1 April 2016
EMA/278085/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Darzalex

International non-proprietary name: daratumumab

Procedure No. EMEA/H/C/004077/0000

Note

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

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List of abbreviations

ADA	Anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
ADCP	antibody-dependent cell phagocytosis
ADR	adverse drug reaction
ALKY	alkylating agent
ANC	absolute neutrophil count
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
AUC	Area under the curve
BORT	bortezomib
CAE	Critical adverse event
CARF	carfilzomib
CCO	Clinical cutoff date
CDC	complement-dependent toxicity
cDNA	complementary deoxyribonucleic acid
CEX	Cation Exchange Chromatography
CHMP	Committee for Medicinal Products for Human Use
CHO	Chinese hamster ovary
CI	confidence interval
cADPR	Cyclic ADP Ribose
cIEF	capillary isoelectric focusing
Cmax	Maximum serum concentration
CL	Total body clearance
CPP	Critical process parameters
CQA	Critical quality attributes
CR	complete response
CRCL	creatinine clearance
cSDS	Capillary sodium dodecyl sulfate
CSR	Clinical study report
DBL	Database lock date
DOR	duration of response
DSC	differential scanning calorimetry
EC	European Commission
EC_{50}	half maximal effective concentration
ECD	Equivalent circular diameter
ECG	electrocardiogram
ECLIA	electrochemiluminescent immunoassay
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
Emax	maximum effect
ERA	Environmental risk assessment
EURD	EU reference dates
FDA	Food and Drug Administration
FLC	Free light chain
FITC	fluorescein isothiocyanate
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCP	Host cell protein
HMW	High molecular weight
HPLC	High Performance Liquid Chromatography
HuMab	Humanized monoclonal antibody
IFE	immunofixation
IgG1κ	immunoglobulin G1 kappa
IHC	Immunohistochemistry
IMiD	immunomodulatory agent
IMWG	International Myeloma Working Group
IPC	In-process controls
IRC	Independent Review Committee
IRR	infusion related reaction
IV	intravenous

kg	kilogram
LC	light chain
LEN	lenalidomide
LLOQ	Lower Limit of Quantification
LMW	Low molecular weight
mAb	monoclonal antibody
mg	milligram
min	minute
mL	milliliter
MM	Multiple myeloma
MR	minimal response
MS	Mass spectrometry
MVM	minute virus of mice
MRPP	Maximal reduction in paraprotein
NE	not evaluable
NGD	nicotinamide guanine dinucleotide
NK	natural killer
NR	Not reported
ORR	overall response rate
OS	overall survival
PAR	proven acceptable ranges
PBMCs	peripheral blood mononuclear cells
PFS	progression free survival
PI	proteasome inhibitor
PK	pharmacokinetic
PL	Package leaflet
PMT	Process monitoring test
PO	orally
POM	pomalidomide
Pom+LD-dex	pomalidomide plus low dose dexamethasone
PR	partial response
PRAC	Pharmacovigilance Risk Assessment Committee
PRV	pseudorabies virus
RBC	Red blood cell
REO	reovirus type 3
RMP	Risk management plan
RP-HPLC	reversed phase high performance liquid chromatography
RP-UPLC	reversed phase ultra performance liquid chromatography
RVLP	retrovirus-like particles
SAE	Serious adverse events
SCID	severe combined immune deficiency
SCT	Stem cell transplant
SmPC	Summary of Product Characteristics
SPE	serum protein electrophoresis
SV-AUC	sedimentation velocity analytical ultracentrifugation
$t_{1/2}$	Terminal elimination half-life
TEAE	treatment emergent adverse event
t_{max}	Time for occurrence of C_{max}
THAL	thalidomide
TTP	time to progression
TTR	time to response
UV	Ultraviolet
VGPR	very good partial response
VIN	viral inactivation and neutralisation
V_z	Volume of distribution during the elimination phase
XMuLV	xenotropic murine leukemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 9 September 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Daratumumab Janssen-Cilag, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 September 2014.

Daratumumab Janssen-Cilag was designated as an orphan medicinal product EU/3/13/1153 on 17 July 2013. Daratumumab Janssen-Cilag was designated as an orphan medicinal product in the following indication:

- treatment of plasma cell myeloma.

The applicant applied for the following indication:

- treatment of patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Darzalex as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The applicant indicated that daratumumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class 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 applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's requests for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in

accordance with Article 14(7) of the above mentioned Regulation based on the following claims:
- The benefit/risk balance of the product is positive.
- It is likely that the Applicant will be able to provide comprehensive data.
- The product fulfils an unmet medical need.
- The benefits to the public health of the immediate availability of the product outweigh the risks inherent in the fact that additional data are still required.

New active Substance status

The applicant requested the active substance daratumumab contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 21 February 2013, 20 February 2014, 22 May 2014, 24 July 2014 and 23 April 2015. The Protocol Assistance pertained to insert quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

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: Arantxa Sancho-Lopez

- The application was received by the EMA on 9 September 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 24 September 2015.
- The procedure started on 1 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 December 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 30 December 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- PRAC endorsed the PRAC Rapporteur’s assessment report on 14 January 2016.
- During the meeting on 28 January 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 1 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 16 March 2016.
- During the meeting on 29 March 2016 - 1 April 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Daratumumab Janssen-Cilag.

- The CHMP adopted a report on similarity with Revlimid, Thalidomide Celgene, Imnovid, Farydak and Kyprolis on 1 April 2016.

2. Scientific discussion

2.1. Introduction

Multiple myeloma, which is a malignant disorder of the plasma cells, is diagnosed in approximately 114,000 patients per year worldwide, which includes over 33,000 patients from the European Union. The median age of patients at diagnosis is 65 years and the disease has a typical course characterized by a chronic phase and several relapses leading to an aggressive terminal phase. Progress, such that survival of patients with newly diagnosed multiple myeloma has increased from approximately 3 years with no improvement from the years 1985 to 1998 (Kyle 2003) to 6 to 10 years today (Moreau 2015).

Despite these advances, multiple myeloma remains incurable. All patients eventually relapse. With each successive relapse, the chance of response and duration of response typically decreases. After relapse from PIs and IMiDs, patients are often retreated with drugs that have the same mechanism of action. Ultimately, the disease becomes refractory. Patients who are heavily pretreated and/or refractory to both a PI and IMiD have a dismal prognosis, are difficult to get back into a durable remission, and median survival is only between 8 to 9 months (Kumar 2012; Usmani 2015, Verelst 2015). The relapsed and refractory setting represents a serious and life threatening disease with an unmet medical need.

First line treatment options contain at least one of the novel therapies, i.e. proteasome inhibitors and/or immunostimulatory drugs, followed by autologous stem cell transplantation (ASCT), if indicated. In Europe, bortezomib, thalidomide (as first line treatment) and lenalidomide are approved in combination regimens for the treatment of multiple myeloma.

Relapsed and/or refractory patients typically receive salvage therapy (if possible, this could include (2nd) autologous or allogeneic hematopoietic stem cell transplantation) until relapse or toxicity and then go onto the next salvage option. In this setting, for patients who have received at least 2 prior therapies, including bortezomib and an IMiD, and have shown relapsed or refractory disease, pomalidomide (in combination with dexamethasone) and panobinostat (in combination with bortezomib and dexamethasone) are approved agents in the EU. The proteasome inhibitor carfilzomib and the monoclonal antibody elotuzumab both in combination with lenalidomide and dexamethasone were approved in the EU for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

In patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy there are not any treatment options, other than the physician's best choice and palliative care.

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity (SmPC section 5.1).

Daratumumab has been shown to potently inhibit the in vivo growth of CD38-expressing tumour cells. Based on in vitro studies, daratumumab may utilize multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity (ADCC),

and antibody-dependent cellular phagocytosis (ADCP) in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+Tregs) and B cells (CD38+Bregs) are susceptible to daratumumab mediated cell lysis (SmPC section 5.1).

Daratumumab induced apoptosis in vitro after Fc mediated cross linking. In addition, daratumumab modulated CD38 enzymatic activity, inhibiting the cyclase enzyme activity and stimulating the hydrolase activity. The significance of these in vitro effects in a clinical setting, and the implications on tumour growth, are not well-understood (SmPC section 5.1).

The sponsor applied for the following indication: Daratumumab Janssen-Cilag is indicated for the treatment of patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

The recommended indication for approval is: DARZALEX as monotherapy is indicated for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy (SmPC section 4.1)

The recommended dose is Daratumumab Janssen-Cilag 16 mg/kg body weight administered as an intravenous infusion weekly (weeks 1 to 8) then once every two weeks (weeks 9 to 24) and once every four weeks from week 25 onwards until disease progression (SmPC section 4.2).

2.2. Quality aspects

2.2.1. Introduction

Daratumumab is a fully human immunoglobulin G1κ (IgG1κ) monoclonal antibody that binds to the extracellular domain of human CD38, a transmembrane glycoprotein.

The daratumumab finished product is supplied as a sterile 20 mg/mL liquid concentrate for solution for infusion in a Type I glass vial. After dilution in commercially available 0.9% sodium chloride, the product is intended for intravenous infusion. Two presentations are proposed for marketing authorisation: packs of 5 mL and 20 mL vials (one vial each).

2.2.2. Active Substance

General Information

Daratumumab is a human monoclonal immunoglobulin G1 (IgG1). The intact molecule contains 2 identical heavy chains (HC) of 452 amino acids (approximately 51 kDa each) and 2 identical kappa light chains (LC) of 214 amino acids (approximately 24 kDa each). The 4 chains are linked together by covalent disulfide bonds and non-covalent protein-protein interactions.

The amino acid sequences were deduced by the Applicant from the complementary deoxyribonucleic acid (cDNA) sequence and confirmed by peptide mapping. The disulfide bonds were predicted from the expected pairings for a human IgG1 antibody and confirmed by peptide mapping. The N-linked glycans (glycosylation site located at HC Asn302) were shown to be bi-antennary structures typical for an IgG1 antibody expressed in CHO cells by oligosaccharide mapping with mass spectrometry analysis.

Manufacture, characterisation and process controls

A concentrated viral inactivation and neutralisation (VIN) intermediate is manufactured by Biogen Inc. in Research Triangle Park, NC, USA. The daratumumab active substance is manufactured by Janssen Biologics (Ireland) in Cork, Ireland, and is designated as active substance.

Daratumumab active substance is manufactured in an 11-stage process consisting of fed batch cell culture followed by purification with a series of chromatography, viral inactivation and filtration steps. Formulation also takes place at the active substance level. The concentrated viral inactivation and neutralisation (VIN) intermediate is obtained at Stage 5b.

There are 2 types of in-process controls (IPCs) in the daratumumab active substance process: (1) an IPC with an Acceptance Criterion, and (2) an IPC with a Predefined Instruction.

A list of IPCs with acceptance criteria used in the daratumumab active substance manufacturing process is provided. It includes a list of the process step in which the IPC test is performed, the test, and the associated acceptance criterion. Acceptance criteria that are exceeded must be investigated and may result in batch rejection. IPC tests for bioburden also have associated action limits that when exceeded, require response, investigation, and correction.

After Stage 5b, the concentrated VIN material is frozen at for up to and transported from Biogen Inc. (BIIB), USA to Janssen Biologics, Ireland for further processing. Release and stability acceptance criteria are established for the stored VIN intermediate and cover testing of relevant quality attributes.

Process Validation and/or Evaluation

Consideration of the process validation and process evaluation efforts began during development. The daratumumab active substance manufacture is developed by QbD concepts. Daratumumab critical quality attributes (CQAs) have been identified based on the quality target product profile (QTPP) for the finished product and scientific knowledge of the monoclonal antibodies. Based on process development and clinical manufacturing experience, criticality assessments were performed and critical quality attributes (CQAs), critical process parameters (CPPs), in-process controls (IPCs), and process monitoring tests (PMTs) were identified. Process parameter control ranges and acceptance criteria were established for CPPs and IPCs, respectively, to control CQAs according to predetermined CQA specifications, and were the basis of a high level process validation master plan and validation acceptance criteria in subordinate protocols. The identified CQAs represent the focal point for the subsequent control strategy development.

Process validation and evaluation studies were executed at both manufacturing and reduced scales according to the process validation master plan. Process intermediate hold times, chromatography resin lifetimes, and reprocessing steps at specific stages of the active substance process were validated in studies according to subordinate protocols. Resin lifetime limits will be verified during commercial processing until the maximum number of cycles or total contact time validated using reduced scale cycling studies is reached.

Following process validation, criticality assessments were repeated as part of the lifecycle management of the active substance manufacturing process. Reduced scale models were employed to evaluate and establish proven acceptable ranges (PARs) for parameters that were not challenged at manufacturing scale. Results from clinical manufacturing, process validation, and reduced scale studies were assessed to establish the final list of CPPs for the commercial-scale active substance manufacturing process.

An integrated control strategy for each stage of the daratumumab active substance manufacturing process as well as the control strategy for each of the identified CQAs are outlined. The overall control strategy includes relevant elements such as control of process parameters and process monitoring tests (PMT), which are established to ensure consistent process stage performance. Control of material attributes that enter the manufacturing process like e.g. raw materials, culture media and buffers, WCB

and process intermediates are controlled. The concentrated VIN intermediate, which is stored frozen and transported from Biogen Inc, USA to Janssen Biologics, Ireland, is controlled by a release specification based on batch data, process validation and stability tests.

Manufacturing Process Development

The CMC strategy for comparability included an evaluation of QC batch release results and additional biochemical, biophysical, and biological characterisation data according to the guidance provided in ICH Q5E. A comparison of degradation pathways and degradation rates was also included in comparability studies.

Characterisation

The analytical characterisation of daratumumab includes a comprehensive analysis of its biochemical, biophysical and biological properties using a wide variety of orthogonal techniques.

The results showed that daratumumab has the expected structure of an IgG1 antibody. It has specificity for CD38 antigen binding in the Fab region and bioactivity via complement-dependent cytotoxicity (CDC) and ADCC mechanisms in the Fc region. All product-related substances and impurities were also characterised. The results from these forced degradation studies, along with the analysis of structural models, release and stability data, and clinical serum samples were used to identify critical quality attributes (CQAs) for daratumumab and develop the appropriate process and analytical control strategy.

Process-related impurities have been identified and their removal was demonstrated by testing during process validation. All process validation protocol acceptance criteria were met, and the active substance process was demonstrated to remove the process-related impurities. Therefore, tests and specifications for these impurities were not established for active substance release.

As part of demonstrating consistency of the daratumumab production process, batches and have also been characterised.

Specification

Release and stability testing of the active substance includes identity, purity, charge heterogeneity, glycan profile, potency safety and other general tests.

Results are presented for active substance batches of Phase 3 material, process validation batches, and post-process validation batches. All of these batches are representative of the commercial manufacturing process. All the results met the commercial release specifications presented in Table 3 above.

