the first 6 cycles; was similar between treatment arms:

- The median total dose of cyclophosphamide ranged from 1022.9 to 1077.7 mg/m2 for CyBorD arm and from 1025.3 to 1041.6 mg/m2 for the daratumumab SC+CyBorD arm. The protocol-specified dose of cyclophosphamide was 1200 mg/m2 per cycle (with a maximum weekly dose of 500 mg).
- The median total dose of bortezomib ranged from 5.1 to 5.2 mg/m2 for the CyBorD arm and 5.1 mg/m2 across all 6 cycles for the daratumumab SC+CyBorD arm. The protocol-specified dose of bortezomib was 5.2 mg/m2 per cycle.
- The median total dose of dexamethasone was 160 mg/cycle for all cycles for both treatment arms. The protocol-specified dose of steroid required per cycle was 160 mg.

The median relative dose intensities for cyclophosphamide, bortezomib, and dexamethasone were consistent across the treatment arms (cyclophosphamide: 85.8% vs 86.1% in the daratumumab SC+CyBorD and CyBorD arms, respectively; bortezomib: 96.6% vs 97.4% respectively; dexamethasone: 100% in each arm). The median relative dose intensity for daratumumab was 100%.

Table 34 USPI: Duration of Study Treatment; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD	Dara SC + CyBorD
Analysis set: safety	188	193
Duration of study treatment, months		
N	188	193
Mean (SD)	4.361 (1.6604)	9.706 (5.2401)
Median	5.322	9.626
Range	(0.03; 7.33)	(0.03; 21.16)
>= 6 months	7 (3.7%)	143 (74.1%)
> 12 months	0	62 (32.1%)

Key: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20); SD=standard deviation

Table 35 Summary of Exposure to Study Treatment; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD	Dara SC + CyBorD
Analysis set: safety	188	193
Duration of study treatment, months		
N	188	193
Mean (SD)	4.361 (1.6604)	9.706 (5.2401)
Median	5.322	9.626
Range	(0.03; 7.33)	(0.03; 21.16)
Number of subjects treated within Cycle, n (%)		
1	188 (100%)	193 (100%)
2	179 (95.2%)	182 (94.3%)
3	163 (86.7%)	177 (91.7%)
4	151 (80.3%)	166 (86.0%)
5	134 (71.3%)	162 (83.9%)
6	121 (64.4%)	159 (82.4%)
>6	0	149 (77.2%)
Maximum number of treatment cycles received		
N	188	193
Mean (SD)	5.0 (1.59)	11.1 (5.76)
Median	6.0	11.0
Range	(1; 6)	(1; 23)
Category, n (%)		
1	9 (4.8%)	11 (5.7%)
2	16 (8.5%)	5 (2.6%)
3	12 (6.4%)	11 (5.7%)
4	17 (9.0%)	4 (2.1%)
5	13 (6.9%)	3 (1.6%)
6	121 (64.4%)	10 (5.2%)
>6	0	149 (77.2%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).

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Adverse events

Nearly all patients (daratumumab SC+CyBorD: 97.9%; CyBorD: 98.4%) in both treatment arms had at least 1 TEAE reported (see table below). TEAEs occurring at ≥25% incidence in either treatment arm were generally balanced between treatment arms, except for peripheral sensory neuropathy and upper respiratory tract infection, and included:

- peripheral edema (daratumumab SC+CyBorD: 35.8%; CyBorD: 36.2%)
- diarrhea (daratumumab SC+CyBorD: 35.8%; CyBorD: 30.3%)
- constipation (daratumumab SC+CyBorD: 34.2%; CyBorD: 28.7%)
- peripheral sensory neuropathy (daratumumab SC+CyBorD: 31.1%; CyBorD: 19.7%)
- fatigue (daratumumab SC+CyBorD: 26.9%; CyBorD: 28.2%)
- nausea (daratumumab SC+CyBorD: 26.9%; CyBorD: 27.7%)
- upper respiratory tract infection (daratumumab SC+CyBorD: 25.9%; CyBorD: 11.2%)
- insomnia (daratumumab SC+CyBorD: 23.8%; CyBorD: 25.0%; Attachment TSFAE02)

Table 36 **Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Any TEAE	185 (98.4%)	189 (97.9%)
At least one related[a]	169 (89.9%)	174 (90.2%)
At least one related to daratumumab	1 (0.5%)[c]	110 (57.0%)
At least one related to cyclophosphamide	131 (69.7%)	122 (63.2%)
At least one related to bortezomib	148 (78.7%)	156 (80.8%)
At least one related to dexamethasone	130 (69.1%)	143 (74.1%)
Maximum toxicity grade		
Grade 1	10 (5.3%)	8 (4.1%)
Grade 2	61 (32.4%)	62 (32.1%)
Grade 3	83 (44.1%)	79 (40.9%)
Grade 4	16 (8.5%)	18 (9.3%)
Grade 5	15 (8.0%)	22 (11.4%)
Any serious TEAE	68 (36.2%)	83 (43.0%)
At least one related[a]	28 (14.9%)	40 (20.7%)
At least one related to daratumumab	0	24 (12.4%)
At least one related to cyclophosphamide	14 (7.4%)	23 (11.9%)
At least one related to bortezomib	14 (7.4%)	30 (15.5%)
At least one related to dexamethasone	23 (12.2%)	28 (14.5%)
TEAE leading to discontinuation of daratumumab	0	9 (4.7%)
Related to daratumumab	0	4 (2.1%)
TEAE leading to discontinuation of cyclophosphamide	12 (6.4%)	11 (5.7%)
Related to cyclophosphamide	4 (2.1%)	6 (3.1%)
TEAE leading to discontinuation of bortezomib	14 (7.4%)	12 (6.2%)
Related to bortezomib	5 (2.7%)	8 (4.1%)
TEAE leading to discontinuation of dexamethasone	13 (6.9%)	12 (6.2%)
Related to dexamethasone	7 (3.7%)	6 (3.1%)
TEAE leading to discontinuation of study treatment[b]	8 (4.3%)	8 (4.1%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab.
[b] TEAEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page.
[c] Site reporting error: site reported at least 1 AE as related to daratumumab in error, for 1 subject randomized to CyBorD arm.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 37 Overall Summary of Treatment-emergent Adverse Events by Cycle; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC + CyBorD n (%)			
	Total	Cycles 1-2	Cycles 3-6	Total	Cycles 1-2	Cycles 3-6	Cycles 7+
Analysis set: safety	188	188	163	193	193	177	149
Any TEAE	185 (98.4%)	175 (93.1%)	150 (92.0%)	189 (97.9%)	180 (93.3%)	167 (94.4%)	121 (81.2%)
At least one related[a]	169 (89.9%)	151 (80.3%)	119 (73.0%)	174 (90.2%)	155 (80.3%)	139 (78.5%)	68 (45.6%)
At least one related to daratumumab	1 (0.5%)	1 (0.5%)	1 (0.6%)	110 (57.0%)	86 (44.6%)	76 (42.9%)	39 (26.2%)
At least one related to cyclophosphamide	131 (69.7%)	100 (53.2%)	83 (50.9%)	122 (63.2%)	94 (48.7%)	93 (52.5%)	25 (16.8%)
At least one related to bortezomib	148 (78.7%)	120 (63.8%)	93 (57.1%)	156 (80.8%)	129 (66.8%)	115 (65.0%)	36 (24.2%)
At least one related to dexamethasone	130 (69.1%)	107 (56.9%)	83 (50.9%)	143 (74.1%)	115 (59.6%)	99 (55.9%)	39 (26.2%)
Maximum toxicity grade							
Grade 1	10 (5.3%)	27 (14.4%)	21 (12.9%)	8 (4.1%)	22 (11.4%)	28 (15.8%)	25 (16.8%)
Grade 2	61 (32.4%)	82 (43.6%)	57 (35.0%)	62 (32.1%)	87 (45.1%)	61 (34.5%)	69 (46.3%)
Grade 3	83 (44.1%)	47 (25.0%)	59 (36.2%)	79 (40.9%)	50 (25.9%)	57 (32.2%)	23 (15.4%)
Grade 4	16 (8.5%)	6 (3.2%)	11 (6.7%)	18 (9.3%)	8 (4.1%)	12 (6.8%)	4 (2.7%)
Grade 5	15 (8.0%)	13 (6.9%)	2 (1.2%)	22 (11.4%)	13 (6.7%)	9 (5.1%)	0
Any serious TEAE	68 (36.2%)	45 (23.9%)	36 (22.1%)	83 (43.0%)	47 (24.4%)	41 (23.2%)	20 (13.4%)
At least one related[a]	28 (14.9%)	19 (10.1%)	16 (9.8%)	40 (20.7%)	24 (12.4%)	22 (12.4%)	1 (0.7%)
At least one related to daratumumab	0	0	0	24 (12.4%)	13 (6.7%)	12 (6.8%)	1 (0.7%)
At least one related to cyclophosphamide	14 (7.4%)	8 (4.3%)	6 (3.7%)	23 (11.9%)	11 (5.7%)	13 (7.3%)	0
At least one related to bortezomib	14 (7.4%)	8 (4.3%)	6 (3.7%)	30 (15.5%)	15 (7.8%)	17 (9.6%)	0
At least one related to dexamethasone	23 (12.2%)	15 (8.0%)	14 (8.6%)	28 (14.5%)	14 (7.3%)	18 (10.2%)	0
TEAE leading to discontinuation of daratumumab	0	0	0	9 (4.7%)	4 (2.1%)	5 (2.8%)	1 (0.7%)
Related to daratumumab	0	0	0	4 (2.1%)	3 (1.6%)	2 (1.1%)	0
TEAE leading to discontinuation of cyclophosphamide	12 (6.4%)	4 (2.1%)	9 (5.5%)	11 (5.7%)	6 (3.1%)	7 (4.0%)	0
Related to cyclophosphamide	4 (2.1%)	1 (0.5%)	3 (1.8%)	6 (3.1%)	4 (2.1%)	3 (1.7%)	0
TEAE leading to discontinuation of bortezomib	14 (7.4%)	4 (2.1%)	11 (6.7%)	12 (6.2%)	4 (2.1%)	9 (5.1%)	0
Related to bortezomib	5 (2.7%)	2 (1.1%)	4 (2.5%)	8 (4.1%)	3 (1.6%)	6 (3.4%)	0
TEAE leading to discontinuation of dexamethasone	13 (6.9%)	5 (2.7%)	8 (4.9%)	12 (6.2%)	6 (3.1%)	7 (4.0%)	0

Table 38 Overall Summary of Treatment-emergent Adverse Events by Cycle; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC + CyBorD n (%)			
	Total	Cycles 1-2	Cycles 3-6	Total	Cycles 1-2	Cycles 3-6	Cycles 7+
Related to dexamethasone	7 (3.7%)	3 (1.6%)	4 (2.5%)	6 (3.1%)	4 (2.1%)	3 (1.7%)	0
TEAE leading to discontinuation of study treatment[b]	8 (4.3%)	4 (2.1%)	6 (3.7%)	8 (4.1%)	3 (1.6%)	5 (2.8%)	1 (0.7%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab.
[b] This table includes AEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.
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Table 39 **Most Commonly Reported (>10%) Treatment-emergent Adverse Events by Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more TEAEs	185 (98.4%)	189 (97.9%)
Preferred term		
Diarrhoea	57 (30.3%)	69 (35.8%)
Oedema peripheral	68 (36.2%)	69 (35.8%)
Constipation	54 (28.7%)	66 (34.2%)
Peripheral sensory neuropathy	37 (19.7%)	60 (31.1%)
Fatigue	53 (28.2%)	52 (26.9%)
Nausea	52 (27.7%)	52 (26.9%)
Upper respiratory tract infection	21 (11.2%)	50 (25.9%)
Anaemia	44 (23.4%)	47 (24.4%)
Insomnia	47 (25.0%)	46 (23.8%)
Dyspnoea	32 (17.0%)	44 (22.8%)
Lymphopenia	28 (14.9%)	36 (18.7%)
Thrombocytopenia	22 (11.7%)	33 (17.1%)
Cough	19 (10.1%)	32 (16.6%)
Asthenia	20 (10.6%)	31 (16.1%)
Dizziness	26 (13.8%)	29 (15.0%)
Hypotension	21 (11.2%)	27 (14.0%)
Vomiting	21 (11.2%)	26 (13.5%)
Headache	18 (9.6%)	25 (13.0%)
Pyrexia	16 (8.5%)	25 (13.0%)
Hypokalaemia	28 (14.9%)	24 (12.4%)
Back pain	11 (5.9%)	23 (11.9%)
Neutropenia	12 (6.4%)	21 (10.9%)
Pneumonia	12 (6.4%)	21 (10.9%)
Arthralgia	9 (4.8%)	20 (10.4%)
Decreased appetite	23 (12.2%)	19 (9.8%)
Injection site erythema	21 (11.2%)	18 (9.3%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA Version 22.1.

Table 40 **Most Commonly Reported (>5%) Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more toxicity grade 3 or 4 TEAEs	108 (57.4%)	113 (58.5%)
Preferred term		
Lymphopenia	19 (10.1%)	25 (13.0%)
Pneumonia	8 (4.3%)	15 (7.8%)
Diarrhoea	7 (3.7%)	11 (5.7%)
Cardiac failure	5 (2.7%)	10 (5.2%)
Neutropenia	5 (2.7%)	10 (5.2%)
Syncope	12 (6.4%)	10 (5.2%)
Oedema peripheral	11 (5.9%)	6 (3.1%)
Hypokalaemia	10 (5.3%)	3 (1.6%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Adverse events are reported using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 41 Most Commonly Reported (>5%) Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more toxicity grade 3 or 4 TEAEs	108 (57.4%)	113 (58.5%)
System organ class Preferred term		
Blood and lymphatic system disorders	33 (17.6%)	35 (18.1%)
Lymphopenia	19 (10.1%)	25 (13.0%)
Neutropenia	5 (2.7%)	10 (5.2%)
Infections and infestations	19 (10.1%)	32 (16.6%)
Pneumonia	8 (4.3%)	15 (7.8%)
Gastrointestinal disorders	11 (5.9%)	25 (13.0%)
Diarrhoea	7 (3.7%)	11 (5.7%)
General disorders and administration site conditions	23 (12.2%)	25 (13.0%)
Oedema peripheral	11 (5.9%)	6 (3.1%)
Metabolism and nutrition disorders	29 (15.4%)	23 (11.9%)
Hypokalaemia	10 (5.3%)	3 (1.6%)
Nervous system disorders	19 (10.1%)	23 (11.9%)
Syncope	12 (6.4%)	10 (5.2%)
Cardiac disorders	18 (9.6%)	22 (11.4%)
Cardiac failure	5 (2.7%)	10 (5.2%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 42 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more toxicity grade 3 or 4 TEAEs	108 (57.4%)	113 (58.5%)
System organ class Preferred term		
Blood and lymphatic system disorders	33 (17.6%)	35 (18.1%)
Lymphopenia	19 (10.1%)	25 (13.0%)
Neutropenia	5 (2.7%)	10 (5.2%)
Anaemia	9 (4.8%)	8 (4.1%)
Thrombocytopenia	5 (2.7%)	6 (3.1%)
Febrile neutropenia	0	2 (1.0%)
Leukopenia	2 (1.1%)	2 (1.0%)
Blood loss anaemia	1 (0.5%)	0
Infections and infestations	19 (10.1%)	32 (16.6%)
Pneumonia	8 (4.3%)	15 (7.8%)
Sepsis	0	6 (3.1%)
Lower respiratory tract infection	2 (1.1%)	2 (1.0%)
Septic shock	1 (0.5%)	2 (1.0%)
Adenovirus infection	0	1 (0.5%)
Bacterial infection	0	1 (0.5%)
Candida sepsis	0	1 (0.5%)
Cellulitis	2 (1.1%)	1 (0.5%)
Cytomegalovirus enterocolitis	0	1 (0.5%)
Ear infection	0	1 (0.5%)
Escherichia bacteraemia	0	1 (0.5%)
Influenza	3 (1.6%)	1 (0.5%)
Neutropenic sepsis	0	1 (0.5%)
Osteomyelitis	0	1 (0.5%)
Peritonitis	0	1 (0.5%)
Pneumonia pneumococcal	1 (0.5%)	1 (0.5%)
Pulmonary sepsis	0	1 (0.5%)
Pyelonephritis acute	0	1 (0.5%)
Respiratory tract infection	0	1 (0.5%)
Upper respiratory tract infection	1 (0.5%)	1 (0.5%)
Urinary tract infection	0	1 (0.5%)
Bronchitis	1 (0.5%)	0
Clostridium bacteraemia	1 (0.5%)	0
Clostridium difficile infection	2 (1.1%)	0
Gastrointestinal infection	1 (0.5%)	0
Herpes zoster	2 (1.1%)	0
Gastrointestinal disorders	11 (5.9%)	25 (13.0%)
Diarrhoea	7 (3.7%)	11 (5.7%)
Constipation	0	3 (1.6%)
Nausea	0	3 (1.6%)
Dysphagia	0	2 (1.0%)
Abdominal pain	1 (0.5%)	1 (0.5%)
Abdominal pain upper	0	1 (0.5%)
Ascites	0	1 (0.5%)
Colitis ischaemic	0	1 (0.5%)
Dental caries	0	1 (0.5%)
Gastric ulcer	0	1 (0.5%)
Melaena	0	1 (0.5%)
Tooth loss	0	1 (0.5%)

Table 43 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Dyspepsia	1 (0.5%)	0
Gastrointestinal haemorrhage	1 (0.5%)	0
Vomiting	1 (0.5%)	0
General disorders and administration site conditions	23 (12.2%)	25 (13.0%)
Fatigue	6 (3.2%)	8 (4.1%)
Oedema peripheral	11 (5.9%)	6 (3.1%)
Asthenia	2 (1.1%)	4 (2.1%)
Generalised oedema	2 (1.1%)	2 (1.0%)
Non-cardiac chest pain	1 (0.5%)	2 (1.0%)
Chills	0	1 (0.5%)
Localised oedema	2 (1.1%)	1 (0.5%)
Oedema	1 (0.5%)	1 (0.5%)
Oedema due to cardiac disease	0	1 (0.5%)
Pain	0	1 (0.5%)
General physical health deterioration	1 (0.5%)	0
Pyrexia	1 (0.5%)	0
Metabolism and nutrition disorders	29 (15.4%)	23 (11.9%)
Hyponatraemia	5 (2.7%)	5 (2.6%)
Hyperglycaemia	1 (0.5%)	4 (2.1%)
Hyperkalaemia	2 (1.1%)	3 (1.6%)
Hypokalaemia	10 (5.3%)	3 (1.6%)
Acidosis	0	1 (0.5%)
Dehydration	1 (0.5%)	1 (0.5%)
Diabetic metabolic decompensation	0	1 (0.5%)
Fluid overload	5 (2.7%)	1 (0.5%)
Hyperamylasaemia	0	1 (0.5%)
Hypercholesterolaemia	2 (1.1%)	1 (0.5%)
Hyperuricaemia	2 (1.1%)	1 (0.5%)
Hypoalbuminaemia	5 (2.7%)	1 (0.5%)
Hypocalcaemia	0	1 (0.5%)
Hypoglycaemia	1 (0.5%)	1 (0.5%)
Hypophosphataemia	0	1 (0.5%)
Starvation	0	1 (0.5%)
Type 2 diabetes mellitus	0	1 (0.5%)
Hyperphosphataemia	1 (0.5%)	0
Hypertriglyceridaemia	1 (0.5%)	0
Metabolic alkalosis	1 (0.5%)	0
Tumour lysis syndrome	1 (0.5%)	0
Nervous system disorders	19 (10.1%)	23 (11.9%)
Syncope	12 (6.4%)	10 (5.2%)
Peripheral sensory neuropathy	4 (2.1%)	5 (2.6%)
Presyncope	0	3 (1.6%)
Autonomic neuropathy	0	1 (0.5%)
Cerebrovascular accident	0	1 (0.5%)
Headache	0	1 (0.5%)
Loss of consciousness	0	1 (0.5%)
Neuralgia	0	1 (0.5%)
Peripheral sensorimotor neuropathy	0	1 (0.5%)
Post herpetic neuralgia	0	1 (0.5%)
Carpal tunnel syndrome	1 (0.5%)	0
Focal dyscognitive seizures	1 (0.5%)	0
Peripheral motor neuropathy	1 (0.5%)	0
Status epilepticus	1 (0.5%)	0
Cardiac disorders	18 (9.6%)	22 (11.4%)
Cardiac failure	5 (2.7%)	10 (5.2%)

Table 44 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Atrial fibrillation	1 (0.5%)	3 (1.6%)
Angina pectoris	1 (0.5%)	2 (1.0%)
Atrial flutter	0	2 (1.0%)
Cardiac arrest	0	2 (1.0%)
Cardiac failure congestive	4 (2.1%)	2 (1.0%)
Arteriospasm coronary	0	1 (0.5%)
Cardiac dysfunction	1 (0.5%)	1 (0.5%)
Cardiac flutter	0	1 (0.5%)
Cardiogenic shock	0	1 (0.5%)
Cardiovascular insufficiency	0	1 (0.5%)
Supraventricular tachycardia	0	1 (0.5%)
Acute coronary syndrome	1 (0.5%)	0
Acute myocardial infarction	1 (0.5%)	0
Atrial tachycardia	1 (0.5%)	0
Cardiomyopathy	1 (0.5%)	0
Mitral valve incompetence	1 (0.5%)	0
Myocardial infarction	1 (0.5%)	0
Sinus bradycardia	1 (0.5%)	0
Sinus node dysfunction	1 (0.5%)	0
Sinus tachycardia	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	14 (7.4%)	17 (8.8%)
Dyspnoea	6 (3.2%)	5 (2.6%)
Pneumothorax	0	3 (1.6%)
Dyspnoea exertional	1 (0.5%)	2 (1.0%)
Pleural effusion	1 (0.5%)	2 (1.0%)
Bronchospasm	0	1 (0.5%)
Chronic obstructive pulmonary disease	0	1 (0.5%)
Cough	0	1 (0.5%)
Epistaxis	0	1 (0.5%)
Nasal congestion	0	1 (0.5%)
Pneumonia aspiration	1 (0.5%)	1 (0.5%)
Pulmonary embolism	2 (1.1%)	1 (0.5%)
Pulmonary oedema	0	1 (0.5%)
Sleep apnoea syndrome	0	1 (0.5%)
Acute pulmonary oedema	2 (1.1%)	0
Acute respiratory distress syndrome	1 (0.5%)	0
Dyspnoea paroxysmal nocturnal	1 (0.5%)	0
Hypoxia	1 (0.5%)	0
Respiratory failure	1 (0.5%)	0
Tachypnoea	1 (0.5%)	0
Investigations	14 (7.4%)	16 (8.3%)
Alanine aminotransferase increased	1 (0.5%)	5 (2.6%)
Aspartate aminotransferase increased	1 (0.5%)	4 (2.1%)
Blood creatinine increased	2 (1.1%)	4 (2.1%)
Gamma-glutamyltransferase increased	6 (3.2%)	2 (1.0%)
Lipase increased	0	2 (1.0%)
Weight decreased	0	2 (1.0%)
Alanine aminotransferase	0	1 (0.5%)
Blood alkaline phosphatase increased	1 (0.5%)	1 (0.5%)
Blood creatine phosphokinase increased	0	1 (0.5%)
Blood growth hormone increased	0	1 (0.5%)
Blood insulin decreased	0	1 (0.5%)
Cortisol increased	0	1 (0.5%)
Electrocardiogram QT prolonged	0	1 (0.5%)
Influenza A virus test positive	0	1 (0.5%)

Table 45 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Procalcitonin increased	0	1 (0.5%)
Troponin I increased	0	1 (0.5%)
Troponin T increased	1 (0.5%)	1 (0.5%)
Blood pressure orthostatic decreased	1 (0.5%)	0
Ejection fraction decreased	1 (0.5%)	0
Myocardial strain	1 (0.5%)	0
N-terminal prohormone brain natriuretic peptide increased	1 (0.5%)	0
Renal and urinary disorders	12 (6.4%)	11 (5.7%)
Acute kidney injury	3 (1.6%)	4 (2.1%)
Chronic kidney disease	2 (1.1%)	4 (2.1%)
Nephropathy	0	1 (0.5%)
Nephrotic syndrome	0	1 (0.5%)
Proteinuria	0	1 (0.5%)
Renal failure	3 (1.6%)	1 (0.5%)
Renal impairment	4 (2.1%)	0
Renal injury	1 (0.5%)	0
Vascular disorders	8 (4.3%)	10 (5.2%)
Hypertension	2 (1.1%)	4 (2.1%)
Hypotension	5 (2.7%)	4 (2.1%)
Orthostatic hypotension	0	2 (1.0%)
Circulatory collapse	1 (0.5%)	0
Shock haemorrhagic	1 (0.5%)	0
Musculoskeletal and connective tissue disorders	3 (1.6%)	9 (4.7%)
Back pain	0	3 (1.6%)
Muscular weakness	1 (0.5%)	3 (1.6%)
Flank pain	0	1 (0.5%)
Muscle spasms	0	1 (0.5%)
Pain in jaw	0	1 (0.5%)
Osteoarthritis	1 (0.5%)	0
Osteoporosis	1 (0.5%)	0
Eye disorders	1 (0.5%)	3 (1.6%)
Blepharitis	1 (0.5%)	2 (1.0%)
Amaurosis fugax	0	1 (0.5%)
Injury, poisoning and procedural complications	3 (1.6%)	2 (1.0%)
Delayed engraftment	0	1 (0.5%)
Hip fracture	0	1 (0.5%)
Joint dislocation	1 (0.5%)	0
Rib fracture	1 (0.5%)	0
Skin laceration	1 (0.5%)	0
Traumatic liver injury	1 (0.5%)	0
Psychiatric disorders	4 (2.1%)	2 (1.0%)
Delirium	0	1 (0.5%)
Depression	1 (0.5%)	1 (0.5%)
Agitation	1 (0.5%)	0
Anxiety	2 (1.1%)	0
Insomnia	2 (1.1%)	0
Mood altered	1 (0.5%)	0
Congenital, familial and genetic disorders	0	1 (0.5%)
Hereditary haemorrhagic telangiectasia	0	1 (0.5%)
Ear and labyrinth disorders	0	1 (0.5%)
Deafness	0	1 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0.5%)
Bladder cancer	0	1 (0.5%)

Table 46 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Skin and subcutaneous tissue disorders	3 (1.6%)	1 (0.5%)
Petechiae	0	1 (0.5%)
Dermatitis exfoliative generalised	1 (0.5%)	0
Drug eruption	1 (0.5%)	0
Dry skin	1 (0.5%)	0
Palmoplantar keratoderma	1 (0.5%)	0
Pruritus	1 (0.5%)	0
Pruritus allergic	1 (0.5%)	0
Skin fissures	1 (0.5%)	0
Hepatobiliary disorders	1 (0.5%)	0
Hyperbilirubinaemia	1 (0.5%)	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Most commonly reported grade 3 or 4 TEAEs were reported in 58.5% of subjects in the daratumumab SC+CyBorD arm and 57.4% of patients in the CyBorD arm (see tables above).

Table 47 : Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Cycle; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC + CyBorD n (%)			
	Total	Cycles 1-2	Cycles 3-6	Total	Cycles 1-2	Cycles 3-6	Cycles 7+
Analysis set: safety	188	188	163	193	193	177	149
Subjects with 1 or more toxicity grade 3 or 4 TEAEs	108 (57.4%)	60 (31.9%)	72 (44.2%)	113 (58.5%)	66 (34.2%)	77 (43.5%)	27 (18.1%)

The incidence of Grade 3 or 4 TEAEs was during Cycles 1-2 (daratumumab SC+CyBorD: 34.2%, CyBorD: 31.9%) and Cycles 3-6 (daratumumab SC+CyBorD: 43.5%, CyBorD: 44.2%), respectively. In the daratumumab SC+CyBorD arm, 18.1% (27/149) of patients had Grade 3 or 4 TEAEs from Cycle 7 onwards (see table above).

The most common (>2%) Grade 3 or 4 TEAEs from Cycle 7 onwards were Blood and Lymphatic System Disorders (4.7% total: lymphopenia (3.4%), neutropenia (1.3%), leukopenia (0.7%)) followed by Infections and Infestations (4.0% total: pneumonia (2.0%), sepsis, lower respiratory tract infection, influenza, and peritonitis (0.7% each)), and Cardiac Disorders (2.7% total: angina pectoris (1.3%), cardiac failure, atrial flutter, and arteriospasm coronary (0.7% each)), and Respiratory, Thoracic and Mediastinal Disorders (2.7% total: dyspnea, pneumothorax, pleural effusion, and chronic obstructive pulmonary disease (0.7% each)) (see tables above).

Adverse events of special interest (AESI)

Infusion-related reactions (IRR), infections and infestations, opportunistic infections, peripheral neuropathies, cardiac disorders, and renal and urinary disorders are considered adverse events of special interest (AESI) for daratumumab SC.

Infusion-related Reactions (IRR)

Table 48 **Number of Subjects with Treatment-emergent Infusion-related Reactions by System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)**

	Dara SC + CyBorD			
	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Analysis set: safety	193			
Subjects with infusion-related reactions associated with daratumumab	14 (7.3%)	0	0	0
Subjects with infusion-related reactions associated with daratumumab in more than 1 infusion	3 (1.6%)	0	0	0
System organ class Preferred term				
General disorders and administration site conditions	7 (3.6%)	0	0	0
Chills	3 (1.6%)	0	0	0
Pyrexia	3 (1.6%)	0	0	0
Asthenia	1 (0.5%)	0	0	0
Swelling face	1 (0.5%)	0	0	0
Nervous system disorders	4 (2.1%)	0	0	0
Dizziness	2 (1.0%)	0	0	0
Headache	1 (0.5%)	0	0	0
Paraesthesia	1 (0.5%)	0	0	0
Tremor	1 (0.5%)	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (2.1%)	0	0	0
Dysphonia	1 (0.5%)	0	0	0
Dyspnoea	1 (0.5%)	0	0	0
Oropharyngeal pain	1 (0.5%)	0	0	0
Throat tightness	1 (0.5%)	0	0	0
Skin and subcutaneous tissue disorders	3 (1.6%)	0	0	0
Erythema	1 (0.5%)	0	0	0
Hyperhidrosis	1 (0.5%)	0	0	0
Rash pruritic	1 (0.5%)	0	0	0
Gastrointestinal disorders	2 (1.0%)	0	0	0
Nausea	2 (1.0%)	0	0	0
Abdominal pain	1 (0.5%)	0	0	0
Musculoskeletal and connective tissue disorders	2 (1.0%)	0	0	0
Back pain	1 (0.5%)	0	0	0
Myalgia	1 (0.5%)	0	0	0
Cardiac disorders	1 (0.5%)	0	0	0
Tachycardia	1 (0.5%)	0	0	0
Ear and labyrinth disorders	1 (0.5%)	0	0	0
Vertigo	1 (0.5%)	0	0	0
Eye disorders	1 (0.5%)	0	0	0
Blepharospasm	1 (0.5%)	0	0	0
Vascular disorders	1 (0.5%)	0	0	0
Hypertension	1 (0.5%)	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: Adverse events are reported using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 49 **Time to Onset of Infusion-related Reaction; Safety Analysis Set (Study 54767414AMY3001)**

	Dara SC + CyBorD Event Onset Time			
	Total	1st Infusion n (%)	2nd Infusion n (%)	Subsequent Infusion n (%)
Analysis set: safety	193			
Subjects with 1 or more infusion-related reactions	14 (7.3%)	12 (6.2%)	2 (1.0%)	3 (1.6%)
Time to onset of infusion-related reactions (minutes)				
N[a]	12	9	1	2
Mean (SD)	143.6 (133.32)	152.6 (150.90)	200.0 (NE)	75.0 (7.07)
Median	80.0	80.0	200.0	75.0
Range	(10; 440)	(10; 440)	(200; 200)	(70; 80)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: NE = not estimable.
[a] Infusion-related reactions with missing onset time are excluded. N represents number of infusion-related reactions.
Time to onset of infusion-related reactions in minutes are calculated as the start of the infusion-related reaction minus the start of the last infusion which is on or prior to this event.

Of the 193 patients who received daratumumab SC+CyBorD, 7.3% of these patients experienced an IRR (see table above), IRRs were Grade 1 or 2 and did not lead to treatment discontinuation. Fourteen patients (7.3%) in daratumumab SC+CyBorD arm had an IRR. The majority of these IRRs occurred during the first dose administration, 12 patients (6.2%). Two (1%) patients had IRRs during the second dose administration and 3 (1.6%) patients during subsequent dose administrations.