Stability

Batches of active substance were placed in the stability monitoring programs to establish shelf life. All these batches were manufactured at full scale and by the commercial manufacturing process. The stability studies with active substance were conducted using small polycarbonate vials representative of the large-scale active substance storage containers.

The quality of active substance clinical- and process validation (and post-process validation) batches placed in the stability program is monitored using multiple analytical procedures, each with an established stability acceptance criterion.

The shelf life for active substance is based on stability data generated at the recommended storage condition of. The shelf-life claim is based on an ongoing stability program for Phase 3 clinical and process validation batches. A statistical trending approach for analysing the real-time stability data is utilized for supporting the shelf life to as per ICH Q1E: *Guidance on Statistical Treatment of Stability Data*. Stability data obtained from accelerated and stressed storage temperature conditions are also presented in support of the shelf-life claim.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The nominal composition of the finished product along with the function and grade of the excipients used in preparation of the finished product (glacial acetic acid, sodium acetate trihydrate, sodium chloride, mannitol, polysorbate 20 and water for injection) are provided for each presentation.

Based on the results from the process development studies, the commercial finished product manufacturing process was established at Cilag for the 100 mg/vial daratumumab finished product and at Vetter for 100 and 400 mg/vial daratumumab finished product.

Manufacture of the product and process controls

Manufacture of the finished product is performed at the following facilities:

100 mg	100 mg and 400 mg
Cilag A.G. Hochstrasse 201 8200 Schaffhausen Switzerland	Vetter Pharma Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany

Batch release of the finished product is performed at the following facilities:
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

An overview of the finished product manufacturing process and in-process controls is presented below. The process consists of thawing active substance, pooling and mixings, prefiltration, sterile filtration, aseptic filling, stoppering and capping, inspection, secondary packaging, and finally storage at 2-8ºC. CPPs and pCPPs were identified.

Process validation was performed in order to demonstrate the ability of the daratumumab finished product manufacturing process to consistently yield a final finished product meeting its predetermined specifications and quality attributes.

Product specification

The release specification of the finished product includes control of identity, charge heterogeneity, purity, potency and other general tests.

Batches have been analysed and all results met the predetermined release acceptance criteria.

Stability of the product

Finished product batches were manufactured and placed in the stability-monitoring programs.

Based on the data provided a shelf life of 18 months for the finished product (unopened vials) when stored at the recommended temperature of 2-8 ºC and protected from light is considered acceptable.

Regarding in-use stability, from a microbiological point of view, unless the method of opening/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used

immediately, in-use storage times and conditions are the responsibility of the user and should be no more than 24 hours at refrigerated conditions (2 °C - 8 °C) protected from light, followed by 15 hours (including infusion time) at room temperature (15°C - 25°C) and room light.

Adventitious agents

During cell line development, rabbit serum and fetal bovine serum have been used. No animal-derived materials, however, have been used to prepare the master cell bank or working cell banks.

Mycoplasma and microbial bioburden are controlled through use of a sanitary process design and appropriate testing. Bioburden and endotoxin contamination is also evaluated as part of routine testing. Manufacturing procedures and 0.2-μm filtration steps throughout the process minimize the risk of microbial contamination.

Viral clearance is achieved through different steps in the purification process.

A viral safety factor for retrovirus-like particles (RVLP) in the manufacturing process was calculated from viral clearance values using xenotropic murine leukaemia virus (XMuLV), a specific model virus for the RVLP in the production CHO cell line used for clinical and commercial manufacturing.

The manufacturing process provides sufficient removal capacity.

With regard to non-specific model virus studies, cumulative minimum clearances were demonstrated.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the Quality dossier is of high quality. No major issues were identified during the review.

Active substance

The preparation of the MCB, WCB and Extended End of production cell bank (EEPCB) are described. These cell banks were characterised according to current guidelines to show their identity and freedom from adventitious agents. On request the generation and use of the, in total, three WCBs, has been described. The first WCB generated was only used for the manufacture of the very early clinical material. The second WCB is currently used for production. A third WCB has been generated and will replace the second one, once it has depleted. A clear procedure to prepare future WCBs has been presented on request. Finally, EEPCB preparation has been described in sufficient detail.

Several concerns were raised in relation to the Viral Inactivation and Neutralisation (VIN) intermediate in the active substance manufacturing process. Pooling of VIN intermediates thawed and pooled for further processing into active substance has been addressed. The strategy for VIN intermediate selection has been described. The acceptance criteria for the VIN intermediate have been aligned with manufacturing experience.

On request a protocol for the VIN intermediate stability has been presented, which includes release and shelf-life acceptance criteria.

The Applicant agreed to introduce a test for protein concentration to the VIN intermediate release specification, and a measure for fragments into the stability specification for the VIN intermediate.

Careful product- and process development has been done with the use of all elements of QbD. CQAs has been identified. Most of the manufacturing process development work is described at high level, e.g. DoE's are described and results summarised but only very limited real data is presented. A reasonable and expected number and type of critical process parameters has been identified and no broad production or control flexibility is requested. Some steps of the process have, on a risk-based level, been chosen

(production bioreactor, VIN intermediate and CEX) for more detailed review. A number of issues, for these steps needed further justification and/or clarification. This has been provided and do not call for comments.

Based on updated active substance stability data, the claimed shelf-life for active substance when stored at is accepted.

Finished product

The use of tolerance intervals, as a statistical tool to set finished product (and active substance) specification acceptance criteria, called for concern but a justification was provided and the issue was considered resolved.

On request the Applicant has discussed the proposed acceptance criteria for all methods included in the finished product specification, taking into account the clinically qualified levels. The specification for potency (CDC and ADCC) and charge heterogeneity has been revised and is considered acceptable. Acceptance criteria in the active substance specification have been revised accordingly.

Altogether, the data presented support the Daratumumab finished product shelf life claim of 18 months when stored at 2-8 ºC and protected from light. However, the Applicant is recommended to continue the stability studies on two 400 mg/vial finished product batches (engineering and clinical) and finished product 400 mg/vial process validation batches () stored at 2-8 ºC in order to confirm the stability profiles of these batches. Should any unexpected issues arise during the studies it is recommended that it is reported to the Rapporteur and the Agency immediately.

Adventitious agents

Two minor issues needed to be solved: the Applicant was asked to provide i) retrovirus-like particles estimation for three unprocessed cell culture supernatant; and ii) raw data for Adventitious agents safety evaluation. These data were provided and the issues were considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Darzalex is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Darzalex is considered acceptable when used in accordance with the conditions defined in the SmPC. However, a quality Recommendation has been made.

2.2.6. Recommendation for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended a point for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Pivotal nonclinical safety studies were conducted in conformance with Good Laboratory Practice (GLP).

Daratumumab binds to human and chimpanzee CD38, but not to CD38 of species typically used for nonclinical toxicology testing, ie, mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey. Therefore, another anti-CD38 mAb, HuMab-CD38, that binds human and cynomolgus monkey CD38 was also characterized and used in some exploratory studies. Normal human cells, cell lines expressing human CD38, and patient derived cells were used *in vitro* or in immunosuppressed mouse models for the pivotal pharmacology studies. Cynomolgus monkeys were used in pilot studies of HuMab-CD38.

Nonclinical PK of daratumumab was evaluated in the 6-week repeat-dose chimpanzee toxicology study. PK of HuMab-CD38 was evaluated in the 2-week repeat-dose pilot cynomolgus monkey toxicology study.

The toxicology program for daratumumab consisted of a GLP 6-week repeat-dose toxicity study in chimpanzees, and in vitro tissue cross-reactivity studies using chimpanzee and human tissues. Additional supportive studies were conducted with HuMab-CD38, a mAb that binds cynomolgus CD38, and included a pilot, non-GLP 2-week repeat-dose toxicity study in cynomolgus monkeys, and an in vitro tissue cross-reactivity study with cynomolgus monkey tissues. Both *in vivo* repeat-dose studies utilized the intended clinical route of administration (ie, intravenous infusion).

2.3.2. Pharmacology

Primary pharmacodynamic studies

Binding characterization to human CD38

The CD38 epitope for binding of daratumumab was determined using the PEPSCAN method which showed that daratumumab bound to the C-terminal region of human CD38, amino acid [aa] 267 to 280) in combination with region aa 233 to 246. In addition, epitope mapping was done by site-directed mutagenesis which showed that the binding of daratumumab to CD38 is sensitive to mutations at positions 272 and 274 in the CD38 protein (Study GMB 3003-008).

The kinetics of daratumumab interaction with human CD38 were investigated by Biacore analysis, which revealed specific, saturable, and high-affinity binding, with a KD of 4.36×10^{-9} M (Study GMB 3003-002). HuMab-CD38 interaction with human CD38 showed a KD of 8.18×10^{-10} M.

ELISA analysis confirmed that daratumumab and HuMab-CD38 bind to hCD38 in a similar, concentration-dependent manner. EC_{50} of daratumumab binding to hCD38 was achieved at 55.2 ng/mL (GMB 3003-002).

The binding of daratumumab and HuMab-CD38 to cell surface-expressed CD38 was characterized by flow cytometry using Daudi cells, CHO transfected cells (CHO-CD38 cells), MM-derived cell lines and freshly isolated MM tumour cells. Daratumumab and HuMab-CD38 bound in a specific, dose-dependent manner. The EC_{50} values for binding to Daudi and CHO-CD38 cells were 0.26 and 0.47 µg/mL for daratumumab, and 0.99 and 0.96 µg/mL for HuMab-CD38, respectively (GMB 3003-002).

Mechanism of action

The binding of daratumumab to CD38 on the surface of tumour cells and engagement/ligation of the Fc domains of bound antibodies leads to multiple biologic effects, including CDC, ADCC, ADCP, tumour cell

apoptosis, and modulation of CD38 enzymatic activity in patient derived cells and cell lines expressing human CD38.

Induction of Complement-Dependent Cytotoxicity

The capacity of daratumumab and HuMab-CD38 to induce CDC was studied *in vitro* using several cell types and cell lines (GMB 3003-003):

Lysis of Daudi-luc cells: Daratumumab induced CDC with maximum lysis of 60%, whereas the surrogate antibody HuMab-CD38 was inefficient in inducing lysis, and did so only at very high concentrations.

Table 1: Maximal lysis and mean EC_{50} values against Daudi-luc cells

Experiment[a] (n)	HuMab-CD38 Max Lysis (EC_{50})[b]	Daratumumab Max Lysis (EC_{50})[b]	Rituximab Max Lysis (EC_{50})[b]
0578-117 DJA (1)	63 (59.09)	64 (0.15)	91 (0.50)
0449-096 DJA (2)	58 (47.95)	71 (0.15)	89 (1.91)
0449-104 DJA (1)		56 (0.44)	81 (3.43)
0449-105 DJA (1)		48 (0.34)	77 (2.80)
0449-106 DJA (1)		62 (0.19)	76 (1.50)
0576-006 KGE (1)	56 (90.84)	56 (0.21)	92 (1.64)
Mean	59 (65.96)	60 (0.25)	84 (1.96)
SD	4 (22.26)	8 (0.12)	7 (1.03)

[a] All experiment numbers noted below are reported in report Mod4.2.1.1/GMB 3003-003.
[b] Max lysis expressed as %; EC_{50} values expressed as µg/mL.

Lysis of CD38-Transfected CHO Cells:

Table 2: Maximal lysis and mean EC50 values against CD38-expressing CHO cells

Experiment	HuMab-CD38 (P3003-003-2F5) Max lysis (EC_{50})[a]	Daratumumab (P3003-005-1F10) Max lysis (EC_{50})[a]	HuMab-CD38 (TH3003-003) Max lysis (EC_{50})[a]	Daratumumab (TH3003-005) Max lysis (EC_{50})[a]
0449-099 DJA	84 (2.421)	89 (0.04)		
0576-005 KGE	50 (4.89)	67 (0.37)		
0650-021 LUO			58.1 (2.93)	76.9 (0.167)
Mean	67 (3.65)	78 (0.21)		

a Max lysis expressed as %. EC_{50} values expressed as µg/ml

Lysis of freshly-isolated MM cells: In 8 out of 12 evaluable tumour cell samples, daratumumab-induced lysis was greater than 48%. In the remaining four tumour cell samples, poor lysis was observed (<23%). With HuMab-CD38 (all forms), only two patients responded at the level of approximately 30% lysis. The mechanism underlying the differences in cell lysis among the patient-derived cells is not known, as levels of CD38 expression were not characterized.

Induction of Antibody-Dependent Cell-Mediated Cytotoxicity

Target cells were loaded with ^{51}Cr, incubated with antibody and effector cells, and lysis was determined by measuring ^{51}Cr release (GMB 3003-004). In studies using the Daudi cell line, daratumumab induced ADCC with an average EC_{50} of 20.9 ng/mL, compared to HuMab-CD38 (52.5 ng/mL) and rituximab (55.3 ng/mL). Similar results were seen in assays using MM-derived cell lines.

In freshly isolated myeloma cells, both CD38 Ab induced ADCC, although the extent of maximal lysis differed per tumour sample and was influenced by the origin of effector cell (PBMC from healthy volunteers).

Induction of Antibody-Dependent Cellular Phagocytosis

To evaluate the capacity of daratumumab to stimulate tumour cell phagocytosis in vivo, variant forms of daratumumab were created to either eliminate complement-activating function by altering a residue in the Fc domain (DARA-K322A), or to reduce phagocytosis-stimulatory function through isotype switching to the IgG2 equivalent (DARA-IgG2-K322A).

In a subcutaneous (SC) mouse model using Daudi-luc tumour cells, DARA-K322A provided stronger inhibition of tumour growth than the DARA-IgG2-K322A isoform, which has impaired phagocytosis-stimulatory capacity. Furthermore, in the IV leukemic Daudi-luc xenograft model, in which mice were treated at the time of tumour challenge, DARA-K322A also showed stronger tumour growth inhibition compared to DARA-IgG2-K322A

To translate these observations from the mouse to a human setting, daratumumab –dependent phagocytosis by human monocyte-derived macrophages was demonstrated ex vivo in 11 out of 12 patient-derived MM cells tested, even at low CD38 expression level (35,000 molecules/cell) (Study GMB 3003-115). Although a clear relationship between expression levels of CD38 and susceptibility to phagocytosis was not evident, MM cells from one patient with very low CD38 expression (~10,000 molecules/cell) were not susceptible to daratumumab-dependent phagocytosis.