Infections and Infestations

Table 50 **Number of Subjects with Toxicity Grade 3 or 4 Treatment-emergent Infections and Infestations by Preferred Term and Relationship; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)				Dara SC + CyBorD n (%)				
	Total	Related to Cy	Related to Bor	Related to Dex	Total	Related to Dara	Related to Cy	Related to Bor	Related to Dex
Analysis set: safety	188				193				
Subjects with 1 or more toxicity grade 3 or 4 treatment-emergent infections and infestations	19 (10.1%)	7 (3.7%)	5 (2.7%)	7 (3.7%)	32 (16.6%)	15 (7.8%)	11 (5.7%)	12 (6.2%)	11 (5.7%)
Preferred term									
Pneumonia	8 (4.3%)	4 (2.1%)	3 (1.6%)	4 (2.1%)	15 (7.8%)	6 (3.1%)	4 (2.1%)	4 (2.1%)	4 (2.1%)
Sepsis	0	0	0	0	6 (3.1%)	2 (1.0%)	2 (1.0%)	3 (1.6%)	1 (0.5%)
Lower respiratory tract infection	2 (1.1%)	1 (0.5%)	0	1 (0.5%)	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Septic shock	1 (0.5%)	0	0	0	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)	2 (1.0%)
Adenovirus infection	0	0	0	0	1 (0.5%)	0	0	0	0
Bacterial infection	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Candida sepsis	0	0	0	0	1 (0.5%)	0	0	0	0
Cellulitis	2 (1.1%)	2 (1.1%)	1 (0.5%)	2 (1.1%)	1 (0.5%)	1 (0.5%)	0	0	1 (0.5%)
Cytomegalovirus enterocolitis	0	0	0	0	1 (0.5%)	0	0	0	0
Ear infection	0	0	0	0	1 (0.5%)	1 (0.5%)	0	0	0
Escherichia bacteraemia	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Influenza	3 (1.6%)	0	0	0	1 (0.5%)	0	0	0	0
Neutropenic sepsis	0	0	0	0	1 (0.5%)	0	0	0	0
Osteomyelitis	0	0	0	0	1 (0.5%)	0	0	0	0
Peritonitis	0	0	0	0	1 (0.5%)	0	0	0	0
Pneumonia pneumococcal	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	0	0
Pulmonary sepsis	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Pyelonephritis acute	0	0	0	0	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Respiratory tract infection	0	0	0	0	1 (0.5%)	0	0	0	0
Upper respiratory tract infection	1 (0.5%)	0	0	0	1 (0.5%)	0	0	0	0
Urinary tract infection	0	0	0	0	1 (0.5%)	0	0	0	0
Bronchitis	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	0	0	0
Clostridium bacteraemia	1 (0.5%)	0	0	0	0	0	0	0	0
Clostridium difficile infection	2 (1.1%)	0	0	0	0	0	0	0	0
Gastrointestinal infection	1 (0.5%)	0	1 (0.5%)	0	0	0	0	0	0
Herpes zoster	2 (1.1%)	0	1 (0.5%)	0	0	0	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: Dara = daratumumab; Cy = cyclophosphamide; Bor = bortezomib; Dex = dexamethasone.
Note: Adverse events are reported using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Opportunistic Infections

Opportunistic infections were defined as a subpopulation of the system organ class of "Infections and Infestations" by manually predefined terms.

Table 51 Number of Subjects With Treatment-emergent Opportunistic Infections by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more treatment-emergent opportunistic infections	16 (8.5%)	23 (11.9%)
System organ class Preferred term		
Infections and infestations	16 (8.5%)	23 (11.9%)
Herpes zoster	12 (6.4%)	10 (5.2%)
Oral candidiasis	2 (1.1%)	9 (4.7%)
Oesophageal candidiasis	0	2 (1.0%)
Candida sepsis	0	1 (0.5%)
Cytomegalovirus enterocolitis	0	1 (0.5%)
Gastrointestinal candidiasis	0	1 (0.5%)
Oral fungal infection	1 (0.5%)	1 (0.5%)
Candida infection	2 (1.1%)	0
Nervous system disorders	1 (0.5%)	2 (1.0%)
Post herpetic neuralgia	1 (0.5%)	2 (1.0%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.

Peripheral Neuropathies

Table 52 Number of Subjects with Treatment-emergent Peripheral Neuropathies by High Level Term and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)		Dara SC + CyBorD n (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Analysis set: safety	188		193	
Subjects with 1 or more treatment-emergent peripheral neuropathy	40 (21.3%)	5 (2.7%)	65 (33.7%)	6 (3.1%)
Higher level term Preferred term				
Peripheral neuropathies NEC	40 (21.3%)	5 (2.7%)	65 (33.7%)	6 (3.1%)
Peripheral sensory neuropathy	37 (19.7%)	4 (2.1%)	60 (31.1%)	5 (2.6%)
Neuropathy peripheral	1 (0.5%)	0	4 (2.1%)	0
Peripheral motor neuropathy	3 (1.6%)	1 (0.5%)	1 (0.5%)	0
Peripheral sensorimotor neuropathy	0	0	1 (0.5%)	1 (0.5%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Note: Adverse events are reported using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 53 Number of Subjects With Treatment-emergent Adverse Events by System Organ Class, Preferred Term and Cycle; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC + CyBorD n (%)			
	Total	Cycles 1-2	Cycles 3-6	Total	Cycles 1-2	Cycles 3-6	Cycles 7+
Herpes dermatitis	1 (0.5%)	1 (0.5%)	0	0	0	0	0
Herpes simplex	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Paronychia	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Postoperative wound infection	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Pulpitis dental	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Serratia infection	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Tinea pedis	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Tracheitis	1 (0.5%)	1 (0.5%)	0	0	0	0	0
Upper respiratory tract infection bacterial	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Viral infection	1 (0.5%)	1 (0.5%)	0	0	0	0	0
Vulvovaginal mycotic infection	1 (0.5%)	0	1 (0.6%)	0	0	0	0
Nervous system disorders	103 (54.8%)	68 (36.2%)	64 (39.3%)	116 (60.1%)	83 (43.0%)	67 (37.9%)	25 (16.8%)
Peripheral sensory neuropathy	37 (19.7%)	18 (9.6%)	24 (14.7%)	60 (31.1%)	20 (10.4%)	39 (22.0%)	13 (8.7%)
Dizziness	26 (13.8%)	18 (9.6%)	8 (4.9%)	29 (15.0%)	24 (12.4%)	5 (2.8%)	1 (0.7%)
Headache	18 (9.6%)	12 (6.4%)	7 (4.3%)	25 (13.0%)	22 (11.4%)	3 (1.7%)	6 (4.0%)
Dysgeusia	11 (5.9%)	5 (2.7%)	6 (3.7%)	15 (7.8%)	10 (5.2%)	5 (2.8%)	1 (0.7%)
Paraesthesia	12 (6.4%)	6 (3.2%)	6 (3.7%)	15 (7.8%)	10 (5.2%)	5 (2.8%)	1 (0.7%)
Syncope	12 (6.4%)	9 (4.8%)	4 (2.5%)	14 (7.3%)	10 (5.2%)	5 (2.8%)	0
Neuralgia	4 (2.1%)	1 (0.5%)	3 (1.8%)	11 (5.7%)	3 (1.6%)	6 (3.4%)	2 (1.3%)
Tremor	2 (1.1%)	1 (0.5%)	1 (0.6%)	10 (5.2%)	5 (2.6%)	5 (2.8%)	0
Presyncope	3 (1.6%)	2 (1.1%)	1 (0.6%)	7 (3.6%)	4 (2.1%)	2 (1.1%)	1 (0.7%)
Hypoaesthesia	3 (1.6%)	2 (1.1%)	1 (0.6%)	6 (3.1%)	1 (0.5%)	4 (2.3%)	1 (0.7%)
Neuropathy peripheral	1 (0.5%)	0	1 (0.6%)	4 (2.1%)	2 (1.0%)	2 (1.1%)	0
Restless legs syndrome	2 (1.1%)	1 (0.5%)	1 (0.6%)	3 (1.6%)	3 (1.6%)	0	0
Somnolence	2 (1.1%)	1 (0.5%)	1 (0.6%)	3 (1.6%)	2 (1.0%)	1 (0.6%)	0
Taste disorder	6 (3.2%)	4 (2.1%)	2 (1.2%)	3 (1.6%)	1 (0.5%)	2 (1.1%)	0
Cerebral infarction	1 (0.5%)	0	1 (0.6%)	2 (1.0%)	2 (1.0%)	0	0
Dizziness postural	1 (0.5%)	1 (0.5%)	0	2 (1.0%)	2 (1.0%)	0	0
Dysaesthesia	0	0	0	2 (1.0%)	1 (0.5%)	0	1 (0.7%)
Facial paralysis	0	0	0	2 (1.0%)	2 (1.0%)	0	0
Lethargy	1 (0.5%)	1 (0.5%)	0	2 (1.0%)	1 (0.5%)	1 (0.6%)	0
Post herpetic neuralgia	1 (0.5%)	0	1 (0.6%)	2 (1.0%)	0	2 (1.1%)	0
Areflexia	0	0	0	1 (0.5%)	0	1 (0.6%)	0
Autonomic nervous system imbalance	0	0	0	1 (0.5%)	0	1 (0.6%)	0
Autonomic neuropathy	3 (1.6%)	2 (1.1%)	1 (0.6%)	1 (0.5%)	0	1 (0.6%)	0
Balance disorder	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	0

Table 54 Number of Subjects with Treatment-emergent Peripheral Neuropathies by Peripheral Nerve System Involvement at Baseline, High Level Term, and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC+CyBorD n (%)		
	Yes	No	Total	Yes	No	Total
Analysis set: safety	22	166	188	32	161	193
Subjects with 1 or more treatment-emergent peripheral neuropathies	4 (18.2%)	36 (21.7%)	40 (21.3%)	10 (31.3%)	55 (34.2%)	65 (33.7%)
High level term						
Preferred Term						
Peripheral neuropathies NEC	4 (18.2%)	36 (21.7%)	40 (21.3%)	10 (31.3%)	55 (34.2%)	65 (33.7%)
Peripheral sensory neuropathy	4 (18.2%)	33 (19.9%)	37 (19.7%)	10 (31.3%)	50 (31.1%)	60 (31.1%)
Neuropathy peripheral	0	1 (0.6%)	1 (0.5%)	0	4 (2.5%)	4 (2.1%)
Peripheral motor neuropathy	1 (4.5%)	2 (1.2%)	3 (1.6%)	0	1 (0.6%)	1 (0.5%)
Peripheral sensorimotor neuropathy	0	0	0	0	1 (0.6%)	1 (0.5%)

Cardiac Disorders

Table 55 **Number of Subjects with Treatment-emergent Cardiac Disorders by High Level Term and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)		Dara SC + CyBorD n (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Analysis set: safety	188		193	
Subjects with 1 or more treatment-emergent cardiac disorders	41 (21.8%)	18 (9.6%)	63 (32.6%)	22 (11.4%)

Table 56 **Summary of Baseline Disease Characteristics; Intent-to-treat Analysis Set (Study 54767414AMY3001)**

	CyBorD	Dara SC + CyBorD	Total
Analysis set: intent-to-treat	193	195	388
Time since initial AL Amyloidosis diagnosis, days			
N	193	195	388
Mean (SD)	62.4 (90.70)	101.5 (220.22)	82.1 (169.63)
Median	43.0	48.0	43.0
Range	(5; 1102)	(8; 1611)	(5; 1611)
Category, n(%)			
<=30	55 (28.5%)	51 (26.2%)	106 (27.3%)
>30-60	83 (43.0%)	74 (37.9%)	157 (40.5%)
>60	55 (28.5%)	70 (35.9%)	125 (32.2%)
Isotype of AL based on either immunofixation or light chain, n (%)			
N	193	195	388
Lambda	149 (77.2%)	158 (81.0%)	307 (79.1%)
Kappa	44 (22.8%)	37 (19.0%)	81 (20.9%)
Organ Involvement, n (%)			
N	193	195	388
Heart	137 (71.0%)	140 (71.8%)	277 (71.4%)
Kidney	114 (59.1%)	115 (59.0%)	229 (59.0%)
Liver	16 (8.3%)	15 (7.7%)	31 (8.0%)
Gastrointestinal tract	29 (15.0%)	30 (15.4%)	59 (15.2%)
Lung	5 (2.6%)	3 (1.5%)	8 (2.1%)
Nerve	33 (17.1%)	42 (21.5%)	75 (19.3%)
PNS	24 (12.4%)	32 (16.4%)	56 (14.4%)
ANS	11 (5.7%)	11 (5.6%)	22 (5.7%)
Soft tissue	55 (28.5%)	51 (26.2%)	106 (27.3%)

Renal and Urinary Disorders

The most commonly (≥2% in either treatment arm) reported Grade 3 or 4 renal and urinary disorder were acute kidney injury (daratumumab SC+CyBorD: 2.1%; CyBorD: 1.6%), chronic kidney disease (daratumumab SC+CyBorD: 2.1%; CyBorD: 1.1%), and renal impairment (daratumumab SC+CyBorD: 0%; CyBorD: 2.1%)

Table 57 3: Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Procalcitonin increased	0	1 (0.5%)
Troponin I increased	0	1 (0.5%)
Troponin T increased	1 (0.5%)	1 (0.5%)
Blood pressure orthostatic decreased	1 (0.5%)	0
Ejection fraction decreased	1 (0.5%)	0
Myocardial strain	1 (0.5%)	0
N-terminal prohormone brain natriuretic peptide increased	1 (0.5%)	0
Renal and urinary disorders	12 (6.4%)	11 (5.7%)
Acute kidney injury	3 (1.6%)	4 (2.1%)
Chronic kidney disease	2 (1.1%)	4 (2.1%)
Nephropathy	0	1 (0.5%)
Nephrotic syndrome	0	1 (0.5%)
Proteinuria	0	1 (0.5%)
Renal failure	3 (1.6%)	1 (0.5%)
Renal impairment	4 (2.1%)	0
Renal injury	1 (0.5%)	0

The MAH presented further results regarding patients who had renal disorders before initiation of treatment at baseline, 113 subjects (58.5% [113/193]) in daratumumab SC+CyBorD arm and 112 subjects (59.6% [112/188]) in the CyBorD arm presented with renal involvement. A higher incidence of (≥10%) of TEAEs was observed in subjects with renal involvement at baseline compared with those without renal involvement at baseline.
In the daratumumab SC+CyBorD arm 50.4% vs 36.3% experienced a higher incidence (≥5%) of anemia, lymphopenia, and thrombocytopenia for those with renal involvement vs those without renal involvement at baseline (31.0% vs 15.0% anemia, 22.1% vs 13.8% lymphopenia, and 19.5% vs 13.8% thrombocytopenia).

Renal and urinary disorders (yes vs no) were equally distributed in the two treatment arms: 26.5% vs 13.8% in the daratumumab SC+CyBorD; 23.2% vs 10.5% in the CyBorD arm. In the daratumumab SC+CyBorD arm, a higher incidence (≥5%) of renal impairment was observed for those who were renally impaired vs not renally impaired at baseline (7.1% vs 1.3%). In the CyBorD arm, a higher incidence (≥5%) of renal impairment was observed for those who were renally impaired at baseline vs not renally impaired (9.8% vs 0%).

Serious adverse event/deaths/other significant events

Deaths

At the time of primary analysis, 27 patients (14.0%) in the daratumumab SC+CyBorD arm died and 28 patients (14.9%) in the CyBorD arm died. Additionally, 1 patient in the CyBorD arm died prior to receiving any treatment.

More patients in the daratumumab SC+CyBorD arm (11.9%) died due to an AE during study compared to the CyBorD arm (7.4%).

Deaths due to AE within 30 days of last study treatment were reported for 10.4% of patients in the daratumumab SC+CyBorD arm and 7.4% of patients in the CyBorD arm (see Table below). TEAEs were to be reported up to 30 days after the last study treatment. As patients could change therapy after 3 cycles for insufficient hematological response and patients in the CyBorD arm could receive subsequent therapy after the 6 cycles of study treatment were completed, deaths and other untoward events

occurring after start of subsequent therapy and during the follow-up period were no longer reported as AEs, contributing to the lower rate of AEs, including AEs leading to deaths, reported in the CyBorD arm.

At the primary cutoff, the number of reported deaths were similar (27 vs 29) between the arms and with longer follow up, fewer deaths were reported in the daratumumab SC+CyBorD arm compared with the CyBorD arm (31 vs 41).

Table 58 **Summary of Death and Cause of Death; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)	Total n (%)
Analysis set: safety	188	193	381
Total number of subjects who died during study	28 (14.9%)	27 (14.0%)	55 (14.4%)
Primary cause of death			
Adverse event	14 (7.4%)	23 (11.9%)	37 (9.7%)
At least one related[a]	2 (1.1%)	6 (3.1%)	8 (2.1%)
AE(s) unrelated	12 (6.4%)	17 (8.8%)	29 (7.6%)
Progressive disease	9 (4.8%)	2 (1.0%)	11 (2.9%)
Other	5 (2.7%)	2 (1.0%)	7 (1.8%)
Total number of subjects who died within 30 days of last study treatment dose	17 (9.0%)	21 (10.9%)	38 (10.0%)
Primary cause of death			
Adverse event	14 (7.4%)	20 (10.4%)	34 (8.9%)
At least one related[a]	2 (1.1%)	6 (3.1%)	8 (2.1%)
AE(s) unrelated	12 (6.4%)	14 (7.3%)	26 (6.8%)
Progressive disease	3 (1.6%)	1 (0.5%)	4 (1.0%)
Other	0	0	0
Total number of subjects who died within 60 days of first study treatment dose	13 (6.9%)	13 (6.7%)	26 (6.8%)
Primary cause of death			
Adverse event	12 (6.4%)	12 (6.2%)	24 (6.3%)
At least one related[a]	2 (1.1%)	5 (2.6%)	7 (1.8%)
AE(s) unrelated	10 (5.3%)	7 (3.6%)	17 (4.5%)
Progressive disease	1 (0.5%)	1 (0.5%)	2 (0.5%)
Other	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
[a] Includes adverse events that were related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab.

The most common (≥2% in either treatment arm) AEs leading to death were cardiac disorders. All patients who died due to cardiac disorders had cardiac involvement at baseline (daratumumab SC+CyBorD: 14/14, CyBorD: 7/7. (Table 32)

Table 59 **Number of Subjects with a Treatment-emergent Adverse Event with Outcome Death by Preferred Term and Relationship; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)				Dara SC + CyBorD n (%)				
Analysis set: safety	Total 188	Related to Cy	Related to Bor	Related to Dex	Total 193	Related to Dara	Related to Cy	Related to Bor	Related to Dex
Subjects with TEAE with outcome death	15 (8.0%)	1 (0.5%)	2 (1.1%)	2 (1.1%)	22 (11.4%)	4 (2.1%)	2 (1.0%)	5 (2.6%)	3 (1.6%)
Preferred term									
Cardiac arrest	3 (1.6%)	0	0	0	6 (3.1%)	1 (0.5%)	0	1 (0.5%)	1 (0.5%)
Sudden death	3 (1.6%)	0	0	0	6 (3.1%)	0	0	0	0
Cardiac failure	1 (0.5%)	0	0	0	5 (2.6%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Sepsis	0	0	0	0	2 (1.0%)	1 (0.5%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Bradyarrhythmia	0	0	0	0	1 (0.5%)	0	0	0	0
Cardiogenic shock	0	0	0	0	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	0
Left ventricular dysfunction	0	0	0	0	1 (0.5%)	0	0	1 (0.5%)	0
Pulmonary haemorrhage	0	0	0	0	1 (0.5%)	0	0	0	0
Acute pulmonary oedema	1 (0.5%)	0	0	1 (0.5%)	0	0	0	0	0
Arrhythmia	1 (0.5%)	0	0	0	0	0	0	0	0
Ischaemic stroke	1 (0.5%)	0	0	0	0	0	0	0	0
Myocardial infarction	1 (0.5%)	0	0	0	0	0	0	0	0
Septic shock	1 (0.5%)	0	0	0	0	0	0	0	0
Sinus node dysfunction	1 (0.5%)	1 (0.5%)	1 (0.5%)	0	0	0	0	0	0
Status epilepticus	1 (0.5%)	0	0	0	0	0	0	0	0
Sudden cardiac death	1 (0.5%)	0	1 (0.5%)	1 (0.5%)	0	0	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: TEAE = treatment-emergent adverse event; Dara = daratumumab; Cy = cyclophosphamide; Bor = bortezomib; Dex = dexamethasone.
Note: Adverse events are reported using MedDRA Version 22.1.

The majority of deaths due to TEAEs in both treatment arms occurred in patients with cardiac involvement at baseline: 21 of the 22 patients in the daratumumab arm had cardiac involvement at baseline and all patients (15/15) in the CyBorD arm had cardiac involvement at baseline. The most common (≥2% in either treatment arm) AEs leading to death were cardiac arrest (daratumumab SC+CyBorD: 3.1%, CyBorD: 1.6%) (see table below).

Table 60 **Number of Subjects with a Treatment-emergent Adverse Event with Outcome Death by Cardiac Involvement at Baseline, System Organ ass and Preferred Term;Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)			Dara SC + CyBorD n (%)		
Analysis set: Safety Analysis Set	Yes 133	No 55	Total 188	Yes 140	No 53	Total 193
Subjects with TEAE with outcome death	15 (11.3%)	0	15 (8.0%)	21 (15.0%)	1 (1.9%)	22 (11.4%)
Cardiac disorders	7 (5.3%)	0	7 (3.7%)	14 (10.0%)	0	14 (7.3%)
Cardiac arrest	3 (2.3%)	0	3 (1.6%)	6 (4.3%)	0	6 (3.1%)
Cardiac failure	1 (0.8%)	0	1 (0.5%)	5 (3.6%)	0	5 (2.6%)
Bradyarrhythmia	0	0	0	1 (0.7%)	0	1 (0.5%)
Cardiogenic shock	0	0	0	1 (0.7%)	0	1 (0.5%)
Left ventricular dysfunction	0	0	0	1 (0.7%)	0	1 (0.5%)
Arrhythmia	1 (0.8%)	0	1 (0.5%)	0	0	0
Myocardial infarction	1 (0.8%)	0	1 (0.5%)	0	0	0
Sinus node dysfunction	1 (0.8%)	0	1 (0.5%)	0	0	0
General disorders and administration site conditions	4 (3.0%)	0	4 (2.1%)	6 (4.3%)	0	6 (3.1%)
Sudden death	3 (2.3%)	0	3 (1.6%)	6 (4.3%)	0	6 (3.1%)
Sudden cardiac death	1 (0.8%)	0	1 (0.5%)	0	0	0
Infections and infestations	1 (0.8%)	0	1 (0.5%)	1 (0.7%)	1 (1.9%)	2 (1.0%)
Sepsis	0	0	0	1 (0.7%)	1 (1.9%)	2 (1.0%)
Septic shock	1 (0.8%)	0	1 (0.5%)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.8%)	0	1 (0.5%)	1 (0.7%)	0	1 (0.5%)
Pulmonary haemorrhage	0	0	0	1 (0.7%)	0	1 (0.5%)
Acute pulmonary oedema	1 (0.8%)	0	1 (0.5%)	0	0	0
Nervous system disorders	2 (1.5%)	0	2 (1.1%)	0	0	0
Ischaemic stroke	1 (0.8%)	0	1 (0.5%)	0	0	0
Status epilepticus	1 (0.8%)	0	1 (0.5%)	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: This table includes AEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page. Adverse events are reported using MedDRA Version 22.1
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

In the table below HemCR rates and cardiac response rates in subjects with cardiac Stage II and Stage III in the daratumumab SC+CyBorD arm are compared with those in the CyBorD arm (cardiac Stage III

daratumumab SC+CyBorD arm: 33.3%, CyBorD: 15.9%; cardiac Stage II daratumumab SC+CyBorD arm: 50.9%, CyBorD: 29.6%).

Table 61 **Summary of Confirmed Complete Hematologic Response Rate and Cardiac Response Based on IRC Assessment, and Deaths (Study 54767414AMY3001)**

	CyBorD			Dara SC + CyBorD		
	HemCR	Cardiac Response	Death	HemCR	Cardiac Response	Death
All patients	35/193 (18.1%)	26/117 (22.2%)	29/193 (15.0%)	104/195 (53.3%)	49/118 (41.5%)	27/195 (13.8%)
Baseline cardiac stage						
Mayo Clinic Cardiac Staging I	12/43 (27.9%)	-	1/43 (2.3%)	21/47 (44.7%)	-	0
Mayo Clinic Cardiac Staging II	16/80 (20.0%)	16/54 (29.6%)	9/80 (11.3%)	41/76 (53.9%)	28/55 (50.9%)	8/76 (10.5%)
Mayo Clinic Cardiac Staging III	7/70 (10.0%)	10/63 (15.9%)	19/70 (27.1%)	42/72 (58.3%)	21/63 (33.3%)	19/72 (26.4%)
NYHA class						
CLASS I	20/94 (21.3%)	12/35 (34.3%)	6/94 (6.4%)	48/101 (47.5%)	21/42 (50.0%)	5/101 (5.0%)
CLASS II	12/89 (13.5%)	12/73 (16.4%)	21/89 (23.6%)	47/77 (61.0%)	25/63 (39.7%)	14/77 (18.2%)
CLASS IIIA	3/10 (30.0%)	2/9 (22.2%)	2/10 (20.0%)	9/17 (52.9%)	3/13 (23.1%)	8/17 (47.1%)

According to table below there are a total of 30 patients in the safety population in the daratumumab SC+CyBorD arm (30/193 (15.5%)) with reported Grade 5 or SAEs of cardiac-related toxicity. In the CyBorD arm, there are 25 patients in the safety population (25/188 (13.3%)) with a reported Grade 5 or SAEs of cardiac-related toxicity. The majority of patients (54/55) reported baseline cardiac Stage II or Stage III; and 46/55 patients reported baseline NYHA Class II or Class IIIA (TSFAE05P).

Table 62 **Number of Subjects With Toxicity Grade 5 or Serious Treatment-emergent Cardiac Disorders by Baseline Cardiac Stage, System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD			Dara SC+CyBorD		
	Cardiac Stage I	Cardiac Stage II	Cardiac Stage IIIa/IIIb	Cardiac Stage I	Cardiac Stage II	Cardiac Stage IIIa/IIIb
Analysis set: safety	42	79	67	46	75	72
Subjects with 1 or more toxicity grade 5 or serious TEAEs	1 (2.4%)	7 (8.9%)	17 (25.4%)	0	10 (13.3%)	20 (27.8%)
System organ class /Preferred term						
Cardiac disorders	1 (2.4%)	7 (8.9%)	17 (25.4%)	0	10 (13.3%)	20 (27.8%)
Acute left ventricular failure	0	0	1 (1.5%)	0	0	0
Acute myocardial infarction	0	0	1 (1.5%)	0	0	0

Table 63 **Number of Subjects With Toxicity Grade 5 or Serious Treatment-emergent Cardiac Disorders by Baseline Cardiac Stage, System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD			Dara SC+CyBorD		
	Cardiac Stage I	Cardiac Stage II	Cardiac Stage IIIa/IIIb	Cardiac Stage I	Cardiac Stage II	Cardiac Stage IIIa/IIIb
Angina pectoris	0	1 (1.3%)	0	0	2 (2.7%)	0
Arrhythmia	0	1 (1.3%)	1 (1.5%)	0	0	0
Arteriospasm coronary	0	0	0	0	1 (1.3%)	0
Atrial fibrillation	0	0	2 (3.0%)	0	1 (1.3%)	3 (4.2%)
Atrial flutter	0	0	0	0	1 (1.3%)	1 (1.4%)
Atrial tachycardia	0	0	1 (1.5%)	0	0	0
Atrial thrombosis	0	0	1 (1.5%)	0	0	0
Bradyarrhythmia	0	0	0	0	0	1 (1.4%)
Cardiac arrest	0	2 (2.5%)	1 (1.5%)	0	2 (2.7%)	5 (6.9%)
Cardiac failure	0	1 (1.3%)	7 (10.4%)	0	2 (2.7%)	10 (13.9%)
Cardiac failure congestive	0	0	2 (3.0%)	0	1 (1.3%)	0
Cardiogenic shock	0	0	0	0	1 (1.3%)	0
Cardiomyopathy	1 (2.4%)	0	0	0	0	0
Cardiovascular insufficiency	0	0	0	0	0	1 (1.4%)
Left ventricular dysfunction	0	0	0	0	1 (1.3%)	0
Mitral valve incompetence	0	0	1 (1.5%)	0	0	0
Myocardial infarction	0	1 (1.3%)	1 (1.5%)	0	0	0
Pericarditis	0	0	0	0	1 (1.3%)	0
Sinus bradycardia	0	1 (1.3%)	0	0	0	0
Sinus node dysfunction	0	0	1 (1.5%)	0	0	0
Sinus tachycardia	0	1 (1.3%)	0	0	0	0

Serious adverse events

43.0% of subjects in the daratumumab SC+CyBorD arm experienced ≥1 treatment-emergent SAE compared with 36.2% in the CyBorD arm (Table below). The most commonly reported treatment-emergent SAEs were pneumonia (daratumumab SC+CyBorD:7.3%; CyBorD: 4.8%) and cardiac failure/cardiac failure congestive combined (daratumumab SC+CyBorD: ((13/193) 6.7%; CyBorD: (10/188) 5.3%).

Table 64 **Most Common (at least 2%) Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more TEAEs	68 (36.2%)	83 (43.0%)
System organ class Preferred term		
Infections and infestations	16 (8.5%)	31 (16.1%)
Pneumonia	9 (4.8%)	14 (7.3%)
Sepsis	0	6 (3.1%)
Cardiac disorders	25 (13.3%)	30 (15.5%)
Cardiac failure	8 (4.3%)	12 (6.2%)
Cardiac arrest	3 (1.6%)	7 (3.6%)
Atrial fibrillation	2 (1.1%)	4 (2.1%)
Respiratory, thoracic and mediastinal disorders	11 (5.9%)	17 (8.8%)
Dyspnoea	3 (1.6%)	4 (2.1%)
Pleural effusion	1 (0.5%)	4 (2.1%)
General disorders and administration site conditions	12 (6.4%)	15 (7.8%)
Sudden death	3 (1.6%)	6 (3.1%)
Gastrointestinal disorders	6 (3.2%)	8 (4.1%)
Diarrhoea	4 (2.1%)	3 (1.6%)
Metabolism and nutrition disorders	10 (5.3%)	7 (3.6%)
Fluid overload	5 (2.7%)	1 (0.5%)
Nervous system disorders	9 (4.8%)	7 (3.6%)
Syncope	6 (3.2%)	3 (1.6%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 22.1.

Gastrointestinal, nervous system and renal treatment-emergent SAEs were reported at similar incidence (<5%) in both treatment arms (TSFAE05).

Table 65 Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more serious TEAEs	68 (36.2%)	83 (43.0%)
System organ class Preferred term		
Infections and infestations	16 (8.5%)	31 (16.1%)
Pneumonia	9 (4.8%)	14 (7.3%)
Sepsis	0	6 (3.1%)
Septic shock	1 (0.5%)	2 (1.0%)
Adenovirus infection	0	1 (0.5%)
Candida sepsis	0	1 (0.5%)
Cellulitis	1 (0.5%)	1 (0.5%)
Escherichia bacteraemia	0	1 (0.5%)
Influenza	2 (1.1%)	1 (0.5%)
Lower respiratory tract infection	3 (1.6%)	1 (0.5%)
Lower respiratory tract infection viral	0	1 (0.5%)
Neutropenic sepsis	0	1 (0.5%)
Peritonitis	0	1 (0.5%)
Pneumonia pneumococcal	1 (0.5%)	1 (0.5%)
Pulmonary sepsis	0	1 (0.5%)
Pyelonephritis acute	0	1 (0.5%)
Respiratory syncytial virus infection	0	1 (0.5%)
Respiratory tract infection	0	1 (0.5%)
Rhinovirus infection	0	1 (0.5%)
Urinary tract infection	0	1 (0.5%)
Wound infection	0	1 (0.5%)
Bronchitis	1 (0.5%)	0
Gastrointestinal infection	1 (0.5%)	0
Herpes zoster	1 (0.5%)	0
Upper respiratory tract infection	1 (0.5%)	0
Cardiac disorders	25 (13.3%)	30 (15.5%)
Cardiac failure	8 (4.3%)	12 (6.2%)
Cardiac arrest	3 (1.6%)	7 (3.6%)
Atrial fibrillation	2 (1.1%)	4 (2.1%)
Angina pectoris	1 (0.5%)	2 (1.0%)
Atrial flutter	0	2 (1.0%)
Arteriospasm coronary	0	1 (0.5%)
Bradyarrhythmia	0	1 (0.5%)
Cardiac failure congestive	2 (1.1%)	1 (0.5%)
Cardiogenic shock	0	1 (0.5%)
Cardiovascular insufficiency	0	1 (0.5%)
Left ventricular dysfunction	0	1 (0.5%)
Pericarditis	0	1 (0.5%)
Acute left ventricular failure	1 (0.5%)	0
Acute myocardial infarction	1 (0.5%)	0
Arrhythmia	2 (1.1%)	0
Atrial tachycardia	1 (0.5%)	0
Atrial thrombosis	1 (0.5%)	0
Cardiomyopathy	1 (0.5%)	0
Mitral valve incompetence	1 (0.5%)	0
Myocardial infarction	2 (1.1%)	0
Sinus bradycardia	1 (0.5%)	0
Sinus node dysfunction	1 (0.5%)	0