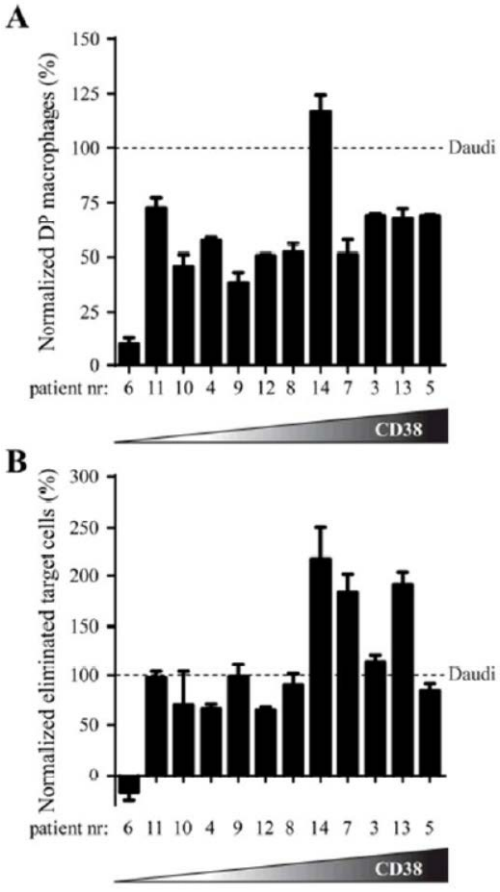


Figure 1*:* Induction of patient myeloma cell phagocytosis by human macrophages

Effects on CD38 Enzymatic Activity

The effect on the ADP-ribosyl cyclase activity of CD38 was evaluated by three methods, either by incubation with recombinant CD38 (figure 2.1.5 A) or cellular CD38 (figure 2.1.5 B) in assays using nicotinamide guanine dinucleotide (NGD) or 8NH2-cADPR as substrate.

In studies using NGD as a substrate, daratumumab, but not HuMab-CD38, induced a concentration-dependent inhibition of cyclase activity. Daratumumab and HuMab-CD38 inhibited 8NH2-cADPR production in a concentration dependent manner.

The effect of daratumumab on cADPR hydrolase activity of CD38 was measured by HPLC to determine the amount of ADPR produced from cADPR, or by measuring the amount of 32P-ADPR produced from 32P-cADPR by thin layer chromatography. Results suggest that daratumumab stimulated cADPR hydrolysis (EC_{50} of 1.2 µg/ml).

Induction of Apoptosis

The capacity of daratumumab to directly induce apoptosis of CD38-expressing cells was studied in a series of experiments employing either Ramos or luciferase-transfected Daudi (Daudi-luc) cells (Study GMB3003-011). Results of these initial studies suggest that daratumumab (1 µg/mL) is able to induce target cell apoptosis upon binding to cell-surface CD38, and that this effect requires cross-linking of the Fc domains.

Because FcγR-mediated antibody crosslinking may be induced by various FcγR-expressing cell types such as polymorphonuclear cells, NK cells, monocytes, macrophages or endothelial cells, depending on the tumour niche, in vivo studies were performed in a syngeneic peritoneal tumour model in NOTAM mice and FcRγ-chain knockout (FcRγ-/-) mice. NOTAM mice have normal surface expression of all activating FcγRs, however without signaling capacity due to a signaling-deficient FcR-associated γ-chain. Leukocytes in the NOTAM mice are therefore capable of FcγR-mediated antibody crosslinking, without inducing cytotoxicity via ADCC or phagocytosis. Leukocytes in FcRγ-/- mice lack expression of all activating FcγRs and solely express the inhibitory FcγRIIb. Daratumumab-mediated CDC induction was excluded by using the K322A mutant form of daratumumab, which lacks CDC activity ((DARA-K322A). CD38-transduced EL4-CD38 cells were inoculated intraperitoneally (IP) and treated with DARA-K322A (~0.1 mg/kg). DARA-K322A induced an increase in Annexin-V positive cells and significantly increased the number of 7-AAD positive cells following 4 h incubation in the FcRγ-/- mice. This indicates that DARA-K322A crosslinking via the inhibitory FcγRIIb was sufficient to induce tumour cell apoptosis in vivo. In NOTAM mice, DARA-K322A treatment also significantly increased the number of Annexin-V positive and 7-AAD positive cells.

The inhibitory FcγRIIb and also the activating murine FcγRs, FγRI, FcγRIII and FcγRIV, can mediate daratumumab crosslinking in vivo, leading to apoptosis.

In Vivo Anti-Tumour Effects of Daratumumab

The effect of daratumumab on the growth of human lymphoma cells *in vivo* was investigated by engrafting luciferase-transfected Daudi cells (Daudi-luc, originated from Burkitt's lymphoma) into SCID mice by IV injection, followed by treatment with daratumumab, HuMab-CD38, or controls (GMB 3003-007). In the first study, antibodies (300 µg per mouse, n = 4 or 5) were administered one week after IV inoculation of Daudi-luc tumour cells, and tumour burden was followed by optical imaging. Both daratumumab and HuMab-CD38 significantly reduced tumour growth compared to control treatment on Days 28 and 34 ($P < 0.001$). On Day 55 after inoculation, tumour burden after treatment with HuMab-CD38 was slightly lower than after treatment with daratumumab ($P < 0.01$); however, values for neither the daratumumab nor the HuMab-CD38 group were different from the rituximab control group.

In the second therapeutic study, antibodies (10 µg per mouse, 0.5 mg/kg body weight, n = 6) were administered 14 days after IV inoculation of Daudi-luc tumour cells. At the end of the study (Day 49), tumour burden in both the daratumumab and HuMab-CD38 groups was reduced compared to control ($P < 0.05$; and was not different from the rituximab control group.

Species selection

To support nonclinical studies, the binding of daratumumab and HuMab-CD38 (a human IgG1 mAb that specifically binds human and cynomolgus monkey CD38, also referred as HuMab-3003-003) to human and animal tissues and cells was characterized by flow cytometry, ELISA and IHC. Daratumumab binds to human and chimpanzee CD38, but not to CD38 of species typically used for nonclinical testing, (mouse, rat, rabbit, pig, and cynomolgus and rhesus monkey). HuMab-CD38 functional activity was also characterized in some exploratory studies.

Binding to human lymphoid and non-lymphoid tissues

Daratumumab and HuMab-CD38 were characterized with respect to their specific cellular staining of lymphoid and non-lymphoid human tissue (Study GMB 3003-006). Results of immunohistochemical analyses showed that both antibodies bound to lymphocytes (T- and B-lymphocytes, plasma B cells), macrophages and lymphatic endothelium as expected. Both antibodies also bound to CD38 on myocytes (in striated muscle) and a subset of differentiated epithelium in lung; HuMab-CD38 was also shown to bind to differentiated epithelium in prostate and fallopian tube.

Reactivity to human and Cynomolgus blood cells

The binding of daratumumab and HuMab-CD38 to individual cell types in human and cynomolgus monkey blood was studied *in vitro* by flow cytometry (Study SR3003-06-31). Distinct differences in the binding of daratumumab and HuMab-CD38 to the various cell types were identified. Daratumumab did not show specific binding to any cynomolgus monkey cell types. Both daratumumab and HuMab-CD38 bound weakly to human B and T cells. In contrast, HuMab-CD38 bound strongly to cynomolgus monkey B and T lymphocytes. Neither daratumumab nor HuMab-CD38 showed specific binding to human or cynomolgus monkey granulocytes.

Daratumumab has a low level of binding to human erythrocytes. In contrast, HuMab-CD38 bound to cynomolgus monkey erythrocytes at concentrations > 3 µg/mL. Overall, higher binding of HuMab-CD38 to cynomolgus monkey blood cells was seen and it may suggest higher levels of CD38 expression in monkey vs. human peripheral blood cells, which could be an important consideration in interpreting results of nonclinical studies in cynomolgus monkeys.

Comparison of Daratumumab interaction with human and chimpanzee CD38 and with blood cells

The coding sequence of chimpanzee CD38 was determined and compared to hCD38. The cDNA of chimpanzee and human CD38 was highly similar, without insertions and with only 4 AA differences (not within the daratumumab binding epitope). Daratumumab was found to bind equally well to chimpanzee and human CD38 in vitro, when assessed using purified CD38 protein (ELISA) and using Pan EBV3 cells and human B cells (flow cytometry). Furthermore, by means of surface plasmon resonance (Biacore), the affinities of daratumumab for hCD38 (KD = 3.50 x 10-9 M + 1.66 x 10-9 M) and for chimpanzee CD38 (KD = 4.46 x 10-9 M + 1.66 x 10-9 M) were found not to be significantly different. Daratumumab was found to inhibit the enzyme activity of both chimpanzee and hCD38 to the same extent (Study GMB 3003-014).

The binding of daratumumab to chimpanzee CD38 was further characterized by flow cytometric analysis of chimpanzee PBMCs (BKV00001). Daratumumab binding was identified on CD4, CD8 or CD56-positive lymphocytes in both human and chimpanzee PBMCs. The percentages of positive cells for each of these lymphocyte subsets were comparable between human and chimpanzee, indicating that daratumumab is able to bind to naturally-occurring chimpanzee CD38.

Furthermore, binding of daratumumab to human and chimpanzee platelets was characterized by flow cytometry (BKV00013 and BKV00015). The binding experiments revealed that chimpanzee platelets express a daratumumab binding site with an affinity (EC_{50} value) of approximately 1 µg/mL, which is not expressed on human platelets. The binding affinity on human platelets could not be determined in the

tested concentration range, since a maximal binding plateau was not reached. It is assumed that the binding affinity of daratumumab to human platelets is at least 15-fold lower than to chimpanzee platelets.

Anti-tumour effects of Daratumumab in combination with other therapeutic agents

The effects of combining daratumumab with other therapeutic agents that are currently used for the treatment of MM were evaluated in two ex vivo studies. Daratumumab in combination with lenalidomide (Study GMB 3003-069): a synergistic interaction was identified between lenalidomide and daratumumab-induced tumour cell lysis in treated samples of bone marrow mononuclear cells from MM patients.

Addition of daratumumab to lenalidomide and/or bortezomib increased MM cell lysis by more than two-fold in all combinations ($p < 0.001$). Combination of daratumumab with either lenalidomide/ bortezomib/ dexamethasone cocktail or melphalan/ prednisone/ bortezomib cocktail resulted in significantly increased tumour cell lysis compared to cocktail alone (Study GMB 3003-070).

Secondary pharmacodynamic studies

Anti-tumour effects of daratumumab in combination with other therapeutic agents ex vivo

The effects of combining daratumumab with other therapeutic agents that are currently used for the treatment of MM were evaluated in two ex vivo studies. The first study addressed the activity of daratumumab in combination with lenalidomide, an immune modulatory drug, against MM cells (Study GMB 3003-069). Daratumumab-dependent killing of purified primary MM cells and the UM-9 myeloma cell line by ADCC was significantly augmented (approximately two-fold) by lenalidomide pre-treatment of effector PBMCs. Furthermore, a synergistic interaction was identified between lenalidomide and daratumumab-induced tumour cell lysis in treated samples of bone marrow mononuclear cells from MM patients. In addition, the capacity to mediate daratumumab-induced ADCC against UM-9 target cells was significantly up-regulated in PBMC derived from three MM patients during lenalidomide treatment.

In a second study, the potential benefit of combining daratumumab with multi-drug chemotherapy regimens was evaluated in fresh tumour cells from MM patients (Study GMB 3003-070). Lysis of primary tumour cells was measured directly in bone marrow mononuclear cell isolates obtained from MM patients. Addition of daratumumab to lenalidomide and/or bortezomib increased MM cell lysis by more than two-fold in all combinations ($p < 0.001$), even in samples from patients that were refractory to lenalidomide and bortezomib treatment. Furthermore, combination of daratumumab with either lenalidomide/bortezomib/ dexamethasone cocktail or melphalan/ prednisone/ bortezomib cocktail resulted in increased tumour cell lysis compared to cocktail alone.

Safety pharmacology programme

No safety pharmacology studies have been conducted (see discussion on non-clinical aspects).

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been conducted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The nonclinical PK of daratumumab was evaluated in the 6-week repeat-dose toxicology study in chimpanzees administered weekly as an IV infusion, and followed by a 91 to 105-day recovery period. PK of HuMab-CD38 was evaluated in the repeat-dose pilot toxicology study conducted in cynomolgus monkeys via weekly IV infusion for 2-weeks, and followed by a 2-month recovery period.

Serum concentrations of daratumumab in chimpanzees and HuMab-CD38 in cynomolgus monkeys were determined using validated GLP-compliant ELISA bioanalytical methods. The lower limit of quantification (LLOQ) was determined to be 21.538 ng/mL in a 1% chimpanzee serum matrix and 22.973 ng/mL in a 2.5% chimpanzee serum matrix. The LLOQ of the cynomolgus assay was determined to be 3.13 ng/mL in 10% serum.

Serum ADA of daratumumab in chimpanzees and HuMab-CD38 in cynomolgus monkeys were determined using validated GLP-compliant ELISA bioanalytical methods. Data obtained from the validation demonstrated that the ELISA-based methods for the detection of antibodies were suitable for use. However, a greater than 30% reduction in ADAs detection signal was observed for concentrations of daratumumab greater than 10 µg/mL in chimpanzee (Study BKV00005)

6-week study in chimpanzees (Study 8754-0701, GLP)

Two chimpanzees (1/sex) received 30 min. IV infusions of 5 mg/kg daratumumab. The male received weekly infusions for 6 consecutive weeks. The female was injured and only received 2 weekly infusions. An additional female died from an IRR shortly after the first infusion and was excluded from PK analysis. Two chimpanzees (1/sex) received IV infusions of 25 mg/kg daratumumab for 6 consecutive weeks. The first infusion of 25 mg/kg infusion was given over 1 h and was preceded by an IV injection of 10 mg daratumumab 24 h before the infusion. Subsequent 25 mg/kg infusions were given over 30 min without a pre-dose. Individual animal data are presented in Table 11.

Table 3: Serum PK parameters in chimpanzees following weekly IV administration of Daratumumab

Dose (mg/kg/wk)	Dose Number	Animal ID No. /sex	C_{max} (µg/mL)	t_{max} (h)	$AUC_{0-\infty}$ (µg·h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	CL (mL/h/kg)
5	1	95A015 F	86	0.58	2,966	36	86.7	1.69
	1	96A009 M	100	0.58	2,246	38	122.7	2.23
	3	96A009 M	129	24.00	15,836	88	43.8	0.34
	6	96A009 M	129	2.00	23,171	132	63.8	0.33
25	1	96A015 M	612	0.58	40,463	103	91.4	0.62
	1	96A017 F	778	0.58	74,458	135	65.6	0.34
	3	96A015 M	630	0.58	96,676	231	240.0	0.72
	3	96A017 F	599	0.58	215,145	335	164.7	0.34
	6	96A015 M	695	0.58	319,583	596	2,205.3	2.56
	6	96A017 F	967	0.58	364,102	461	384.4	0.58

$AUC_{0-\infty}$ = area under the serum concentration time curve from time zero to infinity; CL = total body clearance; C_{max} = maximum serum concentration; F = female; h = hour; ID = identification; IV = intravenous; M = male; No. = number; PK = pharmacokinetics; t_{max} = time for occurrence of C_{max}; $t_{1/2}$ = terminal elimination half-life; V_z = volume of distribution during the elimination phase; wk = week

No daratumumab anti-drug antibodies (ADAs) were detected during the study.

2-week study in Cynomolgus Monkeys (Study No. 509809, non-GLP)

The study consisted of six male and six female cynomolgus monkeys randomized into 3 dose groups of 2 cynomolgus monkeys/sex/group (ie, vehicle, 20, and 100 mg/kg daratumumab). Animals were dosed on Days 1 and 8, with animals assigned to the main study group (1/sex/group) euthanized 2 days after completion of the last dose (Day 11), and the remaining animals (1/sex/group) euthanized after a 2-month (ie, 56 day) treatment-free period. Individual animal data are presented in Table 12.

Table 4: Serum PK parameters in Cynomolgus Monkeys following weekly IV administration of HuMab-CD38

Dosage (mg/kg/wk)	Group Assignment	Anim. ID No./Sex	Dose Day	C_{max} (µg/mL)	t_{max} (h)	AUC_{0-t} (µg·h/mL)	$AUC_{0-\infty}$ (µg·h/mL)	$t_{1/2}$ (h)	V_{ss} (mL/kg)	CL (mL/h/kg)
20	Main	3M	1	1920.0	3.50	35,452.6	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	4M[a]		682.0	2.00	29,122.4	34,387.4	62.92	51.14	0.5816
	Main	9F		416.0	1.00	21,807.9	24,555.8	48.22	61.91	0.8145
	Recovery	10F[a]		498.0	3.50	33,319.3	NR[b]	NR[b]	NR[b]	NR[b]
	Main	3M	8	707.0	0.50	19,698.1	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	4M[a]		815.0	0.50	43,435.5	43,443.0	12.92	30.43	0.4604
	Main	9F		481.0	1.00	14,784.9	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	10F[a]		558.0	12.50	32,000.9	32,003.5	9.38	24.15	0.6249
100	Main	5M	1	2,880.0	0.50	138,086.5	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	6M		3,760.0	3.50	237,890.0	NR[b]	NR[b]	NR[b]	NR[b]
	Main	11F		2,880.0	3.50	196,521.5	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	12F		3,980.0	0.50	189,266.5	NR[b]	NR[b]	NR[b]	NR[b]
	Main	5M	8	3,810.0	2.00	101,670.8	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	6M		3,460.0	0.50	403,617.4	403,619.8	22.20	35.28	0.2478
	Main	11F		3,880.0	0.50	110,092.3	NR[b]	NR[b]	NR[b]	NR[b]
	Recovery	12F		3,820.0	2.00	703,593.1	703,595.0	30.12	26.14	0.1421

[a] Animals 4M and 10F were considered to exhibit a positive antibody response and therefore estimates were excluded from interpretation.

[b] Parameters relying on the determination of the terminal elimination phase were not reported if the coefficient of determination was less than 0.80 and/or if the extrapolation of $AUC_{0-\infty}$ represented more than 20% of the total area.

2.3.4. Toxicology

Single dose toxicity

No single-dose toxicity studies have been conducted (see discussion on non-clinical aspects).

Repeat dose toxicity

Table 5: Repeated-dose toxicity studies

Study ID	Species/Sex/ Number/ Group	Dose/Route	Duration	NOEL/NOAEL (mg/kg/day)	Major findings
8754-0701	Chimpanzees 1/sex/group	5, 25 mg/kg IV infusion	6 weeks	Not identified	- IRR (cytokine release syndrome, increased TNF-α, IL-6 and IFN-γ). - Severe GI problems (diarrhea, soft stool and blood in the stool). - Reduce appetite and hypoactivity/depression) - Thrombocytopenia - Increase in percentage of circulating neutrophils - Decrease in percentage of circulating lymphocytes. - Decrease in lymph node mononuclear cell counts (all populations) - Decrease in bone marrow monocytes (consisted of decreases in most CD14+ populations). - Minor decrease in RBC and haemoglobin levels. - Gross necropsy findings consisted of over-inflation and edema of the lungs, foci of lung anthracosis, thickening of the left ventricle, scaring on the surface of the right ventricle, and multiple adhesions of the stomach and intestinal loops. Death was attributed to fluid accumulation in the lung, considered likely the result of daratumumab-induced acute anaphylaxis.

509809	Cynomolgus Monkeys 2/sex/group	20, 100 mg/kg IV infusion	2 weeks		- Decrease in circulating lymphocytes (marked depletion in B cells, CD4+ and CD8+ T and NK cells expressing CD38). - Decrease in lymph node CD4+ and CD8+ T cell populations. - Decrease in bone marrow lymphocytes - Low hemoglobin concentrations, RBCs and hematocrits, and high reticulocyte counts. - High total bilirubin concentrations. - Histopathological findings consisted of thymic atrophy and lymphoid depletion in the mandibular and mesenteric lymph nodes, Peyer's patches, and spleen.

Genotoxicity

No genotoxicity studies have been conducted (see discussion on non-clinical aspects).

Carcinogenicity

No carcinogenicity studies have been conducted (see discussion on non-clinical aspects).

Reproduction Toxicity

No reproduction toxicity studies have been conducted (see discussion on non-clinical aspects).

Toxicokinetic data

Toxicokinetic data are presented under section ''2.3.3. Pharmacokinetics''.

Local Tolerance

No local tolerance studies have been conducted (see discussion on non-clinical aspects).

Other toxicity studies

Tissue Cross-Reactivity of FITC-Labeled Daratumumab With Chimpanzee Tissues Ex Vivo (Report BKV00003)

This study was conducted to determine the tissue binding specificity of FITC-labeled daratumumab in normal chimpanzee tissue specimens. The following tissues were evaluated: adrenal gland, bone marrow, brain, colon, endothelium (heart), fallopian tube, GI tract (small intestine), heart, kidney (glomerulus and tubule), liver, lung (bronchiole and alveolus), lymph node (including mesenteric lymph node), pancreas, pituitary, skin, spinal cord, spleen, striated muscle, tonsil, and testes.

FITC-labeled daratumumab was applied to cryosections of tissue samples. Binding was detected via a biotinylated goat anti-fluorescein secondary antibody. Bound complexes were visualized with a streptavidin-biotin-horseradish peroxidase complex (ABC) and a diaminobenzidine chromogen substrate.

Specific daratumumab-FITC staining occurred in the lymphoid cells and macrophages, and in hematopoietic cells in the spleen, tonsil, lymph nodes, and lamina propria of the intestinal tract. Specific

binding was also detected in the cytoplasm of multiple chimpanzee tissues (adrenal gland, bone marrow, brain, colon, fallopian tube, GI tract, heart, kidney, liver, lymph node, mesenteric lymph node, pancreas, pituitary, skin, spinal cord, spleen, striated muscle, testes, and tonsil). The only tissue examined that showed no binding was lung.

Daratumumab-FITC: An Immunohistochemical Investigation of Cross-Reactivity in a Range of Human Tissues (Report 28118)

This study was conducted to determine the tissue binding specificity of FITC-labeled daratumumab on normal, adult human tissue specimens. The tissue panel was based on the "suggested list of human tissues to be used for immunohistochemical investigations of cross reactivity" in Annex II of the 1995 European Medicines Evaluation Agency Guideline. All tissues selected for inclusion in this study were stained with hematoxylin and eosin, or giemsa (for blood and bone marrow) and an appropriate antigen marker before acceptance to the study.

Sections of each sample of tissue were treated with FITC-labeled daratumumab at concentrations of 0, 0.5, 1, and 2 µg/mL. Examination of the positive and negative controls showed the validity of the test system. Specific daratumumab-FITC staining occurred in the lymphoid cells in the spleen, tonsil, lymph nodes, and thymus. Specific daratumumab binding was also detected in the cytoplasm of multiple human tissues, ie, capillaries of the pituitary gland, vascular endothelial cells of the fallopian tube, lymphocytes in the ileum serosa, parathyroid, lymph node, spleen, thymus and tonsil, kidney, testis, and thyroid interstitial cells, epithelial cells of the fallopian tube, and the prostate. The subcellular location of staining in vascular endothelial cells of the pituitary gland and fallopian tube could not be determined.

HuMab-CD38-FITC: An Immunohistochemical Investigation of Cross-Reactivity in a Range of Cynomolgus Monkey Tissues (Study 510547)

This study was conducted to determine the tissue binding specificity of the FITC-conjugated HuMab-CD38, which binds to cynomolgus monkey CD38, in a panel of 35 normal cynomolgus monkey tissues: adrenal gland, brain (cerebellum and cerebrum), breast, eye (with retina), fallopian tube, GI tract (stomach, small intestine and large intestine), heart, kidney, liver,lung, lymph node, ovary, pancreas, peripheral nerve, pituitary gland, prostate, parotid salivary gland, skin, spinal cord, spleen, striated muscle, testis, thymus, thyroid and parathyroid gland, tonsil, urinary bladder, ureter, uterus (cervix and endometrium), and vascular endothelium. Haematological samples (blood and bone marrow) prepared as smears or cytospins were also evaluated.

All tissues selected for inclusion in this study were stained with hematoxylin and eosin, or giemsa (for blood and bone marrow) and an appropriate antigen marker before acceptance to the study.

Acetone-fixed cryosections of each sample of tissue were treated with FITC-labeled HuMab-CD38 at concentrations of 0, 0.2, 0.5, and 1 µg/mL.

Staining was observed in the cytoplasm of blood vessels, bone marrow lymphocytes, cerebellum white matter, cerebrum white matter, cervix, colon lamina propria, fallopian tube interstitium, ileum lamina propria, lung alveolar cells, lymph node T-cells, peripheral nerve myelin, retina/choroidea glassy membrane, spinal cord white matter, spleen T-cell zone, stomach, striated muscle fibers, thymus T-cells in medulla and cortex, and tonsil T-cell zone. It was not possible to determine the subcellular location of specific staining in endothelial (capillary) cells, whose cytoplasm is particularly thin, or in the interstitium of glomeruli in the kidney or the sinusoids of the liver. In the kidney and liver, staining in the interstitium/sinusoids may reflect staining of endothelial cells.

2.3.5. Ecotoxicity / environmental risk assessment

No ERA studies were submitted (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

The Applicant has addressed the structural and functional properties of daratumumab and HuMab-CD38 in a comprehensive array of non-clinical *in vitro* and *in vivo* pharmacology studies in support of the use of daratumumab in the proposed indication.

Daratumumab binding to CD38 leads to multiple biologic effects on tumour cells. As an IgG1 antibody, daratumumab has the potential to bind to all FcγRs inducing ADCC, CDC and ADCP. These effector functions were assessed in cell-based studies, showing high tumour cell lysis, though with high variability. The mechanism underlying differences in cell lysis are unknown and could be attribute to effector cells (NK and macrophages) and/or to differences in CD38 expression.

Binding of daratumumab to CD38 also mediated cell apoptosis and to modulate enzymatic activities of CD38, blunting cyclase activity and enhancing hydrolase activity, although the underlying cellular mechanism and the contribution to the overall anti-tumour effect are not clearly understood.

Treatment with daratumumab effectively reduced growth of human lymphoma cells in SCID mice, both in the preventive and therapeutic settings. When administered to mice bearing established disease, therapeutic activity was observed at a dose as low as 10 µg per mouse, corresponding to approximately 0.5 mg/kg body weight. Pharmacological effects other than the primary therapeutic activity (secondary pharmacodynamics) could derive from IgG1 isotype effector functions such as cytokine release and complement-mediated lysis of erythrocytes. Daratumumab has a low level of binding to human erythrocytes but did not induce specific complement-mediated lysis of erythrocytes, however a risk of interference with blood typing may exist (see Clinical safety discussion and RMP). Cytokine release observed with daratumumab was similar to other marketed therapeutic antibodies and it was consistent with adverse effects observed in toxicology studies. Overall, results of these studies support the hypothesis that daratumumab does not exert target-specific agonistic activity, and that the cytokine release observed is mainly caused by the Fc-portion of IgG1.

Distinct differences in the binding of daratumumab and HuMab-CD38 to human and cynomolgus B and T lymphocytes were identified. Daratumumab did not demonstrate specific binding to any cynomolgus monkey cell types while both daratumumab and HuMab-CD38 bound weakly to human B and T cells. In contrast, HuMab-CD38 bound strongly to cynomolgus monkey B and T lymphocytes. HuMab-CD38 bound to cynomolgus monkey erythrocytes at concentrations > 3 µg/mL, which may suggest higher levels of CD38 expression in monkey vs. human peripheral blood cells. No binding to human erythrocytes was seen. The results support the use of HuMab-CD38 as a surrogate antibody for nonclinical studies involving cynomolgus or rhesus monkeys and indeed, the higher binding of HuMab-CD38 to cynomolgus monkey blood cells may suggest higher levels of CD38 expression in monkey vs. human peripheral blood cells, which could be an important consideration in interpreting results of nonclinical studies in cynomolgus monkeys.

Systemic exposure (Cmax and AUC) of daratumumab increased in a greater than dose-proportional manner with increasing dose. Daratumumab t1/2 values generally increased and CL values generally decreased after repeated administration and with increasing dose, which suggested saturation of elimination mechanisms at elevated serum drug concentrations.

No consistent gender differences were observed for any of the PK parameters estimated in the 2-week study with HuMab-CD38 in cynomolgus monkeys. High drug substance concentrations are considered to

interfere with the detection of ADA's and therefore, ADA presence cannot be completely excluded. Collectively, the non-clinical pharmacokinetic data of daratumumab derived from repeat dose toxicology studies is considered limited (as chimpanzees is the only relevant species), however, adequate for the characterization of the pharmacokinetics of daratumumab and the anti-CD38 mAb, HuMab-CD38 after single dose and repeated administration.

No stand-alone safety pharmacology studies were conducted with either daratumumab or HuMab-CD38. Safety pharmacology endpoints were incorporated into the design of the repeat-dose toxicology studies as suggested in ICH S6(R1) and this approach is endorsed. There were no treatment-related adverse effects on cardiovascular, respiratory, or central nervous system parameters in the 6- and 2-week IV repeat-dose toxicology studies in chimpanzees and cynomolgus monkeys administered daratumumab or HuMab-CD38, respectively.

The two primary toxicities in the pivotal chimpanzee study were infusion-related reactions (IRRs) and thrombocytopenia. Measures were taken to avoid the IRRs in the subsequent dosing of high-dose animals, i.e. a pre-dose of 10 mg daratumumab was administered i.v. 24 h before dosing, and infusion time was lengthened to 1 h, resulting in milder IRRs. In the clinical setting, IRRs are one of the safety issues, and measures are addressed accordingly in relevant sections of the SmPC (see discussion on clinical safety).