Table 66 Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Sinus tachycardia	1 (0.5%)	0
Respiratory, thoracic and mediastinal disorders	11 (5.9%)	17 (8.8%)
Dyspnoea	3 (1.6%)	4 (2.1%)
Pleural effusion	1 (0.5%)	4 (2.1%)
Pneumothorax	1 (0.5%)	2 (1.0%)
Bronchospasm	0	1 (0.5%)
Chronic obstructive pulmonary disease	0	1 (0.5%)
Epistaxis	0	1 (0.5%)
Hypoxia	1 (0.5%)	1 (0.5%)
Lung disorder	0	1 (0.5%)
Pneumonia aspiration	0	1 (0.5%)
Pulmonary embolism	1 (0.5%)	1 (0.5%)
Pulmonary haemorrhage	0	1 (0.5%)
Pulmonary oedema	2 (1.1%)	1 (0.5%)
Acute pulmonary oedema	1 (0.5%)	0
Acute respiratory distress syndrome	1 (0.5%)	0
Respiratory failure	1 (0.5%)	0
General disorders and administration site conditions	12 (6.4%)	15 (7.8%)
Sudden death	3 (1.6%)	6 (3.1%)
Asthenia	0	3 (1.6%)
Oedema peripheral	2 (1.1%)	3 (1.6%)
Malaise	1 (0.5%)	1 (0.5%)
Non-cardiac chest pain	1 (0.5%)	1 (0.5%)
Pyrexia	1 (0.5%)	1 (0.5%)
Chest pain	1 (0.5%)	0
Fatigue	1 (0.5%)	0
General physical health deterioration	1 (0.5%)	0
Sudden cardiac death	1 (0.5%)	0
Gastrointestinal disorders	6 (3.2%)	8 (4.1%)
Diarrhoea	4 (2.1%)	3 (1.6%)
Abdominal pain	1 (0.5%)	1 (0.5%)
Colitis ischaemic	0	1 (0.5%)
Gastric ulcer	0	1 (0.5%)
Melaena	0	1 (0.5%)
Vomiting	0	1 (0.5%)
Gastrointestinal haemorrhage	1 (0.5%)	0
Nausea	2 (1.1%)	0
Metabolism and nutrition disorders	10 (5.3%)	7 (3.6%)
Dehydration	2 (1.1%)	2 (1.0%)
Hyperkalaemia	0	2 (1.0%)
Diabetes mellitus	0	1 (0.5%)
Fluid overload	5 (2.7%)	1 (0.5%)
Hypoglycaemia	0	1 (0.5%)
Hyponatraemia	3 (1.6%)	1 (0.5%)
Decreased appetite	1 (0.5%)	0
Hypokalaemia	1 (0.5%)	0
Nervous system disorders	9 (4.8%)	7 (3.6%)
Syncope	6 (3.2%)	3 (1.6%)
Cerebrovascular accident	1 (0.5%)	1 (0.5%)
Facial paralysis	0	1 (0.5%)
Hemiparesis	0	1 (0.5%)
Peripheral sensorimotor neuropathy	0	1 (0.5%)
Ischaemic stroke	1 (0.5%)	0
Status epilepticus	1 (0.5%)	0
Renal and urinary disorders	5 (2.7%)	7 (3.6%)

Table 67 Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Acute kidney injury	1 (0.5%)	2 (1.0%)
Chronic kidney disease	1 (0.5%)	1 (0.5%)
Haematuria	0	1 (0.5%)
Nephropathy	0	1 (0.5%)
Nephrotic syndrome	0	1 (0.5%)
Renal failure	2 (1.1%)	1 (0.5%)
Renal impairment	1 (0.5%)	0
Blood and lymphatic system disorders	2 (1.1%)	4 (2.1%)
Febrile neutropenia	0	1 (0.5%)
Haemorrhagic diathesis	0	1 (0.5%)
Lymphopenia	0	1 (0.5%)
Neutropenia	0	1 (0.5%)
Anaemia	1 (0.5%)	0
Thrombocytopenia	1 (0.5%)	0
Injury, poisoning and procedural complications	2 (1.1%)	3 (1.6%)
Delayed engraftment	0	1 (0.5%)
Head injury	0	1 (0.5%)
Hip fracture	0	1 (0.5%)
Rib fracture	1 (0.5%)	0
Skin laceration	1 (0.5%)	0
Traumatic liver injury	1 (0.5%)	0
Vascular disorders	2 (1.1%)	3 (1.6%)
Hypotension	1 (0.5%)	1 (0.5%)
Orthostatic hypotension	0	1 (0.5%)
Thrombosis	0	1 (0.5%)
Circulatory collapse	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	2 (1.0%)
Basal cell carcinoma	0	1 (0.5%)
Bladder cancer	0	1 (0.5%)
Congenital, familial and genetic disorders	0	1 (0.5%)
Hereditary haemorrhagic telangiectasia	0	1 (0.5%)
Eye disorders	0	1 (0.5%)
Amaurosis fugax	0	1 (0.5%)
Hepatobiliary disorders	0	1 (0.5%)
Hepatomegaly	0	1 (0.5%)
Hyperbilirubinaemia	0	1 (0.5%)
Investigations	0	1 (0.5%)
Influenza A virus test positive	0	1 (0.5%)
Weight decreased	0	1 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.5%)	1 (0.5%)
Connective tissue inflammation	0	1 (0.5%)
Osteoporosis	1 (0.5%)	0
Psychiatric disorders	3 (1.6%)	1 (0.5%)
Delirium	0	1 (0.5%)
Anxiety	2 (1.1%)	0
Depression	1 (0.5%)	0
Skin and subcutaneous tissue disorders	0	1 (0.5%)
Petechiae	0	1 (0.5%)
Surgical and medical procedures	0	1 (0.5%)
Cardiac ablation	0	1 (0.5%)

Laboratory findings

Haematology

The worst toxicity grades observed during treatment for hematology parameters were balanced between treatment arms except for a higher incidence of Grade 4 neutropenia in the daratumumab SC+CyBorD arm (daratumumab SC+CyBorD: 3.2%; CyBorD: 0%; see Table below).

Table 68 Summary of Worst Toxicity Grade During Treatment in Hematology; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n(%)						Dara SC + CyBorD n(%)					
	Toxicity Grade						Toxicity Grade					
	Total	0	1	2	3	4	Total	0	1	2	3	4
Analysis set: safety	188						193					
Hematology												
Hemoglobin low (Anemia)	186 (98.9%)	16 (8.6%)	118 (63.4%)	40 (21.5%)	12 (6.5%)	0	188 (97.4%)	20 (10.6%)	113 (60.1%)	43 (22.9%)	12 (6.4%)	0
Neutrophils low (Neutropenia)	186 (98.9%)	149 (80.1%)	21 (11.3%)	9 (4.8%)	7 (3.8%)	0	188 (97.4%)	130 (69.1%)	31 (16.5%)	15 (8.0%)	6 (3.2%)	6 (3.2%)
Platelets low (Thrombocytopenia)	186 (98.9%)	103 (55.4%)	72 (38.7%)	4 (2.2%)	6 (3.2%)	1 (0.5%)	188 (97.4%)	93 (49.5%)	76 (40.4%)	13 (6.9%)	4 (2.1%)	2 (1.1%)
WBC low (Leukopenia)	186 (98.9%)	95 (51.1%)	64 (34.4%)	19 (10.2%)	8 (4.3%)	0	188 (97.4%)	72 (38.3%)	71 (37.8%)	31 (16.5%)	9 (4.8%)	5 (2.7%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Keys: ALT = alanine aminotransferase; AST = aspartate aminotransferase; WBC = white blood cell.
Note: The laboratory toxicity grades are derived based on the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03. Grade 0 means normal. Subjects reported as Grade 0 are subjects with normal values or a value in the opposite direction (for laboratory tests with bidirectional toxicities defined).
Note: For each parameter, the total column includes all subjects with available data at both baseline and post-baseline, including those whose toxicity grade did not worsen during treatment; percentages in the total column are calculated with the number of treated subjects in each group as denominator. Percentages for toxicity grade columns are calculated with the number of subjects in the total column as denominator. For each subject and each parameter, the worst toxicity grade is selected.
Results are based on both central and local lab data.

Neutropenia/Anemia/Thrombocytopenia

Table 69 Number of Subjects With Toxicity Grade 3 or 4 Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Subjects with 1 or more toxicity grade 3 or 4 TEAEs	108 (57.4%)	113 (58.5%)
System organ class Preferred term		
Blood and lymphatic system disorders	33 (17.6%)	35 (18.1%)
Lymphopenia	19 (10.1%)	25 (13.0%)
Neutropenia	5 (2.7%)	10 (5.2%)
Anaemia	9 (4.8%)	8 (4.1%)
Thrombocytopenia	5 (2.7%)	6 (3.1%)
Febrile neutropenia	0	2 (1.0%)
Leukopenia	2 (1.1%)	2 (1.0%)
Blood loss anaemia	1 (0.5%)	0

Table 70 Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)	Dara SC + CyBorD n (%)
Acute kidney injury	1 (0.5%)	2 (1.0%)
Chronic kidney disease	1 (0.5%)	1 (0.5%)
Haematuria	0	1 (0.5%)
Nephropathy	0	1 (0.5%)
Nephrotic syndrome	0	1 (0.5%)
Renal failure	2 (1.1%)	1 (0.5%)
Renal impairment	1 (0.5%)	0
Blood and lymphatic system disorders	2 (1.1%)	4 (2.1%)
Febrile neutropenia	0	1 (0.5%)
Haemorrhagic diathesis	0	1 (0.5%)
Lymphopenia	0	1 (0.5%)
Neutropenia	0	1 (0.5%)
Anaemia	1 (0.5%)	0
Thrombocytopenia	1 (0.5%)	0

Neutropenia by Body Weight

The incidence of any grade (≤65kg: 19.4%, >65 to 85kg: 9.5%, >85kg: 0%) and Grade 3 or 4 (≤65 kg: 9.7%, >65 to 85 kg: 4.2%, >85 kg: 0%) neutropenia was higher in the lower body weight subgroup (≤65 kg) for the SC+CyBorD arm; this trend was not observed in the CyBorD arm.

Thrombocytopenia by Body Weight

The incidence of any grade (≤65 kg: 21%, >65 to 85 kg: 15.8%, >85 kg: 13.9%) and Grade 3 or 4 (≤65 kg: 6.5%, >65 to 85 kg: 2.1%, >85 kg: 0%) thrombocytopenia was higher in the lower body weight subgroup (≤65 kg) for the SC+CyBorD arm. In the CyBorD arm, Grade 3 or 4 (≤65 kg: 4.2%, >65 to 85 kg: 1.4%, >85 kg: 2.2%) thrombocytopenia was higher in the lower body weight subgroup (≤65 kg). These differences did not lead to an increase in treatment discontinuation due to thrombocytopenia. There were no serious cases of thrombocytopenia in the SC+CyBorD arm.

Haemorrhagic Events as a Consequence of Thrombocytopenia

Table 71 Number of Subjects with Treatment-emergent Hemorrhage Events by System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)					
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Analysis set: safety	188					
Total number of subjects with treatment-emergent hemorrhage events	26 (13.8%)	20 (10.6%)	5 (2.7%)	1 (0.5%)	0	0

Table 72 Number of Subjects with Treatment-emergent Hemorrhage Events by System Organ Class, Preferred Term and Maximum Toxicity Grade; Safety Analysis Set (Study 54767414AMY3001)

	Dara SC + CyBorD n (%)					
	All Grades	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Analysis set: safety	193					
Total number of subjects with treatment-emergent hemorrhage events	57 (29.5%)	40 (20.7%)	12 (6.2%)	4 (2.1%)	0	1 (0.5%)

Safety in special populations

Table 73 : Overview Summary of Treatment-emergent Adverse Events by Age; Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)			Dara SC + CyBorD n (%)		
	<65	>=65	Total	<65	>=65	Total
Analysis set: safety	92	96	188	106	87	193
Any TEAE	91 (98.9%)	94 (97.9%)	185 (98.4%)	104 (98.1%)	85 (97.7%)	189 (97.9%)
At least one related[a]	82 (89.1%)	87 (90.6%)	169 (89.9%)	94 (88.7%)	80 (92.0%)	174 (90.2%)
At least one related to daratumumab	0	1 (1.0%)	1 (0.5%)	60 (56.6%)	50 (57.5%)	110 (57.0%)
At least one related to cyclophosphamide	61 (66.3%)	70 (72.9%)	131 (69.7%)	61 (57.5%)	61 (70.1%)	122 (63.2%)
At least one related to bortezomib	73 (79.3%)	75 (78.1%)	148 (78.7%)	85 (80.2%)	71 (81.6%)	156 (80.8%)
At least one related to dexamethasone	64 (69.6%)	66 (68.8%)	130 (69.1%)	79 (74.5%)	64 (73.6%)	143 (74.1%)
Maximum toxicity grade						
Grade 1	6 (6.5%)	4 (4.2%)	10 (5.3%)	6 (5.7%)	2 (2.3%)	8 (4.1%)
Grade 2	38 (41.3%)	23 (24.0%)	61 (32.4%)	40 (37.7%)	22 (25.3%)	62 (32.1%)
Grade 3	39 (42.4%)	44 (45.8%)	83 (44.1%)	37 (34.9%)	42 (48.3%)	79 (40.9%)
Grade 4	5 (5.4%)	11 (11.5%)	16 (8.5%)	11 (10.4%)	7 (8.0%)	18 (9.3%)
Grade 5	3 (3.3%)	12 (12.5%)	15 (8.0%)	10 (9.4%)	12 (13.8%)	22 (11.4%)
Any serious TEAE	22 (23.9%)	46 (47.9%)	68 (36.2%)	39 (36.8%)	44 (50.6%)	83 (43.0%)
At least one related[a]	10 (10.9%)	18 (18.8%)	28 (14.9%)	21 (19.8%)	19 (21.8%)	40 (20.7%)
At least one related to daratumumab	0	0	0	13 (12.3%)	11 (12.6%)	24 (12.4%)
At least one related to cyclophosphamide	5 (5.4%)	9 (9.4%)	14 (7.4%)	10 (9.4%)	13 (14.9%)	23 (11.9%)
At least one related to bortezomib	3 (3.3%)	11 (11.5%)	14 (7.4%)	18 (17.0%)	12 (13.8%)	30 (15.5%)
At least one related to dexamethasone	10 (10.9%)	13 (13.5%)	23 (12.2%)	13 (12.3%)	15 (17.2%)	28 (14.5%)
TEAE leading to discontinuation of daratumumab	0	0	0	3 (2.8%)	6 (6.9%)	9 (4.7%)
Related to daratumumab	0	0	0	2 (1.9%)	2 (2.3%)	4 (2.1%)
TEAE leading to discontinuation of cyclophosphamide	5 (5.4%)	7 (7.3%)	12 (6.4%)	3 (2.8%)	8 (9.2%)	11 (5.7%)
Related to cyclophosphamide	2 (2.2%)	2 (2.1%)	4 (2.1%)	1 (0.9%)	5 (5.7%)	6 (3.1%)
TEAE leading to discontinuation of bortezomib	5 (5.4%)	9 (9.4%)	14 (7.4%)	7 (6.6%)	5 (5.7%)	12 (6.2%)
Related to bortezomib	2 (2.2%)	3 (3.1%)	5 (2.7%)	6 (5.7%)	2 (2.3%)	8 (4.1%)
TEAE leading to discontinuation of dexamethasone	5 (5.4%)	8 (8.3%)	13 (6.9%)	6 (5.7%)	6 (6.9%)	12 (6.2%)
Related to dexamethasone	3 (3.3%)	4 (4.2%)	7 (3.7%)	3 (2.8%)	3 (3.4%)	6 (3.1%)
TEAE leading to discontinuation of study treatment[b]	3 (3.3%)	5 (5.2%)	8 (4.3%)	2 (1.9%)	6 (6.9%)	8 (4.1%)

The MAH was asked to provide the main safety data (frequency, types and severity of AEs, SAEs, deaths) for the following patients' subgroups: - patients ≥75 years old; - patients between the ages of 65 and 75, with important co-morbidities (ex. renal- and liver status) and/or a poor performance status (i.e. ECOG 2), given that this population could be more fragile and could have a worse tolerability to the drugs combination. Results are presented in tables below:

Table 74: Overview Summary of Treatment-emergent Adverse Events by Age - ECOG Performance Score of 2 or Renal/Liver Disorders Subjects (CCO= 13Nov2020); Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)				Dara SC+CyBorD n (%)			
	<65	>=65 to <75	>=75	Total	<65	>=65 to <75	>=75	Total
Analysis set: Safety - ECOG performance score of 2 or renal/liver disorders subjects	22	22	10	54	31	23	7	61
Any TEAE	22 (100.0%)	22 (100.0%)	10 (100.0%)	54 (100.0%)	31 (100.0%)	23 (100.0%)	7 (100.0%)	61 (100.0%)
At least one related[a]	20 (90.9%)	22 (100.0%)	10 (100.0%)	52 (96.3%)	30 (96.8%)	21 (91.3%)	7 (100.0%)	58 (95.1%)
At least one related to daratumumab	0	0	0	0	22 (71.0%)	16 (69.6%)	4 (57.1%)	42 (68.9%)
At least one related to cyclophosphamide	17 (77.3%)	19 (86.4%)	10 (100.0%)	46 (85.2%)	25 (80.6%)	15 (65.2%)	5 (71.4%)	45 (73.8%)
At least one related to bortezomib	18 (81.8%)	20 (90.9%)	10 (100.0%)	48 (88.9%)	27 (87.1%)	18 (78.3%)	7 (100.0%)	52 (85.2%)
At least one related to dexamethasone	13 (59.1%)	17 (77.3%)	10 (100.0%)	40 (74.1%)	29 (93.5%)	17 (73.9%)	5 (71.4%)	51 (83.6%)
Maximum toxicity grade								
1	0	2 (9.1%)	0	2 (3.7%)	0	0	0	0
2	5 (22.7%)	3 (13.6%)	1 (10.0%)	9 (16.7%)	6 (19.4%)	1 (4.3%)	1 (14.3%)	8 (13.1%)
3	15 (68.2%)	8 (36.4%)	5 (50.0%)	28 (51.9%)	17 (54.8%)	13 (56.5%)	4 (57.1%)	34 (55.7%)
4	2 (9.1%)	5 (22.7%)	2 (20.0%)	9 (16.7%)	5 (16.1%)	2 (8.7%)	0	7 (11.5%)
5	0	4 (18.2%)	2 (20.0%)	6 (11.1%)	3 (9.7%)	7 (30.4%)	2 (28.6%)	12 (19.7%)
Any serious TEAE	6 (27.3%)	13 (59.1%)	8 (80.0%)	27 (50.0%)	18 (58.1%)	17 (73.9%)	5 (71.4%)	40 (65.6%)

At least one related	3 (13.6%)	7 (31.8%)	5 (50.0%)	15 (27.8%)	9 (29.0%)	6 (26.1%)	2 (28.6%)	17 (27.9%)
At least one related to bortezomib	0	5 (22.7%)	3 (30.0%)	8 (14.8%)	7 (22.6%)	3 (13.0%)	1 (14.3%)	11 (18.0%)
At least one related to cyclophosphamide	1 (4.5%)	4 (18.2%)	3 (30.0%)	8 (14.8%)	6 (19.4%)	3 (13.0%)	1 (14.3%)	10 (16.4%)
At least one related to daratumumab	0	0	0	0	9 (29.0%)	4 (17.4%)	1 (14.3%)	14 (23.0%)
At least one related to dexamethasone	3 (13.6%)	5 (22.7%)	4 (40.0%)	12 (22.2%)	7 (22.6%)	4 (17.4%)	2 (28.6%)	13 (21.3%)
TEAE leading to discontinuation of daratumumab	0	0	0	0	0	1 (4.3%)	1 (14.3%)	2 (3.3%)
TEAE leading to discontinuation of cyclophosphamide	3 (13.6%)	5 (22.7%)	0	8 (14.8%)	0	0	2 (28.6%)	2 (3.3%)
related to cyclophosphamide	0	2 (9.1%)	0	2 (3.7%)	0	0	1 (14.3%)	1 (1.6%)
TEAE leading to discontinuation of bortezomib	4 (18.2%)	5 (22.7%)	0	9 (16.7%)	2 (6.5%)	0	1 (14.3%)	3 (4.9%)
related to bortezomib	1 (4.5%)	2 (9.1%)	0	3 (5.6%)	2 (6.5%)	0	0	2 (3.3%)
TEAE leading to discontinuation of dexamethasone	4 (18.2%)	5 (22.7%)	0	9 (16.7%)	1 (3.2%)	0	1 (14.3%)	2 (3.3%)
related to dexamethasone	2 (9.1%)	2 (9.1%)	0	4 (7.4%)	1 (3.2%)	0	0	1 (1.6%)
TEAE leading to discontinuation of study treatment[b]	2 (9.1%)	3 (13.6%)	0	5 (9.3%)	0	1 (4.3%)	1 (14.3%)	2 (3.3%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab.
[b] This table includes AEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 75: Overview Summary of Treatment-emergent Adverse Events by Age (CCO=13Nov2020); Safety Analysis Set (Study 54767414AMY3001)

	CyBorD n (%)				Dara SC+CyBorD n (%)			
	<65	>=65 to <75	>=75	Total	<65	>=65 to <75	>=75	Total
Analysis set: Safety Analysis Set	92	69	27	188	106	67	20	193
Any TEAE	91 (98.9%)	67 (97.1%)	27 (100.0%)	185 (98.4%)	104 (98.1%)	65 (97.0%)	20 (100.0%)	189 (97.9%)
At least one related[a]	82 (89.1%)	61 (88.4%)	26 (96.3%)	169 (89.9%)	94 (88.7%)	60 (89.6%)	20 (100.0%)	174 (90.2%)
At least one related to daratumumab	0	0	0	0	63 (59.4%)	37 (55.2%)	13 (65.0%)	113 (58.5%)
At least one related to cyclophosphamide	61 (66.3%)	48 (69.6%)	23 (85.2%)	132 (70.2%)	63 (59.4%)	47 (70.1%)	14 (70.0%)	124 (64.2%)
At least one related to bortezomib	73 (79.3%)	51 (73.9%)	24 (88.9%)	148 (78.7%)	85 (80.2%)	52 (77.6%)	19 (95.0%)	156 (80.8%)
At least one related to dexamethasone	64 (69.6%)	45 (65.2%)	21 (77.8%)	130 (69.1%)	79 (74.5%)	48 (71.6%)	16 (80.0%)	143 (74.1%)
Maximum toxicity grade								
1	6 (6.5%)	4 (5.8%)	0	10 (5.3%)	5 (4.7%)	2 (3.0%)	0	7 (3.6%)
2	38 (41.3%)	17 (24.6%)	6 (22.2%)	61 (32.4%)	38 (35.8%)	15 (22.4%)	5 (25.0%)	58 (30.1%)
3	39 (42.4%)	27 (39.1%)	17 (63.0%)	83 (44.1%)	38 (35.8%)	34 (50.7%)	8 (40.0%)	80 (41.5%)
4	4 (4.3%)	9 (13.0%)	2 (7.4%)	15 (8.0%)	13 (12.3%)	5 (7.5%)	2 (10.0%)	20 (10.4%)
5	4 (4.3%)	10 (14.5%)	2 (7.4%)	16 (8.5%)	10 (9.4%)	9 (13.4%)	5 (25.0%)	24 (12.4%)
Any serious TEAE	22 (23.9%)	31 (44.9%)	15 (55.6%)	68 (36.2%)	43 (40.6%)	33 (49.3%)	13 (65.0%)	89 (46.1%)
At least one related	10 (10.9%)	11 (15.9%)	7 (25.9%)	28 (14.9%)	23 (21.7%)	16 (23.9%)	4 (20.0%)	43 (22.3%)
At least one related to bortezomib	3 (3.3%)	7 (10.1%)	4 (14.8%)	14 (7.4%)	18 (17.0%)	9 (13.4%)	3 (15.0%)	30 (15.5%)
At least one related to cyclophosphamide	5 (5.4%)	5 (7.2%)	4 (14.8%)	14 (7.4%)	10 (9.4%)	11 (16.4%)	2 (10.0%)	23 (11.9%)
At least one related to daratumumab	0	0	0	0	16 (15.1%)	9 (13.4%)	2 (10.0%)	27 (14.0%)
At least one related to dexamethasone	10 (10.9%)	8 (11.6%)	5 (18.5%)	23 (12.2%)	13 (12.3%)	12 (17.9%)	4 (20.0%)	29 (15.0%)
TEAE leading to discontinuation of daratumumab	0	0	0	0	3 (2.8%)	6 (9.0%)	2 (10.0%)	11 (5.7%)
related to daratumumab	0	0	0	0	2 (1.9%)	2 (3.0%)	1 (5.0%)	5 (2.6%)
TEAE leading to discontinuation of cyclophosphamide	5 (5.4%)	6 (8.7%)	1 (3.7%)	12 (6.4%)	3 (2.8%)	4 (6.0%)	4 (20.0%)	11 (5.7%)
related to cyclophosphamide	2 (2.2%)	2 (2.9%)	0	4 (2.1%)	1 (0.9%)	3 (4.5%)	2 (10.0%)	6 (3.1%)
TEAE leading to discontinuation of bortezomib	5 (5.4%)	7 (10.1%)	2 (7.4%)	14 (7.4%)	7 (6.6%)	3 (4.5%)	2 (10.0%)	12 (6.2%)
related to bortezomib	2 (2.2%)	2 (2.9%)	1 (3.7%)	5 (2.7%)	6 (5.7%)	1 (1.5%)	1 (5.0%)	8 (4.1%)
TEAE leading to discontinuation of dexamethasone	5 (5.4%)	6 (8.7%)	2 (7.4%)	13 (6.9%)	6 (5.7%)	4 (6.0%)	2 (10.0%)	12 (6.2%)

related to dexamethasone	3 (3.3%)	2 (2.9%)	2 (7.4%)	7 (3.7%)	3 (2.8%)	2 (3.0%)	1 (5.0%)	6 (3.1%)
TEAE leading to discontinuation of study treatment	3 (3.3%)	4 (5.8%)	1 (3.7%)	8 (4.3%)	2 (1.9%)	6 (9.0%)	2 (10.0%)	10 (5.2%)
COVID-19 related TEAEs								
COVID-19 related AEs	0	0	0	0	1 (0.9%)	0	0	1 (0.5%)
COVID-19 related SAEs	0	0	0	0	0	0	0	0
COVID-19 related non-serious AEs	0	0	0	0	1 (0.9%)	0	0	1 (0.5%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
[a] TEAEs related to at least 1 of the 4 components of study treatment: cyclophosphamide, bortezomib, dexamethasone and daratumumab.
[b] This table includes AEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

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Safety related to drug-drug interactions and other interactions

No PK drug-drug interaction studies have been conducted with Darzalex.

Clinical pharmacokinetic assessments with daratumumab intravenous or subcutaneous formulations and lenalidomide, pomalidomide, thalidomide, bortezomib, melphalan, prednisone, carfilzomib, cyclophosphamide and dexamethasone indicated no clinically relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Discontinuation due to adverse events

The incidence of any grade AE was 4.1% for Daratumumab SC+CyBorD: and 4.3% for CyBorD and of Grade 3 or 4 3.1% and 2.7%, respectively. TEAEs leading to discontinuation of study treatment are shown in Table 79. TEAEs leading to discontinuation of either study treatment are shown in Table 80.

Table 76 **Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Treatment by System Organ Class and Preferred Term; Safety Analysis Set (Study 54767414AMY3001)**

	CyBorD n (%)		Dara SC + CyBorD n (%)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Analysis set: safety	188		193	
Subjects with 1 or more TEAEs leading to discontinuation of study treatment	8 (4.3%)	5 (2.7%)	8 (4.1%)	6 (3.1%)
System organ class Preferred term				
Infections and infestations	1 (0.5%)	1 (0.5%)	3 (1.6%)	2 (1.0%)
Pneumonia	1 (0.5%)	1 (0.5%)	1 (0.5%)	0
Pulmonary sepsis	0	0	1 (0.5%)	1 (0.5%)
Septic shock	0	0	1 (0.5%)	1 (0.5%)
Cardiac disorders	2 (1.1%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Cardiovascular insufficiency	0	0	1 (0.5%)	1 (0.5%)
Cardiac failure	2 (1.1%)	1 (0.5%)	0	0
Gastrointestinal disorders	2 (1.1%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
Ascites	0	0	1 (0.5%)	0
Gastric ulcer	0	0	1 (0.5%)	1 (0.5%)
Gastrointestinal haemorrhage	1 (0.5%)	1 (0.5%)	0	0
Nausea	1 (0.5%)	0	0	0
General disorders and administration site conditions	2 (1.1%)	1 (0.5%)	1 (0.5%)	0
Sudden death	0	0	1 (0.5%)	0
Fatigue	2 (1.1%)	1 (0.5%)	0	0
Investigations	0	0	1 (0.5%)	0
Cytomegalovirus test positive	0	0	1 (0.5%)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.5%)	1 (0.5%)
Bladder cancer	0	0	1 (0.5%)	1 (0.5%)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.5%)	1 (0.5%)
Pneumonia aspiration	0	0	1 (0.5%)	1 (0.5%)
Blood and lymphatic system disorders	1 (0.5%)	0	0	0
Thrombocytopenia	1 (0.5%)	0	0	0
Eye disorders	1 (0.5%)	0	0	0
Blepharitis	1 (0.5%)	0	0	0
Psychiatric disorders	2 (1.1%)	1 (0.5%)	0	0
Anxiety	1 (0.5%)	0	0	0
Depression	1 (0.5%)	1 (0.5%)	0	0
Irritability	1 (0.5%)	0	0	0
Mood altered	1 (0.5%)	0	0	0

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: This table includes AEs leading to discontinuation of all study treatment due to an adverse event on the end of treatment CRF page.
Adverse events are reported using MedDRA Version 22.1.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Table 77	Overall Summary of Treatment-emergent Adverse Events; Safety Analysis Set (Study 54767414AMY3001)	
	CyBorD n (%)	Dara SC + CyBorD n (%)
Analysis set: safety	188	193
Any TEAE	185 (98.4%)	189 (97.9%)
Any grade 3 or 4 TEAE	108 (57.4%)	113 (58.5%)
Any serious TEAE	68 (36.2%)	83 (43.0%)
TEAE leading to discontinuation of daratumumab	0	9 (4.7%)
TEAE leading to discontinuation of cyclophosphamide	12 (6.4%)	11 (5.7%)
TEAE leading to discontinuation of bortezomib	14 (7.4%)	12 (6.2%)
TEAE leading to discontinuation of dexamethasone	13 (6.9%)	12 (6.2%)
TEAE leading to discontinuation of study treatment	8 (4.3%)	8 (4.1%)
TEAE leading to death	15 (8.0%)	22 (11.4%)

Keys: CyBorD = cyclophosphamide-bortezomib-dexamethasone; Dara SC = daratumumab subcutaneous + recombinant human hyaluronidase PH20 (rHuPH20).
Key: TEAE = treatment-emergent adverse event.
Note: Toxicity grade is defined according to the NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Version 4.03.

Post marketing experience

Daratumumab SC has only recently been authorised for use in the US, EU and other countries worldwide.

Daratumumab SC has not been authorised for use in subjects with AL amyloidosis in any country worldwide.

Post-marketing safety information is available for daratumumab IV and from a commercially available rHuPH20 formulation, Hylenex.

Daratumumab IV:

A cumulative review was performed on all post-marketing spontaneous cases of daratumumab IV and all events received by the Global Medical Safety (GMS) global safety database cumulatively through 31 March 2020. The results suggest that the drug's post-marketing safety profile is consistent with the known safety profile of daratumumab as a single agent or in combination therapy.

Based on the cumulative review, a total of 2,122,655,000 mg of daratumumab distributed from launch (cumulative to 31 March 2020), the estimated cumulative exposure to daratumumab in marketed use is 81,059 person years.

A search of the GMS global safety database through 31 March 2020 retrieved a total of 6,820 cases. Of these, 621 cases were excluded due to medical unconfirmed cases or multiple unidentifiable patients, and 6,199 were further analysed. Of the cases reporting patient sex, slightly more than half (55.4%, 2,158/3,893) concerned males and where age or age group was reported, the majority of the cases concerned elderly patients (62.0%; 1,949/3,145).

The patients ranged in age from 1.7 to 100 years (mean age 66.5 years and median age 69 years). Among the 6,199 cases, 3,539 were serious. Review of the serious cases revealed that the following preferred terms were reported with the greatest frequency (≥2% event rate): infusion-related reaction (9.3%),

disease progression (4.4%), death (3.6%), neutropenia (3.2%), pneumonia (3%), plasma cell myeloma and thrombocytopenia (2.8% each), and dyspnea (2.7%).

A total of 621 cases reported events with a fatal outcome. Among these cases, the most common fatal preferred terms (≥2% event rate) were death (29.7%), disease progression (10.4%), plasma cell myeloma (7.2%), pneumonia and sepsis (3.5% each), septic shock (2.4%), and infection (2.1%).

Overall, review of post-marketing spontaneous reports did not identify any new safety signal.

rHuPH20: rHuPH20 is the active ingredient of Halozyme's commercial product Hylenex recombinant (hyaluronidase human injection), hereafter referred to as HYLENEX, which was approved in December 2005 by FDA for marketing in the U.S. HYLENEX is a tissue permeability modifier indicated as an adjuvant in SC fluid administration for achieving hydration, to increase the dispersion and absorption of other injected drugs, and in SC urography, for improving resorption of radiopaque agents (HYLENEX PI 2016).

The cumulative patient exposure to HYLENEX from December 2005 to 16 November 2019 is estimated to be approximately 2,504,064 based on the total number of vials distributed less those returned, and on the presumed dose of 150 U rHuPH20 per treated patient. In addition, a total of 1,592 clinical study subjects are known to have been exposed to HYLENEX and other rHuPH20 drug products in 30 clinical studies conducted under the HYLENEX Investigational New Drug (IND) 66,888 or in post-marketing Phase 4 studies. A review of safety information for HYLENEX from the Periodic Safety Update Report reporting period from 16 November 2018 to 15 November 2019 did not identify any new significant safety issues for HYLENEX and other rHuPH20 drug products from post-marketing safety reports.

Further, the safety findings from clinical studies completed during the reporting period were consistent with the known safety profile for HYLENEX and other rHuPH20 drug products.

2.5.1. Discussion on clinical safety

For this application, the safety of daratumumab SC (DARZALEX) in combination with CyBorD (cyclophosmamide-bortezomib-dexamethasone) in subjects with newly diagnosed AL amyloidosis is based on results from the Phase 3 Study AMY3001. Safety data and exposure were evaluated in the Safety Analysis Set, which included all randomized subjects who received at least 1 administration of any study treatment. The clinical cut-off date was 14 February 2020. Safety analyses were based on the safety analysis population, which included subjects treated in the Safety Run-in and randomized parts of the study. There were 193 and 188 subjects treated with daratumumab SC+CyBorD or CyBorD, respectively. Per protocol, subjects in the CyBorD arm were to receive up to a maximum of 6 cycles of study treatment. Whereas, subjects in the daratumumab SC+CyBorD arm were to receive combination therapy for up to 6 cycles, followed by daratumumab SC monotherapy after Cycle 6 until disease progression, start of subsequent therapy, or up to a maximum of 24 cycles (~2 years) from the first dose of study treatment.

The enrolled population was considered adequate and representative for the target population. The median follow-up for this study was 11.4 months.

As reflected in the SmPC, the safety of daratumumab SC (1,800 mg) has been evaluated in total 490 patients with multiple myeloma. The data shows exposure to daratumumab subcutaneous formulation (1,800 mg) in 490 patients with multiple myeloma (MM) including 260 patients from a Phase III active controlled trial (Study MMY3012) who received daratumumab solution for subcutaneous injection as monotherapy and three open label, clinical studies in which patients received daratumumab solution for subcutaneous injection either as monotherapy (N=31, MMY1004 and MMY1008) and MMY2040 in which patients received daratumumab solution for subcutaneous injection in combination with either bortezomib, melphalan and prednisone (D VMP, n=67), lenalidomide and dexamethasone (D Rd, n=65) or bortezomib, lenalidomide and dexamethasone (D VRd, n=67).

All 28 patients in the Safety Run-in cohort had 1 or more **TEAE**s, and 75% had 1 or more Grade 3 or 4 TEAEs and nearly all patients in study AMY3001 in both treatment arms had at least 1 TEAE reported. Twelve patients (42.9%) experienced serious TEAEs, however, no subjects discontinued treatment or withdrew from the study due to an AE. Serious TEAEs were reported for more than 1 (3.6%) patient including cellulitis and pneumonia (7.1% each) and fall and kidney injury (10.7% each).

Due to study design of AMY3001, the median duration of study treatment was nearly 2-fold longer in the daratumumab SC-CyBorD arm (9.6 months) than the CyBorD arm (5.3 months). The median number of treatment cycles received was 11 (range: 1-23) for the daratumumab SC-CyBorD arm and 6 (range: 1-6) for the CyBorD arm. Among patients receiving daratumumab SC-CyBorD, 74.1% were exposed ≥6 months and 32.1% were exposed >1 year. Among patients receiving CyBorD, 3.7% were exposed ≥6 months and no subjects were exposed >1 year. The median total dose of the chemotherapy during the treatment course was well balanced in the two arms with slightly higher dose in the daratumumab arm in cycle 3-6 due to more patients in the CyBorD arm discontinuing study treatment. The extent of exposure of individual study agents was as well balanced in the two arms.

Nearly all patients (SC+CyBorD: 97.9%, CyBorD: 98.4%) in both treatment arms had at least 1 TEAE reported (Table 39). TEAEs related to either type of chemotherapy is balanced between the 2 arms with falling incidence from cycle 7+ in the SC+CyBorD arm (Table 40).

Grade 3 and 4 TEAEs were reported for ≥10% of patients including fatigue (21.4%), lymphopenia (17.9%), diarrhoea, anemia, and peripheral oedema (14.3% each, and pneumonia and fall (10.7%). The incidence of Grade 3 or 4 TEAEs was balanced between the treatment arms during Cycles 1-2 and the most common (>2%) Grade 3 or 4 TEAEs from Cycle 7 onwards were Blood and Lymphatic System Disorders followed by Infections and Infestations, Cardiac Disorders, and Respiratory, Thoracic and Mediastinal Disorders. By preferred term the incidence was for all ≤3.4%.

Adverse events of special interest include **IRR** of which 7.3% of patients experienced this. The incidence, preferred terms, severity, and onset of IRRs were consistent with those previously reported for daratumumab SC. Grade 3 or 4 TEAEs of **opportunistic infections** were low in both treatment arms. There was no pattern regarding the specific preferred terms of infections and infestations associated with the use of daratumumab SC. The incidence of **peripheral neuropathy** was higher in the daratumumab SC+CyBorD arm (22.0% vs 14.7%) during Cycles 3-6. The incidence of peripheral sensory neuropathy subsequently decreased significantly from Cycle 7 onwards in the daratumumab SC+CyBorD arm to 8.7%, however Daratumumab may increase peripheral neuropathy induced by background therapy with bortezomib (very commonly associated with peripheral neuropathy) and the disease associated neuropathy, the additional neurotoxicity that can be added by daratumumab could lead to a worse QoL. Based on available and limited (few patients) data, baseline involvement seemed not to impact the risk of peripheral neuropathy on study treatment. The incidence of **cardiac disorders** All Grades was higher in the daratumumab SC+CyBorD arm (32.6% vs 21.8%), but the incidence of Grade 3 or 4 was similar in the two arms (11.4% and 9.6%, respectively) and the majority of treatment-emergent cardiac SAEs occurred in patients with baseline cardiac involvement. The majority of patients (54/55) reported baseline cardiac Stage II or Stage III; and 46/55 patients reported baseline NYHA Class II or Class IIIA (TSFAE05P). These data suggest that most of these cardiac-related deaths are attributable to the underlying AL amyloidosis-related cardiomyopathy. A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis will be conducted (please see RMP section below) in order to further characterise cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome. It will also investigate the use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.

The MAH presented further results regarding patients who had renal disorders before initiation of treatment

which showed that patients with renal disorders at baseline are more prone to develop AEs but the observed differences in frequencies of reported AEs between treatment arms did not reveal a clinically relevant pattern.

More patients in the daratumumab SC+CyBorD arm (11.9%) **died** due to an AE during study compared to the CyBorD arm (7.4%). Deaths due to AE within 30 days of last study treatment were reported for 10.4% of patients in the daratumumab SC+CyBorD arm and 7.4% of patients in the CyBorD arm. The most common (≥2% in either treatment arm) AEs leading to death were cardiac disorders. All patients who died due to cardiac disorders had cardiac involvement at baseline. There were more fatal AEs reported in the daratumumab SC+CyBorD arm along with a longer median duration of exposure. At the primary cut-off, the number of reported deaths were similar (27 vs 29) between the arms and with longer follow up, fewer deaths were reported in the daratumumab SC+CyBorD arm compared with the CyBorD arm (31 vs 41).

More patients in the daratumumab SC+CyBorD arm experienced ≥1 treatment-emergent **SAE** compared with the CyBorD arm (43.0% vs 36.2%). The most commonly reported treatment-emergent SAEs were pneumonia and cardiac failure/cardiac failure congestive combined.

Laboratory findings: The worst toxicity grades were balanced between the two arms regarding anemia, thrombocytopenia and leukopenia except a higher level of Grade 4 neutropenia in the daratumumab SC+CyBorD arm compared with the CyBorD arm (3.2% vs 0%), suggesting that daratumumab may increase neutropenia induced by background therapy. However, the incidence of any grade cytopenia was higher in subjects with low body weight. This did not lead to a higher frequency of infections or discontinuation of study treatment compared to those with higher body weight and these cytopenias did not lead to differences in tolerability or clinically meaningful AEs in either treatment arm. Dose modifications would therefore not be required.

Since the incidence of any grade cytopenia was higher in subjects with low body weight the MAH was asked to determine whether dose modifications may be required in this patient population. The MAH provided a comparison of observed daratumumab exposures across body weight subgroups and, overall, the results of the exposure-safety analyses show that there is no apparent relationship between daratumumab SC exposure, based on Cpeak,max, and the rate of cytopenia in subjects with amyloidosis. Additionally, the MAH states that even though the incidence of any grade cytopenia was higher in subjects with low body weight (<65 kg), this did not lead to a higher frequency of infections or discontinuation of study treatment compared to those with higher body weight. The MAH also notes that these cytopenias did not lead to differences in tolerability or clinically meaningful AEs in either treatment arm. Taking the above into account the MAH considers that 1800 mg daratumumab SC dose regimen is expected to show similar benefit-risk profile across all bodyweight subgroups in subjects with AL amyloidosis and suggests that dose modifications would not be required. This was considered acceptable.

The incidence of any grade and Grade 3 or 4 TEAEs leading to **discontinuation** of study treatment were low.

Available post-marketing data have been submitted and no notable differences in the safety profile of daratumumab SC compared to daratumumab IV have been observed. Spontaneous post-marketing case review did not identify new safety signals. The results suggested that the post-marketing drug safety profile of daratumumab SC is consistent with the known safety profile of daratumumab IV as a single agent or in combination therapy in multiple myeloma which support the use of SC daratumumab in this new indication.

2.5.2. Conclusions on clinical safety

The safety profile of SC daratumumab in combination with CyBorD or as single agent in AL amyloidosis patients is as observed when used in the indication for multiple myeloma patients. The level of observed

AEs is considered acceptable and TEAEs leading to discontinuation of study treatment were low. Cardiac involvement at baseline which is an adverse event of interest in amyloidosis patients was present in the majority of patients in both treatment arms, and the majority of treatment-emergent cardiac SAEs occurred in patients with baseline cardiac involvement. Data suggest that most of the cardiac-related deaths are attributable to the underlying AL amyloidosis-related cardiomyopathy. There are no new safety findings, no new adverse drug reactions (ADRs) nor any major concerns. A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis will be conducted (please see RMP section below) in order to further charactersze cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome. It will also investigate the use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.

2.5.3. PSUR cycle

The PSUR cycle set in the EURD list entry of daratumumab does not need to be amended, based on the data submitted in the application, as no new safety findings, no new adverse drug reactions (ADRs) nor any major concerns were identified.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP endorsed the Risk Management Plan version 8.6 (consolidating RMP versions 8.2 and 8.5) with the following content:

Safety concerns

Table 78 . Summary of the Safety Concerns

Important identified risks	Interference for blood typing (minor antigen) (positive indirect Coombs' test)
	Hepatitis B virus reactivation
Important potential risks	None
Missing information	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement

Pharmacovigilance plan

Table 79. Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Planned	Primary objective is to further characterize cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome.	Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Draft Protocol: Interim report: Final report:	Aug 2021 2nd Quarter 2024 1st Quarter 2026

Risk minimisation measures

Table 80. ***Risk minimisation measures***

Interference for blood typing (minor antigen) (positive indirect Coombs' test)	Routine risk minimization measures: SmPC Section 4.4 and 4.5 PL Section 2 Additional risk minimization measures: Distribution of educational materials and Patient Alert Cards to HCPs and blood banks as described in the PL, in Annex II, D.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: A guided targeted follow-up questionnaire to collect additional information concerning adverse events associated with interference and transfusion reactions. Additional pharmacovigilance activities: None.
Hepatitis B virus reactivation	Routine risk minimization measures: SmPC Sections 4.4 and 4.8; PL Sections 2 and 4; Additional risk minimization measures: Distribution of a DHPC to HCPs who prescribe daratumumab was issued in the EU member states in June 2019.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in patients with AL amyloidosis who have pre-existing serious cardiac involvement	Routine risk minimization measures: SmPC Section 5.1. Additional risk minimization measures: None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis. Final report by 1st Quarter 2026.

Table 80. ***Risk minimisation measures***

Key: AL amyloidosis = light chain amyloidosis; DHPC = Direct Healthcare Professional Communication; DTT = dithiothreitol; HBC = hepatitis B virus; HCP = healthcare professional; PL = package leaflet; RBC = red blood cell; SmPC = Summary of Product Characteristics.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing additional user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

- Full user testing in compliance with the above-mentioned legislative requirements was performed (n=20 participants) on the package leaflet developed for DARZALEX for the initial Marketing Authorisation Application.
- An additional user testing (n= 10 participants) was conducted for a bridging report on the package leaflet developed for the Line extension Application of the DARZALEX subcutaneous formulation.
- The package leaflet included in this current application has the same format as the one previously approved.
- With the currently proposed indication extension, minimal changes have been introduced to the package leaflet and the proposed changes reflect language and a format that is consistent with that in the currently approved leaflet for the subcutaneous formulation.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Systemic AL amyloidosis is a rare and incurable malignant plasma cell disorder characterized by clonal expansion of CD38+ plasma cells and extracellular deposition of insoluble fibrillar proteins in tissues and organs affecting the normal hematopoiesis as well as different organs, especially the heart and kidney, resulting in serious and life-threatening organ dysfunction. The incidence of the disease is estimated between 3 and 12 cases per million persons per year, and an estimated prevalence of 30 000 to 45 000 AL amyloidosis patients in the United States and the European Union. The majority of patients are over the age of 65 years (Nienhuis et al 2016, Quock et al. 2018). Amyloidosis has a poor prognosis as the median survival without treatment is 13 months from diagnosis (Sanchorawala 2007, Chaulagain 2013). Approximately one-third of patients die largely due to cardiac involvement within the first year of diagnosis. Cardiac involvement has the worst prognosis and results in death in about 6 months after onset of congestive heart failure. Only 5% of the patients with primary amyloidosis survive beyond 10 years. Almost one third of patients with renal involvement progress to dialysis. The involvement of other organs, e.g.

liver, gastrointestinal tract and peripheral and autonomic nerves, contributes to significant chronic morbidity and mortality, such that the OS rate at 2 years is only 60% (Muchtar 2017; Wechalekar 2015).

The agreed indication is the following: "DARZALEX is indicated in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis."

3.1.2. Available therapies and unmet medical need

No regimen has been approved for amyloidosis (Wechalekar 2015) and no optimal treatment has been identified (Anderson 2014, NCCN).

As both AL amyloidosis and Multiple Myeloma (MM) are clonal plasma cell disorders, the treatment approach is to use MM regimens. Eradicating the clonal plasma cell in AL amyloidosis eliminates the production of the light chain that is both amyloidogenic and proteotoxic leading to organ failure. Despite this, there are key differences in the efficacy and safety between these 2 populations. The achievement of a rapid and deep hematologic response is the essential goal of therapy in AL amyloidosis and an indicator for clinical outcome. The depth of hematologic response is associated with organ improvement and survival (Palladini 2012, Kastritis 2020). Thus, the goal of therapy for patients with AL amyloidosis is to achieve complete hematologic response (CHR) or at a minimum very good partial response (VGPR) in order to prevent further end-organ damage, reverse existing organ dysfunction, and prolong OS (Chaulagain 2013, Merlini 2018). In AL amyloidosis, achieving a partial hematologic response or stable disease may not offer a clinical benefit, because ongoing light chain production may result in further organ damage.

The entire armamentarium of multiple myeloma regimens has been used in AL amyloidosis. The use of CyBorD is recommended by the NCCN and consensus guidelines (Comenzo 2012, Anderson 2014; Mahmood 2014, Wechalekar 2008), and it is now the preferred regimen for patients with newly diagnosed and relapsed AL amyloidosis due to the limited feasibility and high mortality rate of HDM/ASCT, and the cardiac and renal toxicities associated with IMiDs and other combinations (D'Souza 2015).

Thalidomide and lenalidomide-based regimens are associated with severe toxicities including bradycardia, syncope, and renal failure (Merlini 2018). Carfilzomib is known to be associated with severe cardiac toxicity in multiple myeloma and is prohibitively toxic in AL amyloidosis (Waxman 2018; Cohen 2016). Lenalidomide-containing regimens have been used in AL amyloidosis with similar results as thalidomide-containing regimens. The overall hematologic response rate for lenalidomide-based regimens has been 46% with a CHR of 25% (Cibeira 2015). Although lenalidomide is associated with lower rates of peripheral neuropathy than thalidomide, it is also a challenging drug in AL amyloidosis.