At the histopathologic examination, thymic atrophy was observed in animals from the main study groups. Lymphoid atrophy or depletion was also observed in the mandibular and mesenteric lymph nodes and spleen in animals that received 20 or 100 mg/kg. Following the recovery period, there was minimal thymic atrophy in the 100 mg/kg-dosed female and minimal lymphoid depletion in the mesenteric lymph node in the 100 mg/kg-dosed male. A NOAEL was not established in this study.

ADAs to HuMab-CD38 were detected in both monkeys in the 20 mg/kg recovery group. The development of ADA in non-clinical species is not necessarily predictive of potential immunogenicity in humans, however, positive Coombs' tests have been observed in patients, and methods to ameliorate the interference of daratumumab in the assay have been developed and this has been addressed in the SmPC (see discussion on clinical safety).

No developmental and reproductive toxicity studies were performed. Developmental and reproductive toxicity testing is not feasible in chimpanzees. The use of a surrogate antibody in cynomolgus monkeys was considered, but anaemia and formation of ADAs limit the dosages and duration of any additional studies in this species. In addition, as the majority of patient population is beyond reproductive age it is therefore acknowledged that such studies are not deemed necessary for marketing authorisation however in order to address the whole population studied, reproductive and developmental toxicity is included as missing information in the RMP (see discussion on clinical safety). The lack of such data is addressed in the SmPC as follows: ''There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus'' (see SmPC section 4.6).

No genotoxicity and carcinogenicity studies are required for daratumumab.

Local tolerance assessment was incorporated into repeat-dose studies with no relevant findings suggesting local toxicity.

Tissue cross-reactivity studies were conducted using FITC-labeled daratumumab and normal chimpanzee and human tissue specimens. In addition, a tissue cross-reactivity study was conducted with FITC-labeled

HuMab-CD38 and normal cynomolgus monkey tissue samples. Specific binding was observed in most lymphoid tissues which confirmed that HuMab-CD38 and daratumumab binds to target sites of the lymphoid tissues in all species. Furthermore, binding was observed in the cytoplasm in multiple tissues in all three species. However, cytoplasmic binding is generally not relevant for mAbs as they do not diffuse into cells and do not have access to the cytoplasm.

The justification provided by the Applicant for not performing environmental risk assessment studies was considered acceptable since daratumumab is a protein therefore, unlikely to result in significant risk to the environment. This is in accordance with the "Guideline on Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 corr 21*).

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical pharmacology data for daratumumab and HuMab-CD38, is considered sufficient for the proposed cancer indication. The relevant information has been included in the SmPC (sections 4.6, 5.1 and 5.3).

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant 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 6: Overview of clinical studies

Study ID	No. of study centres / locations	Design	Study Posology	Patient characteristics	Total No of Patients Enrolled
GEN501 Key study	Part1: 4 sites in Denmark, Netherlands and Sweden. Part 2: 6 sites in Part 1 countries and USA	Phase 1/2 Monotherapy	Part 1, 0.005-24mg/kg:n=32 Part 2, 16mg/kg: n=42 Part 2, 8mg/kg: n=30	MM patients relapsed from or refractory to at least 2 different cytoreductive therapies and without further treatment options.	104
MMY2002 Key study	26 sites in USA, Canada and Spain	Phase 2 Monotherapy	16mg/kg: n= 106 8mg/kg :n= 18	MM patients who have received at least 3 prior lines of therapy (incl. PI and IMiD) or double refractory to PI and IMiD	124
MMY1001	21 sites in USA, France and Spain	Phase 1/2 + various chemotherapy	16 mg/kg: n=49	MM patients who received various chemotherapy, usually a combination incl. Velcade	49
GEN503	11 sites in France, Italy, Denmark, Netherlands, UK, and USA	Phase 1/2 +len/dex	16mg/kg: n=32 2-16mg/kg: n=13	MM patients who had relapsed or were refractory to at least 1 prior regimen	45
MMY1002	2 sites in Japan	Phase 1 Monotherapy	16mg/kg: n=5 8mg/kg: n=4	MM patients with relapsed or refractory disease	9

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of daratumumab following intravenous administration were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg. A population PK model of daratumumab was developed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma. The population PK analysis included 223 patients receiving daratumumab in two clinical trials (150 subjects received 16 mg/kg) (SmPC section 5.2).

The exposure-response analyses were performed on the combined data from studies GEN501 (N=104) and MMY2002 (N=124) as well as the data from Study MMY1002.

Absorption

No bioavailability studies were performed. As daratumumab is administered intravenously, bioavailability is 100%.

Distribution

The volume of distribution (Vd) was investigated in the Phase I Study GEN501 (Part 1 and Part 2), in the Japanese Phase I Study MMY1002 and in the Phase II Study MMY2002.

In GEN501 (Part 1), following the first IV administration of daratumumab, the mean Vz across dose levels (0.1-24 mg/kg) ranged from 38.24 to 58.94 mL/kg, and the mean values across the same dose range following the last infusion ranged from 31.90 to 104.77 mL/kg . In the larger sample of 42 subjects administered the recommended dose of 16 mg/kg (Study GEN501, Part 2), Vd was 90.19±43.40 mL/kg after the first dose and 59.51±54.68 mL/kg following the last dose.

The values volumes observed in subjects receiving 8 mg/kg in Study MMY2002 were mean Vd: 61.99±18.43 mL/kg), and in Japanese subjects participating in Study MMY1002: Mean Vd in subjects receiving 8 mg/kg was 66.94±30.89 mL/kg and mean Vd in subjects receiving 16 mg/kg was 57.97±3.29 mL/kg.

The population PK estimate for the central volume of distribution is 56.98±18.07 mL/kg.

Elimination

As observed in the Phase I GEN501 study (Part 1), clearance decreased with multiple doses, particularly in the dose groups receiving at least 2 mg/kg daratumumab: In the 2 mg/kg group, mean clearance decreased from 1.06 mL/h/kg after the first full infusion to 0.59 mL/h/kg after the seventh (last) full infusion. In the 24 mg/kg group, mean clearance decreased from 0.29 mL/h/kg after the first full infusion to 0.16 mL/h/kg after the seventh (last) full infusion.

The elimination halftime (T½) increased with multiple doses: from 25.62±5.61 hours for 2 mg/kg to 154.65±36.48 hours for 24 mg/kg. In the 16 mg/kg group, mean T½ increased from 109.9±42.05 hours after the first full infusion to 586.56±486.89 hours after the seventh (last) full infusion (Study GEN501, Part 1).

In the population PK analysis, the model-derived half-life (mean±standard deviation) associated with linear elimination was approximately 18±9 days.

Dose proportionality and time dependencies

Table 7: Summary of Daratumumab Pharmacokinetic Parameters for the First Full Infusion: Pharmacokinetic Analysis Set (Study GEN501 Part 1)

	0.1 mg/kg N = 6	0.5 mg/kg N = 3	1 mg/kg N = 6	2 mg/kg N = 3	4 mg/kg N = 3	8 mg/kg N = 3	16 mg/kg N = 3	24 mg/kg N = 3
Ctrough (µg/mL)								
n	6	3	6	3	3	3	3	3
Mean	0.000	0.000	0.000	0.000	0.596	3.733	7.023	0.000
SD	0.0000	0.0000	0.0000	0.0000	1.0329	6.4663	12.1636	0.0000
CV (%)					173.2	173.2	173.2	
Cmax (µg/mL)								
n	6	3	6	3	3	3	3	3
Mean	0.297	4.764	20.279	38.139	83.403	153.611	405.754	500.104
SD	0.2721	3.6521	5.8662	7.3573	15.9857	40.8315	72.5004	80.4271
CV (%)	91.7	76.7	28.9	19.3	19.2	26.6	17.9	16.1
Tmax (h)								
n	4	3	6	3	3	3	3	3
Median	5.833	8.083	6.017	9.667	9.583	9.933	8.000	10.000
Range	5.83 – 6.00	6.08 – 21.92	5.67 – 8.00	8.42 - 11.00	7.58 - 9.92	9.50 - 11.60	8.00 - 12.17	8.33 - 10.72
AUC(0-t) (µg·h/mL)								
n	6	3	6	3	3	3	3	3
Mean	1.126	110.061	715.885	1853.260	6575.376	15615.308	34319.272	48778.049
SD	1.5648	153.8467	673.3481	420.8798	3574.4199	6208.0563	6665.3957	13192.1517
CV (%)	138.9	139.8	94.1	22.7	54.4	39.8	19.4	27.0
AUC(0-inf) (µg·h/mL)								
n	0	1	5	3	3	3	3	3
Mean		313.276	977.236	1927.138	10062.880	27916.416	56893.559	97175.647
SD			758.0958	373.2869	6886.0158	16155.6804	22030.4204	39899.8745
CV (%)			77.6	19.4	68.4	57.9	38.7	41.1
AUC(0-7day) (µg·h/mL)								
n	1	3	6	3	3	3	3	3
Mean	6.482	118.694	762.755	1936.018	6354.139	14899.574	35613.298	47678.061
SD		161.1607	656.7838	302.4440	3400.8875	5256.1083	7686.8697	14396.5478
CV (%)		135.8	86.1	15.6	53.5	35.3	21.6	30.2
T (1/2) (h)								
n	0	1	5	3	3	3	3	3
Mean		20.011	28.273	25.615	91.492	131.776	109.900	154.651
SD			17.8534	5.6050	59.8914	68.1924	42.0480	36.4843
CV (%)			63.1	21.9	65.5	51.7	38.3	23.6
CL (mL/h/kg)								
N	0	1	5	3	3	3	3	3
Mean		1.596	1.500	1.064	0.726	0.404	0.315	0.287
SD			0.9601	0.2034	0.7459	0.3139	0.1336	0.1487
CV (%)			64.0	19.1	102.7	77.7	42.4	51.7
V (mL/kg)								
n	0	1	5	3	3	3	3	3
Mean		46.077	44.659	38.240	54.257	56.827	45.220	58.940
SD			5.7036	1.0545	4.0001	6.2621	5.9543	14.1501
CV (%)			12.8	2.8	7.4	11.0	13.2	24.0

Table 8: Summary of Daratumumab Pharmacokinetic Parameters for the Last (7th) Full Infusion: Pharmacokinetic Analysis Set (Study GEN501 Part 1)

	0.1 mg/kg N = 6	0.5 mg/kg N = 3	1 mg/kg N = 6	2 mg/kg N = 3	4 mg/kg N = 3	8 mg/kg N = 3	16 mg/kg N = 3	24 mg/kg N = 3
Ctrough (µg/mL)								
N	1	3	2	1	2	3	2	2
Mean	0.000	0.000	2.679	6.083	123.293	213.853	574.962	753.943
SD		0.0000	3.7880		86.0259	117.2155	94.6109	387.2286
CV (%)			141.4		69.8	54.8	16.5	51.4
Cmax (µg/mL)								
n	1	3	2	1	2	3	2	2
Mean	0.000	6.759	20.235	39.279	218.496	426.615	993.648	1163.338
SD		3.7585	11.9084		101.2563	176.5507	127.0395	333.9474
CV (%)		55.6	58.9		46.3	41.4	12.8	28.7
Tmax (h)								
n	0	3	2	1	2	3	2	2
Median		5.917	5.808	12.917	8.725	8.417	11.100	9.475
Range		5.75 - 6.00	5.67 - 5.95	12.92 - 12.92	7.53 - 9.92	7.78 - 22.80	9.95 - 12.25	9.42 - 9.53
AUC(0-t) (µg·h/mL)								
N	1	3	2	1	2	3	2	2
Mean	0.000	96.577	1194.031	3623.794	28495.376	51844.829	169590.533	180029.359
SD		82.2914	1441.2007		17598.3565	20030.0645	80851.4261	98543.2379
CV (%)		85.2	120.7		61.8	38.6	47.7	54.7
AUC(0-inf) (µg·h/mL)								
N	0	3	2	1	2	2	1	2
Mean		179.660	1345.216	4231.701	138149.094	186611.920	371159.322	1018233.501
SD		220.7550	1620.2447		163369.9648	90617.6371		1029108.3627
CV (%)		122.9	120.4		118.3	48.6		101.1
AUC(0-8day) (µg·h/mL)								
N	0	3	2	1	2	2	1	2
Mean		253.782	1226.337	3596.853	30832.564	66765.805	171652.702	185591.882
SD		338.7561	1394.0483		20789.3243	12571.4743		88439.3124
CV (%)		133.5	113.7		67.4	18.8		47.7
T (1/2) (h)								
N	0	3	2	1	2	2	1	2
Mean		12.682	35.684	72.140	396.487	289.499	215.329	586.564
SD		12.3041	37.5450		408.0819	121.8816		486.8880
CV (%)		97.0	105.2		102.9	42.1		83.0
CL (mL/h/kg)								
N	0	3	2	1	2	3	1	2
Mean		6.715	2.315	0.586	0.183	0.189	0.104	0.162
SD		6.1807	2.6047		0.1182	0.0946		0.0756
CV (%)		92.0	112.5		64.7	50.0		46.5
V (mL/kg)								
N	0	0	1	1	2	2	1	2
Mean			40.814	58.434	67.374	53.592	31.902	104.767
SD					40.1334	12.3612		43.6716
CV (%)					59.6	23.1		41.7

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days (SmPC section 5.2).

At the end of weekly dosing for the recommended schedule and dose of 16 mg/kg, the mean (SD) serum Cmax value was 915 (410.3) micrograms/mL, approximately 2.9-fold higher than following the first infusion. The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (331.5) micrograms/mL (SmPC section 5.2).

Based on the population PK analysis, daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of Cmax at steady-state to Cmax after the first dose was 1.6 (0.5) (SmPC section 5.2).

Special populations

Table 9: Number of subjects in different age groups

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	0/237	0/237	0/237
Non Controlled Trials	84/237	20/237	0/237

Based on population PK analysis, age (range: 31-84 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged < 65 years, n = 127) and older (aged ≥ 65 years, n = 96; aged ≥ 75years, n = 18; aged ≥ 85 years, n = 0) patients. (SmPC section 5.2).

Gender [female (n = 91), male (n = 132)] did not affect exposure of daratumumab to a clinically relevant degree (SmPC section 5.2).

No formal studies of daratumumab in patients with renal impairment have been conducted. A population PK analysis was performed based on pre-existing renal function data in patients receiving daratumumab, including 71 with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min), 78 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 68 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 6 with severe renal impairment or end stage renal disease (CRCL< 30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function (SmPC section 5.2).

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolised through hepatic pathways. A population PK analysis was performed to evaluate the effect of hepatic impairment as defined using the National Cancer Institute (NCI) criteria of hepatic dysfunction on the clearance of daratumumab based on pre existing hepatic function data in 223 patients. No clinically important differences in the exposure to daratumumab were observed between patients with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST > ULN; n = 34) and those with normal hepatic function (TB and AST ≤ ULN; n = 189). Daratumumab has not been studied in patients with moderate (TB > 1.5 x to 3 x ULN and any AST) or severe (TB > 3 x ULN and any AST) hepatic impairment (SmPC section 5.2).