Most studies in AL amyloidosis have been retrospective or small uncontrolled studies. The largest retrospective cohort of newly diagnosed patients with AL amyloidosis reported for CyBorD an overall response rate (OrRR, PR or better) of 62% (125/201 patients with measurable disease) compared with 100% in newly diagnosed multiple myeloma patients. Additionally, HemCR was reported in 21% (42 patients) and VGPR in 22% (45 patients). Cardiac response was achieved in 17% of the patients, while renal response was observed in 25% of the patients (Kumar 2012; Palladini 2015).

High-dose melphalan and ASCT demonstrate a high efficacy profile; however, only a minority of patients are candidates (~20%) and it is associated with much higher treatment-related mortality 5-24% compared to 1% for multiple myeloma (Jaccard 2007; D'Souza 2015). In long-term data out of 701 patients evaluated at the Boston Amyloidosis Center 394 (56%) were deemed eligible for transplant and 312 patients were treated with HDM/ASCT (Skinner 2004) while the CHR rate was 40% and the transplant-related mortality was 13%. The organ response rate at 1-year post-transplant among those who achieved a CHR was 27% for cardiac and 63% for renal (NCCN 2019).

In conclusion, the MM regimens demonstrate similar or lower hematologic responses in AL amyloidosis but are associated with higher rates of toxicity, and although CyBorD is currently considered the standard of care, certain subgroups like cardiac Stage III, high dFLC (>180 mg/L) and t(11;14) continue to have dismal outcomes. Thus, a substantial unmet medical need exists for therapies in AL amyloidosis, that can provide clinical efficacy translating into survival benefits at a lower toxicity.

3.1.3. Main clinical studies

The current marketing application includes one pivotal randomized open-label phase 3 study for newly diagnosed AL amyloidosis:

- Study AMY3001 is a randomized phase 3 study to evaluate the efficacy and safety of daratumumab SC in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared with CyBorD alone in newly diagnosed systemic AL amyloidosis

3.2. Favourable effects

The addition of daratumumab SC to CyBorD resulted in a CHR of 53.3% compared with 18.1% in the CyBorD arm, odds ratio [95% CI] =5.13 (3.22, 8.16); p<0.0001 with a median of 11.4 months follow-up, which is considered highly clinically meaningful in a group of patients newly diagnosed AL amyloidosis with organ involvement. The CHR results were consistent among all pre-planned sensitivity analysis and across different clinically relevant prespecified subgroups and the pre-planned stratification factors (cardiac stage, renal function and whether countries offer ASCT or not) in favour of the daratumumabSC + CyBorD arm compared with the CyBorD arm.

The VGPR or better rate, was 78.5% significantly higher in the Dara SC + CyBorD group compared with 49.2% for CyBorD alone. (Odds ratio 3.75; 95% CI:2.40, 5.85; p< 0.0001).

Subjects may switch to, subsequent non-cross resistant, anti-plasma cell therapy due to insufficient hematologic response or aggravating organ function. The median MOD-EFS was 8.8 months for the CyBorD arm, but not reached in the dara SC+CyBorD arm (HR=0.39; 95% CI: 0.27, 0.56; nominal p-value <0.0001).

The median time to response (≥VGPR) was short in both treatment arms (D- CyBorD: 17 days; CyBorD: 25 days). CHR was reached faster in the D-CyBorD arm compared with the CyBorD arm (median time to CHR: 60 days vs. 85 days, respectively).

The responses were durable: with a median follow-up of 11.4 months, the median duration of CHR (DoP) has not been reached in either treatment groups which is reassuring.

3.3. Uncertainties and limitations about favourable effects

The planned 'treatment until progression' is the general strategy in multiple myeloma. There is, however, the remaining uncertainty about whether shorter duration of daratumumab maintenance (e.g. less than 2 years) could lead to similar outcomes, particularly in patients achieving deep responses.

Although subgroup analyses of CHR were consistent with the overall population for the pre-specified subgroups in favour of the dara SC+ CyBorD arm vs. the CyBorD arm, in general interpretation of the results in the subgroups are hampered by the small sample size.

Overall survival data were not mature at the time of the clinical data cut-off with few events having occurred. Even if there seems to be a reasonably well established association between complete

haematological response and long-term outcomes (MOD-PFS and OS), OS data are still of noticeable importance in the intended treatment setting and the MAH will provide the primary and final analyses of OS as a post-authorisation efficacy study. Of note, OS data reported after further 9 months of follow-up (13/11/2020) were still immature but thus far do not suggest a detrimental effect of dara SC + CyBorD on OS. Besides published data indicate that 55% of subjects with newly diagnosed AL amyloidosis were projected to survive 5 years.

Although the Kaplan-Meier curves for MOD-PFS separates after 6.5 months, the results for the dara SC+CyBorD compared with CyBorD alone are not statistically significant, and the data are not mature with only 43% of the 200 planned events at the time of analysis. Despite MOD-PFS is not a standard acceptable endpoint in AL amyloidosis, it may be of value from a clinical point of view. However, the IPW method used is regarded as hypothetical, indicating the results should be considered exploratory.

The odds ratio for standard risk cytogenetics favoured the dara SC+CYBorD arm, but no conclusion can be drawn on cytogenetic high-risk subjects. Analysing poor prognostic groups: the presence of t(11;14) analysed by FISH, Cardiac stage III and dFLC > 180 mg/L indicated a trend towards a beneficial effect of the Dara SC+CyBorD arm compared with CyBorD, however, the interpretation of the results in the subgroups are hampered by the small sample size and no statistically significant difference could be demonstrated.

A trend towards improvement of cardiac – and renal 6-month response was noted, although no statistically significant difference could be demonstrated.

The addition of daratumumab to CyBorD does not have an impact on patient's health-related quality of life as assessed by patient-reported outcomes (PROs).

3.4. Unfavourable effects

Grade 3 or 4 TEAEs of **opportunistic infections** were low in both treatment arms. There was no pattern regarding the specific preferred terms of infections and infestations associated with the use of daratumumab SC.

The incidence of any grade and Grade 3 or 4 TEAEs leading to **discontinuation** of study treatment were low.

Overall there are no new safety findings, no new adverse drug reactions (ADRs) nor any major concerns.

Grade 3 and 4 TEAEs were reported for ≥10% of patients including fatigue (21.4%), lymphopenia (17.9%), diarrhoea, anaemia, and peripheral oedema (14.3% each), and pneumonia and fall (10.7%).

Adverse events of special interest include **IRR** of which 7.3% of patients experienced this. The incidence of **peripheral neuropathy** was higher in the daratumumab SC+CyBorD arm (22.0% vs 14.7%) during Cycles 3-6. The incidence of peripheral sensory neuropathy subsequently decreased significantly from Cycle 7 onwards in the daratumumab SC+CyBorD arm to 8.7%, however daratumumab may increase peripheral neuropathy induced by background therapy, as reflected in the SmPC. The incidence of **cardiac disorders** All Grades was higher in the daratumumab SC+CyBorD arm (32.6% vs 21.8%), but the incidence of Grade 3 or 4 was similar in the two arms (11.4% and 9.6%, respectively) and the majority of treatment-emergent cardiac SAEs occurred in patients with baseline cardiac involvement.

The incidence of any grade cytopenia was higher in subjects with low body weight. However, this did not lead to a higher frequency of infections or discontinuation of study treatment compared to those with higher

body weight and the cytopenias did not lead to differences in tolerability or clinically meaningful AEs in either treatment arm.

More patients in the daratumumab SC+CyBorD arm (11.9%) **died** due to an AE during study compared to the CyBorD arm (7.4%). Deaths due to AE within 30 days of last study treatment were reported for 10.4% of patients in the daratumumab SC+CyBorD arm and 7.4% of patients in the CyBorD arm. The most common (≥2% in either treatment arm) AEs leading to death were cardiac disorders. All patients who died due to cardiac disorders had cardiac involvement at baseline.

More patients in the daratumumab SC+CyBorD arm experienced ≥1 treatment-emergent **SAE** compared with the CyBorD arm (43.0% vs 36.2%). The most commonly reported treatment-emergent SAEs were pneumonia and cardiac failure/cardiac failure congestive combined.

3.5. Uncertainties and limitations about unfavourable effects

Peripheral neuropathy was higher in the daratumumab SC+CyBorD arm suggesting that daratumumab may increase peripheral neuropathy by background therapy. **Cardiac disorders** were higher in the daratumumab arm even though the majority of SAEs occurred in patients with baseline cardiac involvement. More **deaths** due to AE within 30 days were seen in the daratumumab arm. However, at the primary cut-off, the number of reported deaths were similar (27 vs 29) between the arms and with longer follow up, fewer deaths were reported in the daratumumab SC+CyBorD arm compared with the CyBorD arm (31 vs 41).

Further safety characterisation of relevant patient subgroups (e.g. those 75 years of age or older, 65 years plus important comorbidities and/or poor performance status) is needed for a more complete characterisation of the safety profile of the proposed combination in the intended indication.

A multicenter prospective study of daratumumab-based therapy in patients with newly diagnosed AL amyloidosis will be conducted (please see RMP section) in order to further characterise cardiac adverse events in patients with newly diagnosed AL amyloidosis treated with subcutaneous daratumumab-based therapy in terms of the incidence, severity, clinical presentation, management, and outcome. It will also investigate the use in patients with AL amyloidosis who have pre-existing serious cardiac involvement.

3.6. Effects Table

Table 81 Effects Table for daratumumab SC in combination with cyclofosfamide +bortezomib+ dexamethasone in systemic light chain (AL) amyloidosis, data cut-off 14-February 2020

Effect	Short Description	Unit	Treatment Daratumumab SC +CyBorD N=195	Control CyBorD N=193	Uncertainties/ Strength of evidence	References
	Number of patients		195	193		
Favourable Effects						
CHR	Complete hematologic response	%	53.3	18.1	Odds ratio 5.13 (95%CI: 3.22, 8.16) p <0.0001	See clinical efficacy AR and discussion
MOD-PFS	Time from the date of randomization to event	Median months	Median not reached No. events: 34 (17.4%)	Median not reached No. events:	HR= 0.580 (95%CI:0.363; 0.926) p=0.0211	-

Effect	Short Description	Unit	Treatment Daratumumab SC +CyBorD N=195	Control CyBorD N=193	Uncertainties/ Strength of evidence	References
				53 (27.5%)		
OS	Time from the date of randomization to death.	Median months	Median not reached No. events: 27 (13.8%)	Median not reached No. events: 29 (15.0%)	HR=0.91 (95% CI: 0.54, 1.53) P= 0.7140	-
VGPR or better	The proportion of subjects who achieve a confirmed hem CR or VGPR.	%	78.5	49.2	Odds ratio 3.75 (95%CI: 2.40; 5.85) P<0.0001	See clinical efficacy AR and discussion
Unfavourable Effects						
TEAEs of at least 10% in either treatment group	AE	%	97.9	98.4	NA	
≥ Grade 3	AE(ADR)	%	61.7	60.6	NA	
SAEs	AE(ADR)	%	43.0	36.2	NA	
AEs leading to discount. of daratumumab	AE(ADR)	%	4.7	0	NE	
Peripheral edema	ADR	%	35.8	36.2	NA	
IRR	ADR	%	7.3	0	NE	
Peripheral sensory neuropathy	ADR	%	31.1	19.7	NA	
Opportunistic infections	ADR	%	11.9	8.5	NA	
Upper resp. tract infections	ADR	%	25.9	11.2	NA	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Light chain (AL) amyloidosis is a rare disease associated with significant morbidity and mortality. The prognosis is in general dismal, not only due to the effect on the bone marrow, but also the extent of organ involvement. The goal of therapy in AL amyloidosis is achievement of a rapid and deep CHR, which has been demonstrated to be associated with organ improvement and better survival. No regimen has been approved for amyloidosis, and no optimal treatment has been identified. Different multiple myeloma

regimens have demonstrated similar or lower hematologic responses in AL amyloidosis compared with the treatment of multiple myeloma. But they are in general associated with higher rates of toxicity. The use of CyBorD is recommended by the NCCN and consensus guidelines, and it is now the preferred regimen for patients with newly diagnosed and relapsed AL amyloidosis due to the cardiac and renal toxicities associated with IMiDs and other combinations. Despite this, a substantial unmet medical need exists for therapies in AL amyloidosis, that can provide clinical efficacy translating into survival benefits at a lower toxicity. The availability of a novel therapy with a new mechanism of action, targeting CD38+ plasma cells added to the traditionally used backbone therapy is interesting.

An overall CHR rate of 53.1% in the dara SC+CyBorD arm compared with 18.1% in the CyBorD arm (odds ratio=5.13; 95% CI: 3.22, 8.16; p<0.0001) is therefore considered clinically relevant and meaningful in this group of newly diagnosed AL amyloidosis with organ involvement. A significant beneficial and clinically meaningful effect was shown on overall CHR and VGPR or better, higher than when compared with the backbone therapy alone in patients with *newly diagnosed* AL amyloidosis in study AMY3001. Of note, however, OS data are still immature and although thus far do not suggest a detrimental effect of dara SC + CyBorD on OS. Provision of final OS data is considered key to benefit risk. In this regard the MAH will provide the primary and final analyses of OS from study AMY3001 as a post-authorisation efficacy study. The MAH has narrowed the indication to include adults with newly diagnosed AL amyloidosis with a backbone regimen of CyBorD, which is considered acceptable.

The proposed dosing regimen of subcutaneous daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone in patients with AL amyloidosis is considered adequate.

The safety profile is in general as expected in the context of the patient population, the backbone therapy and the known safety profile of daratumumab SC. Overall there are no new safety findings or new adverse drug reactions, although daratumumab may increase peripheral neuropathy induced by background therapy. The incidence of cardiac disorders was higher in the daratumumab SC+CyBorD arm, but no difference was noted for Grade 3 or 4 and the majority of treatment-emergent cardiac SAEs occurred in patients with baseline cardiac involvement. The MAH plans to conduct a multicenter, prospective study (overall duration of the study, including recruitment and follow-up, is anticipated to be approximately 5 years (by Q3 2025)) of daratumumab-based therapy in newly diagnosed patients with AL amyloidosis, in which they will characterise cardiac AEs in terms of incidence, severity, clinical presentation, management, and outcome (including non-fatal myocardial infarction, cardiac failure, arrhythmia, as well as fatal cardiac events and events of sudden death (please see RMP section). Management and outcome of major cardiac events, including hospitalisations will also be analysed). The use of this study is considered appropriate and will allow to collect further data on the safety profile of daratumumab in patients with AL amyloidosis who have the most advanced cardiac disease (NYHA Class IIIB and IV cardiac disease). The MAH has committed to submit the study protocol for PRAC assessment within 3 months after the CHMP positive opinion. No difference in number of infections or discontinuation due to adverse events was reported. No difference in number of infections or discontinuation due to adverse events was reported.

3.7.2. Balance of benefits and risks

Daratumumab added to standard backbone therapy, cyclofosfamide, bortezomib and dexamethasone has a favourable benefit/risk profile in patients with newly diagnosed AL amyloidosis and one or more organ involvement. The benefit/risk balance is considered positive.

3.7.3. Additional considerations on the benefit-risk balance

3.8. Conclusions

The following measure is considered necessary as an Annex II condition to address issues related to efficacy. It is imposed on the grounds that the initial efficacy assessment is based on surrogate endpoints, which requires verification of the impact of the intervention on clinical outcome or disease progression or confirmation of previous efficacy assumptions.

Description	Due date
Post-authorisation efficacy study (PAES): In order to further evaluate the efficacy of subcutaneous daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone for the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis, the MAH should submit the final OS results of the AMY3001 study.	Q3 2025

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis in combination with cyclophosphamide, bortezomib and dexamethasone; The variation leads to amendments to the Summary of Product Characteristics, Annex II, Package Leaflet and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I, II and IIIB and to the Risk Management Plan are recommended.

Similarity with authorised orphan medicinal products

Not applicable.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Darzalex H-C-004077-II-0043

Attachments

1. SmPC, Annex II, Labelling, Package Leaflet (changes highlighted)

Appendix

N/A

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by 04 June 2021. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by 04 June 2021. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) within 15 days after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If the approved RMP is using Rev. 2 of the 'Guidance on the format of the RMP in the EU' and the RMP 'Part VI: Summary of the risk management plan' has been updated in the procedure, the MAH is reminded to provide to the EMA Procedure Assistant by Eudralink a PDF version of the 'Part VI: Summary of the risk management plan' as a standalone document, within 14 calendar days of the receipt of the CHMP Opinion. The PDF should contain only text and tables and be free of metadata, headers and footers.