Based on the population PK analysis the exposure to daratumumab was similar between white (n = 197) and non-white (n = 26) subjects (SmPC section 5.2).

Based on population PK analysis body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients (SmPC section 5.2).

Pharmacokinetic interaction studies

No *in vitro* or *in vivo* studies on pharmacokinetic drug interactions have been submitted.

2.4.3. Pharmacodynamics

Mechanism of action

Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Primary and Secondary pharmacology

Primary pharmacology

In Study GEN501, peripheral blood samples were immunophenotyped to track specific immune cell subtypes (NK cells, T cells, and B cells), which may act as effector cells to induce tumour cell death with daratumumab. Decreases in NK cells were observed post-treatment in all treatment groups and were most pronounced in all treatment groups ≥2 mg/kg in both peripheral blood and bone marrow. In Part 2, the change in total NK cells (as a percentage of lymphocytes in bone marrow) decreased from a median of 14.50% at baseline to 2.80% on treatment in the 8 mg/kg group and from a median of 19.90% at baseline to 5.90% on treatment in the 16 mg/kg group; these changes were statistically significant ($p=0.0468$ in 8 mg/kg group; $p<0.0001$ in the 16 mg/kg group).

Baseline absolute counts of total NK cells and post-baseline changes in NK cells were compared between responders and non-responders for 8 mg/kg and 16 mg/kg groups in Study GEN501 Part 2. A decrease in total NK cells was observed in both responders and non-responders and there was no association observed between the percentage of NK cell decrease and clinical response in either blood or bone marrow.

In addition to NK cells, other lymphocytes known to express CD38 such as B cells and T cells were measured at baseline and following daratumumab treatment. B cells (CD19+) were maintained in the peripheral blood and bone marrow following daratumumab treatment. T cells, both CD3+CD4+ and CD3+CD8+, were noted to increase over time with daratumumab treatment both in the periphery and the bone marrow (absolute counts as well as percentage of lymphocytes).

In study MMY2002, total NK cells (CD45+CD3-CD16+CD56+) were evaluated as a possible pharmacodynamic biomarker for daratumumab. A decrease in absolute counts (cells/µL) of total NK cells in peripheral blood was observed following daratumumab treatment in both the 8 mg/kg and 16 mg/kg groups. In the 8 mg/kg group with monthly dosing of daratumumab, total NK cells were reduced by Cycle 1 Day 2, but started to recover by Cycle 1 Day 4. Absolute counts of total NK cells increased until the next dose of daratumumab at Cycle 2, after which total NK cells decreased and did not recover during the treatment period.

In the 16 mg/kg group (daratumumab dosing weekly for 8 weeks, every 2 weeks for 16 weeks, and every 4 weeks thereafter), reduced absolute cell counts of total NK cells were observed by Cycle 1 Day 8 and remained at low levels during daratumumab treatment. In addition, activated NK cells (CD16+CD56dim) in blood also decreased following daratumumab dosing similar to total NK cells, and remained low while on treatment. The change in total NK cells (as a percentage of lymphocytes in bone marrow) decreased from a median of 14.80% at baseline to 8.00% on treatment in the 8 mg/kg group and from a median of

19.80% at baseline to 4.60% on treatment in the 16 mg/kg group; these changes were statistically significant (p=0.0039 in 8 mg/kg; p<0.0001 in 16 mg/kg group).

Baseline absolute counts of total NK cells were also compared between responders and non-responders for the 8 mg/kg and 16 mg/kg groups. The baseline total NK cells counts in blood or bone marrow did not show any difference between responders and non-responders. There was also no association observed between the percentage of NK cell decrease and clinical response.

Daratumumab treatment-associated changes were also observed in other immune cells. Evaluation of T cells indicated a significant increase of CD3+CD4+ and CD3+CD8+ T-cells over time with daratumumab treatment in the peripheral blood and bone marrow (both absolute counts and percentage of lymphocytes).

Secondary pharmacology

QTc interval

The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg) (SmPC section 5.1).

Pharmacokinetic-pharmacodynamic analyses was performed using a linear mixed effects modeling approach to examine the relationship between the baseline-adjusted/corrected change in QTcF intervals and time-matched (within 3 hours) serum concentrations of daratumumab.

In GEN501 Part 1, no statistically significant or clinically relevant change in QTcF vs. daratumumab serum concentrations was observed (Table 18).

Table 10: Change from Baseline Versus the Daratumumab Serum Concentration - Estimates From Linear Mixed Model [1,2] QTc Fridericia Interval (msec) (Part 1, Pharmacokinetic-Pharmacodynamic Population)

					Overall Daratumumab Dose Levels	
QT Parameter	Slope of Serum Conc. Effect on Δ QTc [1]	Standard Error of Slope of Serum Conc. Effect on Δ QTc [1]	p-value [1]	Overall Model Fit [1]	Predicted Δ QTc at Average Cmax 227900 ng/mL	One-sided Upper 95% Confidence Bound of Predicted Δ QTc [2]
QTcF	-0.00000384	0.00000417	0.3588	0.0126	3.84	6.80

[1] Linear mixed effects model is fit for change from baseline versus the daratumumab serum concentration. Subject random effects on the intercept are also included, concentration could not be included in the random effects. The Overall Model Fit p-value is based on the null likelihood ratio test using an estimation method of REML.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

A separate analysis was performed for 72 subjects (8 mg/kg n=30; 16 mg/kg n=42) in Study GEN501 Part 2. Pharmacokinetic- and pharmacodynamic analysis was performed using a linear mixed effects modeling approach to examine the relationship between the baseline-adjusted/corrected change in QTcF intervals and time-matched (within 3 hours) serum concentrations of daratumumab. The primary QT correction method was the Fridericia corrected QT (QTcF) because the Bazett correction is often less reliable. A statistically significant and borderline clinically relevant change in QTcF vs. daratumumab serum concentrations was observed with a ΔQTc of 12.34 msec at average daratumumab Cmax of 700 µg/mL (p<0.0001) (Table 19). No QTcF increase >60 ms, no new QTcF >500 ms, and no new abnormal U waves were observed.

Table 11: Change from Baseline Versus the Daratumumab Serum Concentration - Estimates From Linear Mixed Model [1,2] QTc Fridericia Interval (msec) (Part 2 Pharmacokinetic-Pharmacodynamic Population)

					Overall Daratumumab Dose Levels	
QT Parameter	Slope of Serum Conc. Effect on Δ QTc [1]	Standard Error of Slope of Serum Conc. Effect on Δ QTc [1]	p-value Slope pf Serum Conc. Effect on ΔQTc [1]	Overall Model Fit [1]	Predicted Δ QTc at Average Cmax 700 µg/mL	One-sided Upper 95% Confidence Bound of Predicted Δ QTc [2]
QTcF	0.01548926	0.00381245	<0.0001	<0.0001	12.34	16.37

[1] Linear Mixed Model is fit for change from baseline versus the Daratumumab serum concentration. Subject random effects on the intercept are also included; concentration could not be included in the random effects. The Overall Model Fit p-value is based on the null likelihood ratio test using an estimation method of REML.
[2] Upper Bound = upper one-sided 95% linear mixed model based confidence limit.

Immunogenicity

The immunogenicity of daratumumab has been evaluated in 2 monotherapy daratumumab studies (GEN501 and MMY2002) using validated ECLIA methods.

Patients (n = 199) were evaluated for anti-therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the patients tested positive for anti-daratumumab antibodies (SmPC section 5.1).

Relationship between plasma concentration and effect

The exposure-response analyses were performed on the combined data from studies GEN501 (N=104) and MMY2002 (N=124) as well as the data from study MMY2002 alone. Different exposure metrics were predicted and derived using estimated individual PK parameters based on the population PK model and actual dosing information for each subject. The exposure metrics included (1) maximal pre-infusion (trough) concentration (Cpre-infusion,max), (2) maximal end-of-infusion concentration (Cpost-infusion,max), (3) pre-infusion concentration before the last dose received, (4) end-of-infusion concentration after the last dose received, and (5) average concentration during the treatment. For the 5 subjects without measurable concentrations and excluded from the population PK analyses, the exposures (ie, concentrations) were set to half of the lower limit of the quantification (ie, 0.1 µg/mL).

The exposure-efficacy analyses were performed for ORR, the primary efficacy endpoint in study MMY2002, and other secondary endpoints (DOR, TTP, TTR, OS, PFS, and maximal reduction in paraprotein [MRPP]). For study GEN501, the response and progression data were based on a computerised algorithm since IRC data were not available from the study. The clinical relevance of significant covariates identified from the population PK analyses (ie, body weight, albumin, gender, drug product, and type of myeloma) was evaluated using ORR in the exposure-efficacy analyses.

Overall response rate significantly increased with daratumumab systemic exposure, and there was a maximum effect (Emax) relationship between daratumumab exposure and ORR . Among the tested exposure metrics, Cpre-infusion,max had the strongest correlation with ORR as it best described the data and provided the lowest Akaike Information Criterion (AIC) value. The estimated half maximal effect Cpre-infusion,max EC_{50}^{ORR} was 261 µg/mL, and the slope factor was approximately 45. Therefore, the 90% maximal effect on ORR may be achieved when Cpre-infusion,max = 274 µg/mL (EC_{90}^{ORR}), and limited additional benefit in ORR could be obtained when Cpre-infusion,max was above the predicted EC_{90}^{ORR}. Sensitivity analyses were conducted based on (1) subjects who completed at least 8 doses in the pooled

GEN501/MMY2002 dataset, (2) data from Study MMY2002 alone, and (3) subjects who completed at least 8 doses in Study MMY2002 alone. Both predicted and observed concentration data showed that approximately 80% of the subjects who were in the 16 mg/kg dose group and completed at least 8 infusions had Cpre-infusion,max above the estimated EC_{90}^{ORR}.

The figure below shows an apparent separation in the observed trough concentration over time between responders and non-responders, and maximum separation was observed around the maximal trough concentrations for both groups. The mean maximum trough concentration in non-responders appears below the EC_{90}^{ORR}, while it is well above the threshold in responders.

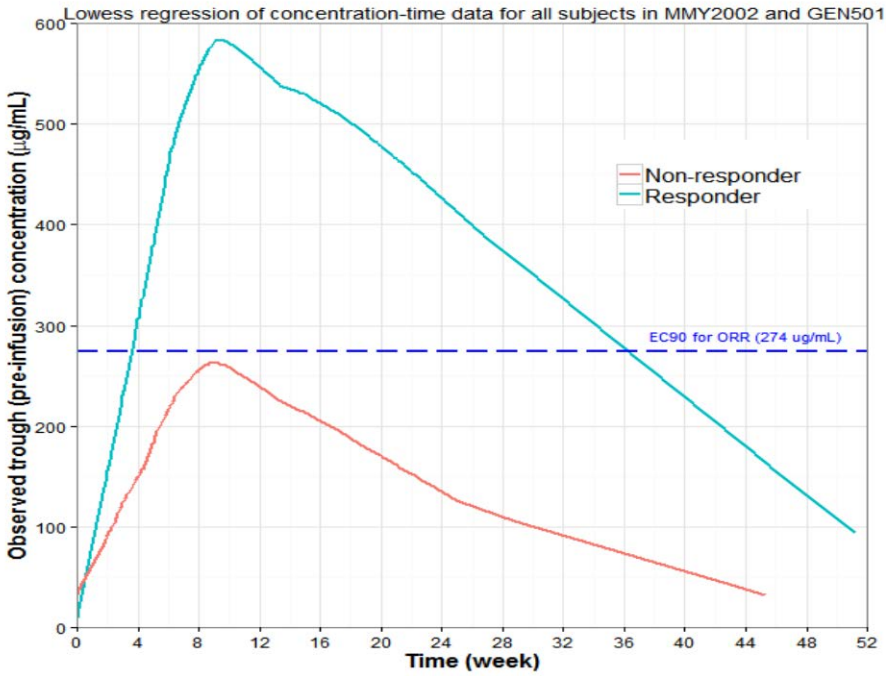


Figure 2: Comparison of Observed Pre-infusion (Trough) Concentration Over Time Between Responders and Non-responders

Comparison of Daratumumab 8 mg/kg and 16 mg/kg

Simulations were conducted to compare the trough concentrations for 8 mg/kg and 16 mg/kg dose levels under the recommended dosing schedule (ie, QW for 8 weeks, Q2W for 16 weeks, and then Q4W [8 doses for the current simulation] thereafter). Individual post hoc PK parameters based on the final population PK model for the 223 subjects from Studies GEN501 and MMY2002 were used.

The percentage of subjects that would achieve 90% and 99% target saturation at the end of the QW and Q4W dosing period was calculated. The simulations showed that the majority of subjects (ie, >80%) may achieve the 99% predicted target saturations after weekly dosing, and 90% predicted target saturations after Q4W (ie, at steady state) dosing at 16 mg/kg. However, in comparison, only approximately 50% of subjects may achieve 99% predicted target saturation after the QW dosing of 8 mg/kg daratumumab, and approximately 70% of subjects may achieve 90% target saturation at 8 mg/kg daratumumab after the Q4W dosing (Figure 8).

Conclusively, the response rates were consistently and significantly higher and deeper at the 16 mg/kg dose level as compared to various schedules at the 8 mg/kg dose level.

In Study GEN501, assessment of NK cells in peripheral blood was performed for the following dosing groups: ≤1 mg/kg, 2 mg/kg, 4 mg/kg, 8 mg/kg, 16 mg/kg and 24 mg/kg. Decreases in NK cells were observed post-treatment in all treatment groups and were most pronounced in treatment groups ≥2 mg/kg in both peripheral blood and bone marrow.

Dosing regimen

The total clearance of daratumumab decreased over time, possibly due to the depletion of the target (CD38). The intensive weekly dosing at the beginning of the treatment was therefore helpful to overcome the high clearance initially, and rapidly establish the efficacious concentration. Thereafter, the every 2 week and every 4 week dosing at 16 mg/kg appeared to be adequate to saturate the target and maintain the total clearance close to the non-specific linear clearance. The reduction in daratumumab concentration over time during less frequent dosing was not associated with either shorter duration of response or higher risk of disease progression. This result corroborates the finding based on the clinical analysis in which the rate of subjects who had disease progression was consistent in every 2 week and every 4 week dosing periods.

Exposure-safety

Exposure-safety analyses were conducted for selected AEs, including infusion-related reactions (IRRs), thrombocytopenia, anaemia, neutropenia, lymphopenia, and infections. Both treatment-emergent and drug-related adverse events (AEs) were investigated. The predicted end-of-infusion concentration after the first infusion (ie, Cmax after first dose, Cmax,1st) was explored for IRRs because the majority of IRRs occurred after the first dose, while the predicted maximal end-of-infusion concentration (ie, multiple-dose Cmax, Cpost-infusion,max) was investigated for the other AEs. Safety data were based on either the data from Study GEN501 and Study MMY2002 combined (n=228) or Study MMY2002 alone (n=124). No apparent relationship between the drug exposure and IRR, thrombocytopenia, anaemia, neutropenia, and lymphopenia was identified. Although the overall event rate of infection appeared to numerically increase with drug exposure, this trend was not observed for infections Grade 3 or higher. Further analysis showed that there was no significant difference in the rate of infections/infestations between IgG and non-IgG multiple myeloma subjects, although higher exposure was observed in non-IgG multiple myeloma subjects.

Pharmacodynamic interactions

There is no information available regarding pharmacodynamic interactions with other medicinal products or substances. A decrease in total NK cells in peripheral blood and bone marrow aspirates was observed following daratumumab treatment with lenalidomide/dexamethasone in all cohorts (Phase 1 and Phase 2 of Study GEN503). The NK cell decrease observed in this combination study was comparable to that observed with daratumumab monotherapy treatment in earlier studies (Studies MMY2002 and GEN501). In vitro studies have shown that glucocorticoid inhibits CD38 expression in human airway smooth muscle (HASM) cells (Kang BN et al. The FASEB Journ, 2006 May, vol 20: 1000-2 [E170-8], Tirumurugaan KG et al. Resp Research 2008,9:26-40). No significant difference in median steroid dose between responders and non-responders though no statistical analyses have been observed.

In vitro studies have also shown that novobiocin increases CD38 expression (Thiele A et al. Biochimica Biophysica Acta, 2002:32-40). An analysis of baseline CD38 expression between responders and non-responders in studies GEN501 and MMY2002 shown that the baseline median expression levels of CD38 in bone marrow multiple myeloma cells (CD138+) were lower in non-responders compared to responders, but a substantial overlap of the CD38 level between the two response groups were observed.

2.4.4. Discussion on clinical pharmacology

The PK of daratumumab has been reasonably well investigated and generally in accordance with the current guideline on the clinical investigation of pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004) and scientific advice provided by EMA/CHMP/SAWP (EMA/CHMP/SAWP/69790/2013). The overall approach of combined phase I/II trials and additional population PK- and exposure–response analyses can be supported. Of note, all pharmacokinetic and pharmacodynamic investigations were performed on target population namely patients with multiple myeloma relapsed from or refractory to 2 or more different prior therapies and therefore no extrapolation from e.g. healthy volunteers is necessary.

The primary PK of daratumumab is well characterised and is in accordance with the expected for an immunoglobulin (IgG). PK data demonstrated a model-derived mean half-life of approximately 18±9 days, which is approximate to the half-life of endogenous IgG (reported to be approximately 21 days [Keizer et al. 2010]). The model-derived mean half-life is based on data included in the population PK analyses and thus is expected to be for the doses of the pooled dataset however, data for patients treated with the recommended dose of 16 mg/kg and in steady state (i.e. after the last full infusion) is limited to less than 10 patients and therefore, the model-derived mean half-life is based on the population PK analyses is considered to be most representative.

Inter-individual variability has not been specifically addressed but generally, the inter-individual variability in PK parameters was moderate to high (25-50%). As expected also the intra-individual variability was moderate (32.7%).

The PPK analysis was overall performed using well recognised model building techniques.

Limited data were available for the following categories of the covariates, limiting the possibility for a robust assessment of the PK in these patients: age (≥ 75 years: n=18); races (White, Hispanic or Latino: 3% n=7; Asian: 2% n=4; other: 2% n=5); creatinine clearance category (≥15-≤29 ml/min: 2%, n=5; <15 ml/min: 0%, n=1); hepatic dysfunction (mild dysfunction: 15% n=34); baseline ECOG score (2: 6%, n=14); refractory status (None: 10%, n=23; PI only: 4%, n=8; IMiD only: 6%, n=14). The CHMP recommended the Applicant to perform additional analyses of the age, gender, renal impairment, hepatic impairment, ECOG score and refractory status with larger sample sizes as current Phase 3 studies reach maturation.

With reference to hepatic impairment, changes in hepatic function are unlikely to have a direct effect on the elimination of daratumumab since IgG1 molecules are not metabolised through hepatic pathways. Nevertheless, relevance of mild hepatic impairment on PK exposure cannot be completely ruled out since number of patients with mild hepatic impairment patients are limited (n=34) although the 95%CIs (normal and mild) are overlapped. Additionally, the low limit of the 95%CI of mild hepatic impairment (235.77 µg/mL) is under 274 µg/mL (EC90 ORR) which may have impact on efficacy. It is reassuring that mild hepatic impairment was not a significant covariate based on the model-based covariate analyses. Moreover, an analysis of the response-rate between patients with normal and mild hepatic function revealed no clinically relevant difference: The overall response rate (ORR) for patients treated with 16 mg/kg and with mild hepatic impairment (n=24) was 33% (95%CI: 16.9%-53.2%) compared with 31% (95%CI: 23.1%-39.1%) in the patients treated with at 16 mg/kg and with normal hepatic function (n=127). Hepatic impairment may also have impact on levels of albumin or indirect pathway of elimination of daratumumab. This was evaluated by studying albumin's (<35 g/L vs. ≥ 35 g/L) effect on overall response rate (ORR) before and after adjusting for drug exposure. The effect of albumin (<35 g/L vs. ≥ 35 g/L) on ORR before and after adjusting for daratumumab exposure is similar and these results are in line with the results of the analysis performed with albumin as a continuous variable supporting that albumin does not affect the effect of daratumumab. The CHMP recommended that the impact of baseline

hepatic impairment on safety and efficacy of daratumumab should be further characterized through the collection and analysis of additional PK data from the ongoing clinical studies.

NK cells are known to express high levels of CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56dim) NK cells in peripheral whole blood and bone marrow were observed with daratumumab treatment. However, baseline levels of NK cells or kinetics of NK cell decrease did not show an association with clinical response (SmPC section 5.1).

T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response (SmPC section 5.1).

The immunogenicity of daratumumab has been evaluated in 2 monotherapy daratumumab studies (GEN501 and MMY2002) using validated Charles River ECLIA methods. Limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab cannot be ruled out. Therefore, the Applicant should develop a new method for detecting ADAs. Immunogenicity has been classified as an important potential risk in the Risk Management Plan (RMP) however until further information are available, the following text is included in section 5.1 of the SmPC: ‘‘Patients (n = 199) were evaluated for anti therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the patients tested positive for anti-daratumumab antibodies. However, the employed assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab. Therefore, the incidence of antibody development might not have been reliably determined”.

The optimised method JRD, which was used in studies MMY2002, had a sufficient drug tolerance up to 31,250 ng/mL (without dilution 625 µg/mL). According to protocol, immunogenicity was tested on C1D1 pre, C3D1 pre, C6D1 pre, C12D1 pre and after the end of treatment. It should be noted that the mean ± SD through concentration at the end of weekly dosing (Cycle 3 Day 1 predose) was 573.49±331.49 µg/mL. Consequently, the presence of anti-daratumumab antibodies in studies MMY2002 may have been underestimated because observed concentration could be higher than drug tolerance at some time points.

Exposure-response analyses have demonstrated that the response rate significantly increased with daratumumab systemic exposure. The choice of 16 mg/kg rather than 8 mg/kg has been sufficiently justified as the recommended dose however, considered the seriousness of the disease and the poor prognosis for this group of patients, it was questioned if additional treatment response can be obtained by increasing the percentage of patients reaching a Cpre-infusion,max above the estimated. However a dose of 24 mg/kg compared with the recommended dose of 16 mg/kg, will only result in approximately 10% more subjects with a a Cpre-infusion,max above the estimated. It is acknowledged that most of the patients (i.e. the approximately 80% with a 99% predicted target saturation after weekly dosing) will not benefit from a higher dose but considering the seriousness of the disease and the dismissing prognosis for the patients not responding to daratumumab treatment, an increase of 10% patients with a clinically relevant increase in effect appears compelling. In addition, the experience with 24 mg/kg is indeed very limited (3 patients) thus naturally insufficient for a benefit-risk assessment. Therefore, 24 mg/kg is not a realistic alternative to 16 mg/kg, which remains the recommended dose.

The results from the analyses of ORR in the IgG and the ORR in the non-IgG groups are almost similar supporting the fact that the decreased estimated in patients with IgG multiple myeloma is counter-balanced by an increased sensitivity. Thus, the difference in drug exposure in the IgG and the non-IgG groups seems not to be clinically relevant and despite the fact that an increase in treatment dose can be expected to increase efficacy (including ORR, PFS and DoR), this is expected to be of similar magnitude for both IgG and non-IgG patients. Therefore, there is no apparent reason for different dosing regimen depending on IgG-status.

No interaction studies have been performed. As an IgG1κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes (SmPC section 5.1).

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, other methods to evaluate the depth of response should be considered (SmPC section 4.5).

In agreement with the EMA/CHMP/SAWP scientific advice (EMA/CHMP/SAWP/69790/2013), no thorough QT study was conducted. It is unlikely that daratumumab inhibits the hERG channel or causes a (clinically relevant) prolongation of the QTc. Nevertheless, conflicting results were observed in Study GEN501 Part 1 and Part 2. Part 1 investigates QTc changes over a wider range of daratumumab exposure but results from the PK-PD studies showed that most patients have serum daratumumab concentrations around 101-103 µg/mL and therefore, results from the Part 2 are considered representative for the majority of patients treated with the recommended dosage. An analysis of daratumumab concentration and QTc prolongation did not find a linear association. Likewise, subgroup analyses of patients concomitantly treated with known QTc prolonging medication and subgroups by age, gender, electrolyte abnormalities, and CHF did not find an association between any of these subgroups and QTc prolongation either. Thus, taken together, no plausible cause for the findings of the statistically significant QTc prolongation in Study GEN501 Part 2 has been identified.

Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e., greater than 20ms) at daratumumab C_{max} (SmPC section 5.1).

A thorough QTc study is not feasible but the Applicant will incorporate well-controlled data collection in a substudy of the ongoing Study SMM2001 to further evaluate a relationship between datatumumab concentration and QTc. QTc prolongation has been classified as an important potential risk in the RMP (See Clinical Safety discussion and RMP).

2.4.5. Conclusions on clinical pharmacology

Overall, the clinical pharmacology of daratumumab has been reasonably well investigated and generally in accordance with the current guideline (CHMP/EWP/89249/2004).

2.5. Clinical efficacy

2.5.1. Dose response studies

Study GEN501

Study GEN501 was a Phase 1/2, open-label, non-randomized, first-in-human study in subjects with multiple myeloma whose disease was relapsed or refractory to at least 2 prior lines of therapies.

In Part 1 of Study GEN501 (the First-in-Human dose escalation study), escalating doses of daratumumab were administered (0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, and 24 mg/kg) as a single dose, followed by a 3 week resting period, followed by 6 weekly doses for a total of 7 doses. The subjects in the 4 mg/kg, 8 mg/kg, 16 mg/kg and 24 mg/kg were included in the Part 1 efficacy analysis (n=3 subjects at each dose level). The best response at any dose level in this 8 week treatment period of Part 1 was a partial rtesponse (PR). A maximum tolerated dose (MTD) was not identified. An IDMC determined that, based on data from Part 1, the study could move forward with daratumumab doses ≥ 8 mg/kg. Based on the PK and efficacy data in Part 1, the 8 mg/kg dose was chosen as the Part 2 dose. However, during Part 2, it was identified that the 8 mg/kg dose may not saturate a majority of the target (CD38) throughout dosing, as indicated by the high inter-subject variability in pharmacokinetics. Therefore, the 8 mg/kg dose in Part 2 was changed to 16 mg/kg (Protocol Amendment 13) to assess whether high-dose intensity (leading to higher levels of systemic exposure and consistent saturation of the CD38 target), was needed to optimize the efficacy of daratumumab.

In Part 2 of Study GEN501, daratumumab 16 mg/kg was administered as a single dose, followed by a 3 week resting period, followed by weekly doses for 7 weeks, then every other week for an additional 14 weeks, and every 4 weeks thereafter for up to 96 weeks. In Part 2, the 16 mg/kg dose level (n=42, ORR of 36%) had an acceptable safety profile and resulted in higher and deeper response rates as compared to the 8 mg/kg dose level (n=30, ORR of 10%).

Table 12: Overview of treatment-related AEs (All treated analysis set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg	Total
Analysis set: all treated	30	42	72
Any TEAE	30 (100.0%)	41 (97.6%)	71 (98.6%)
Drug-related	27 (90.0%)	33 (78.6%)	60 (83.3%)
Any serious TEAE	12 (40.0%)	14 (33.3%)	26 (36.1%)
Drug-related	0	5 (11.9%)	5 (6.9%)
Maximum severity of any TEAE			
Grade 1	0	2 (4.8%)	2 (2.8%)
Grade 2	14 (46.7%)	28 (66.7%)	42 (58.3%)
Grade 3	12 (40.0%)	8 (19.0%)	20 (27.8%)
Grade 4	4 (13.3%)	2 (4.8%)	6 (8.3%)
Grade 5	0	1 (2.4%)	1 (1.4%)
Treatment discontinuation due to TEAE[a]	0	1 (2.4%)	1 (1.4%)
Drug-related	0	0	0
Death due to TEAE[b]	0	1 (2.4%)	1 (1.4%)
Drug-related	0	0	0

Keys: TEAE = treatment-emergent adverse event.
[a] Adverse events reported as the reason for treatment discontinuation on the end of treatment CRF page.
[b] Death due to adverse event on the death CRF page.
Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TSFAE01

Study MMY2002

Study MMY2002 was an open-label, 2-part, multicentre, Phase 2 study in subjects with multiple myeloma who received at least 3 prior lines of therapy including a PI and an IMiD or whose disease was double refractory to both a PI and an IMiD. The purpose of Part 1 was to select the optimal dose and schedule with a higher overall response rate (ORR) using Phase 1/2 pre-change drug product. Within each randomized treatment group in Part 1, a 2-stage design was utilized to allow an inefficacious dose schedule to be terminated early for futility. The purpose of Part 2 was to evaluate the efficacy of the selected dosing regimen identified in Part 1 in a population using Phase 3 (large scale production) drug product.

Part 1 of Study MMY2002 began at approximately the same time as the implementation of Protocol Amendment 13 in Study GEN501 (i.e., amendment to allow for administration of 16 mg/kg in Part 2). In Part 1 of Study MMY2002, 2 dosing regimens were evaluated in a randomized fashion (8 mg/kg every 4 weeks and 16 mg/kg weekly for 8 weeks, then every other week for 16 weeks, then every 4 weeks thereafter). It was expected that the 16 mg/kg dose would result in complete saturation of the target for all time points in the majority of subjects. The ORR for subjects treated with 8 mg/kg (n=18) in Part 1 was 11% as compared to 32% for subjects in Part 1 treated with 16 mg/kg (n=41). Furthermore, the VGPR or better rate for the 16 mg/kg group in Part 1 was 20% (8 of 41 subjects) as compared to 6% (1 of 18 subjects) at the 8 mg/kg dose level. The observed ORR at the 8 mg/kg dose level did not meet the protocol-specified criteria for continuation. Based on the totality of the data including efficacy, safety, and pharmacokinetics, the 8 mg/kg dose schedule was discontinued.

Table 13: Overall best response based on IRC assessment (All Treated Analysis Set; Study MMY2002)

	8 mg/kg		16 mg/kg					
			Part 1		Part 2		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	18	-	41	-	65	-	106	-
Best response								
Stringent complete response (sCR)	0	-	2 (4.9%)	(0.6%, 16.5%)	1 (1.5%)	(0.0%, 8.3%)	3 (2.8%)	(0.6%, 8.0%)
Complete response (CR)	0	-	0	-	0	-	0	-
Very good partial response (VGPR)	1 (5.6%)	(0.1%, 27.3%)	6 (14.6%)	(5.6%, 29.2%)	4 (6.2%)	(1.7%, 15.0%)	10 (9.4%)	(4.6%, 16.7%)
Partial response (PR)	1 (5.6%)	(0.1%, 27.3%)	5 (12.2%)	(4.1%, 26.2%)	13 (20.0%)	(11.1%, 31.8%)	18 (17.0%)	(10.4%, 25.5%)
Minimal response (MR)	2 (11.1%)	(1.4%, 34.7%)	0	-	5 (7.7%)	(2.5%, 17.0%)	5 (4.7%)	(1.5%, 10.7%)
Stable disease (SD)	10 (55.6%)	(30.8%, 78.5%)	16 (39.0%)	(24.2%, 55.5%)	30 (46.2%)	(33.7%, 59.0%)	46 (43.4%)	(33.8%, 53.4%)
Progressive disease (PD)	1 (5.6%)	(0.1%, 27.3%)	9 (22.0%)	(10.6%, 37.6%)	9 (13.8%)	(6.5%, 24.7%)	18 (17.0%)	(10.4%, 25.5%)
Not evaluable (NE)	3 (16.7%)	(3.6%, 41.4%)	3 (7.3%)	(1.5%, 19.9%)	3 (4.6%)	(1.0%, 12.9%)	6 (5.7%)	(2.1%, 11.9%)
Overall response (sCR+CR+VGPR+PR)	2 (11.1%)	(1.4%, 34.7%)	13 (31.7%)	(18.1%, 48.1%)	18 (27.7%)	(17.3%, 40.2%)	31 (29.2%)	(20.8%, 38.9%)
Clinical benefit (Overall response + MR)	4 (22.2%)	(6.4%, 47.6%)	13 (31.7%)	(18.1%, 48.1%)	23 (35.4%)	(23.9%, 48.2%)	36 (34.0%)	(25.0%, 43.8%)
VGPR or better (sCR + CR + VGPR)	1 (5.6%)	(0.1%, 27.3%)	8 (19.5%)	(8.8%, 34.9%)	5 (7.7%)	(2.5%, 17.0%)	13 (12.3%)	(6.7%, 20.1%)
CR or better (sCR + CR)	0	-	2 (4.9%)	(0.6%, 16.5%)	1 (1.5%)	(0.0%, 8.3%)	3 (2.8%)	(0.6%, 8.0%)

Keys: IRC = independent review committee; CI = confidence interval.
Note: Response was assessed by independent review committee, based on international Uniform Response Criteria Consensus Recommendations
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Exact 95% confidence intervals are provided.

[TEFRSP01A.rtf] [JNJ-54767414\MMY2002\DBR_CSR\RE_CSR\tefrsp01a.sas] 13FEB2015, 14:33

Table 14: Overview of treatment-related AEs (All Treated Analysis Set; Study MMY2002)

		16 mg/kg			
	8 mg/kg	Part 1	Part 2	Total	Total
Analysis set: all treated	**18**	**41**	**65**	**106**	**124**
Any TEAE	18 (100.0%)	40 (97.6%)	65 (100.0%)	105 (99.1%)	123 (99.2%)
Drug-related	14 (77.8%)	27 (65.9%)	54 (83.1%)	81 (76.4%)	95 (76.6%)
Any serious TEAE	6 (33.3%)	11 (26.8%)	21 (32.3%)	32 (30.2%)	38 (30.6%)
Drug-related	0	2 (4.9%)	6 (9.2%)	8 (7.5%)	8 (6.5%)
Maximum severity of any TEAE					
Grade 1	2 (11.1%)	5 (12.2%)	3 (4.6%)	8 (7.5%)	10 (8.1%)
Grade 2	5 (27.8%)	5 (12.2%)	21 (32.3%)	26 (24.5%)	31 (25.0%)
Grade 3	8 (44.4%)	22 (53.7%)	26 (40.0%)	48 (45.3%)	56 (45.2%)
Grade 4	3 (16.7%)	4 (9.8%)	10 (15.4%)	14 (13.2%)	17 (13.7%)
Grade 5	0	4 (9.8%)	5 (7.7%)	9 (8.5%)	9 (7.3%)
Treatment discontinuation due to TEAE[a]	0	1 (2.4%)	4 (6.2%)	5 (4.7%)	5 (4.0%)
Drug-related	0	0	0	0	0
Death due to TEAE[b]	0	1 (2.4%)	1 (1.5%)	2 (1.9%)	2 (1.6%)
Drug-related	0	0	0	0	0

Keys: TEAE = treatment-emergent adverse event.
[a]Treatment discontinuation due to adverse event on the end of treatment CRF page.
[b]Death due to adverse event on the death CRF page.
Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TSFAE01

2.5.2. Main studies

MMY2002

Study MMY2002 was an open-label, multicentre, phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor and IMiD) or are double refractory to a proteasome inhibitor and an IMiD.

Methods

Study Participants

Patients ≥ 18 years of age with documented multiple myeloma, were eligible to enter the study.

The key inclusion criteria were the following:

- Documented multiple myeloma as defined by the criteria below and evidence of disease progression on the most recent prior treatment regimen based on IMWG criteria:
  - Prior documentation of monoclonal plasma cells in the bone marrow ≥ 10% or presence of a biopsy-proven plasmacytoma.
  - Presence of measurable disease at baseline as defined by any of the following: serum M-protein level ≥ 1.0 g/dL or urine M-protein level ≥ 200 mg/24 hours; or IgA multiple myeloma: Serum M-protein level ≥ 0.5 g/dL or urine M-protein level 200 mg/24 hours; or light chain multiple myeloma: Serum immunoglobulin free light chain (FLC) 10 mg/dL and abnormal serum immunoglobulin kappa lambda FLC ratio.

- Evidence of response (ie, achieved ≥ 25% reduction in M-protein for ≥ 6 weeks [MR]) to at least 1 of their prior treatment regimens.
- Received an alkylating agent (≥ 2 cycles or 2 months) either alone or in combination with other myeloma treatments. One course of an alkylating agent for autologous stem cell transplantation (ASCT) alone or in combination was acceptable. A list of alkylating agents is provided in the National Cancer Comprehensive Network (NCCN) Guidelines (NCCN 2013).
- Received at least 3 prior lines of therapy (definition below) including a PI (≥ 2 cycles or 2 months of treatment) and an IMiD (≥ 2 cycles or 2 months of treatment) in any order during the course of treatment (except for patients who discontinued either of these treatments due to a severe allergic reaction within the first 2 cycles/months).

  OR

  Disease was double refractory to a PI and an IMiD. For patients who received more than 1 type of PI or IMID, their disease was to be refractory to the most recent one of them.
- ECOG performance status score of 0, 1, or 2.

The key exclusion criteria were the following:

- Previously received daratumumab or other anti-CD38 therapies.
- Received anti-myeloma treatment within 2 weeks before Cycle 1, Day 1.
- Nonsecretory multiple myeloma based upon standard M-component criteria (ie, measurable serum/urine M-component) unless the baseline serum FLC level was elevated.
- Previously received an allogeneic stem cell transplant or ASCT within 12 weeks before Cycle 1, Day 1.
- Received a cumulative dose of corticosteroids more than the equivalent of ≥ 140 mg of prednisone within the 2–week period before Cycle 1, Day 1.
- History of malignancy (other than multiple myeloma) within 5 years before Cycle 1, Day 1 (exceptions were squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, was considered cured with minimal risk of recurrence).
- Exhibited clinical signs of meningeal involvement of multiple myeloma.

Treatments

Daratumumab was administered as an IV infusion in 28-day cycles until disease progression, unacceptable toxicity, or other reasons as listed in the CSR.

In Part 1, patients received 1 of the following 2 treatment regimens:

- Group A: daratumumab 16 mg/kg: Cycles 1 and 2: Days 1, 8, 15, and 22 (weekly), Cycle 3 to 6: Days 1 and 15 (every other week), and Cycles 7+: Day 1 (every 4 weeks)
- Group B: daratumumab 8 mg/kg: Cycle 1+: Day 1 (every 4 weeks)

As of Amendment 2, subjects in Group B were given the option to cross over to Group A. Patients who crossed over to Group A could begin receiving daratumumab at 16 mg/kg after consultation between the investigator and the sponsor’s medical monitor.

Patients enrolled in Part 2 of the study received a dose of 16 mg/kg.

A schematic of the study design is provided in the figure below:

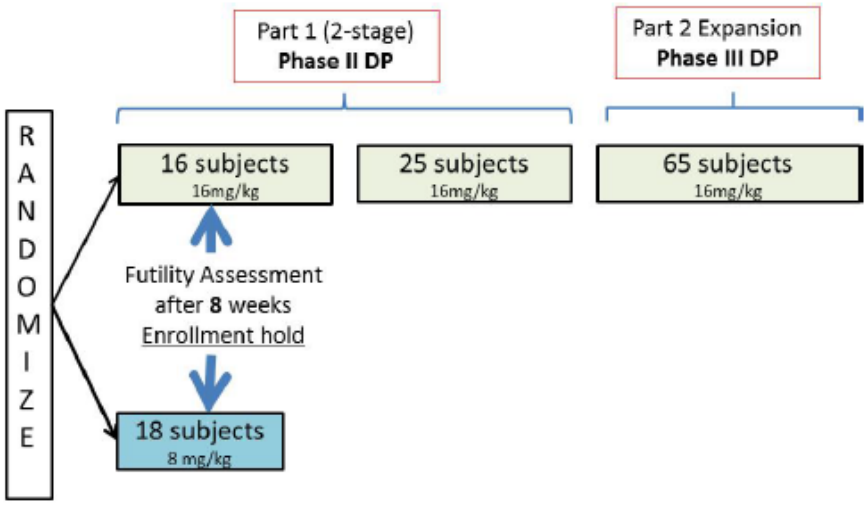


Figure 3: Design of Study MMY2002

All subjects received pre-infusion medication as shown in the following table:

Table 15: Pre-infusion medication (Study MMY2002)

	First and Second Infusions	Subsequent Infusions
	1 hour (±15 minutes) prior to dose	1 hour (±15 minutes) prior to dose
Methylprednisolone[a]	100 mg IV	60 mg IV
Paracetamol	X	X
Diphenhydramine[b]	X	X

[a] Or equivalent dose of an intermediate-acting or long-acting corticosteroid. Intravenously administered steroids are preferred, but oral may be substituted.
[b] Or alternative antihistamine at a proper dose.

For the prevention of delayed IRRs, all subjects were to receive corticosteroid orally (20 mg methylprednisolone or equivalent in accordance with local standards) on the 2 days following all daratumumab infusions (beginning the day after the infusion). For subjects with a higher risk of respiratory complications (eg, subjects who had a forced expiratory volume in 1 second (FEV1) % from predicted <75%), the following post-infusion medications should have been considered:

- Antihistamine (diphenhydramine or equivalent) on the first and second days after all infusions
- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (eg, inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ±inhaled corticosteroids for subjects with chronic obstructive pulmonary disease)

Objectives

The primary objective was to evaluate the efficacy of 2 treatment regimens of daratumumab, as measured by the ORR (PR or better) in patients with MM who had received at least 3 prior lines of therapy including a PI and an IMiD or whose disease was double refractory to both a PI and an IMiD agent.

The secondary objectives were:

- To assess the safety and tolerability of daratumumab.
- To assess the pharmacokinetics of Phase 2 drug product and Phase 3 drug product.
- To evaluate duration of and time to response to daratumumab.
- To determine the clinical benefit (minimal response [MR] or better) rate following treatment with daratumumab.
- To evaluate clinical outcomes including time to disease progression (TTP), progression-free survival (PFS), and overall survival (OS).
- To assess the pharmacokinetics, pharmacodynamics, and generation of antibodies to daratumumab (immunogenicity).
- To explore biomarkers predictive of response to daratumumab.

Outcomes / endpoints

The primary endpoint was the overall response rate (ORR), which was defined as the proportion of subjects who achieved PR or better according to the IMWG criteria (Durie 2007, Rajkumar 2011).

The secondary efficacy endpoints included:

- Duration of response, defined as the time from the date of initial response (PR or better) to the date of first documented evidence of progressive disease, according to IMWG criteria.
- Overall survival (OS), defined as the time from the date of first dose of daratumumab to the date of death from any cause.
- Clinical benefit rate (MR or better), defined as the proportion of subjects with best response of MR or better (including PR, very good partial response (VGPR), CR, and sCR).
- Time to response, defined as the time from the date of first dose of daratumumab to the date of initial documentation of a response (PR or better).
- Progression-free survival (PFS), defined as the time between the date of first dose of daratumumab and either disease progression or death, whichever occurred first.
- Time to disease progression (TTP), defined as the number of days from the date of first dose of daratumumab to the date of first record of disease progression.

Disease evaluations were to be performed by a central laboratory (unless otherwise specified) according to the Time and Events Schedule in the protocol until disease progression. The study used the IMWG consensus recommendation for multiple myeloma treatment response criteria (Durie 2007, Rajkumar 2011)4,13 presented in Table 24.

Table 16: International Uniform Response Criteria Consensus Recommendations

Response	Response Criteria
Stringent complete Response (sCR)	• CR as defined below, *plus* • Normal FLC ratio, *and* • Absence of clonal PCs by immunohistochemistry, immunofluorescence[a] or 2- to 4-color flow cytometry
Complete response (CR)*	• Negative immunofixation on the serum and urine, *and* • Disappearance of any soft tissue plasmacytomas, *and* • <5% PCs in bone marrow
Very good partial Response (VGPR)*	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, *or* • ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24 hours • If the serum and urine M-protein are not measurable, a decrease of ≥50% in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in bone marrow PCs is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • In addition to the above criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Minimal response (MR)	• In subjects with relapsed refractory myeloma adopted from the EBMT criteria (Blade 1998):[2] • ≥25% but ≤49% reduction of serum M-protein *and* reduction in 24-hour urine M-protein by 50% to 89% • In addition to the above criteria, if present at baseline, 25% to 49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Stable disease (SD)	• Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease (PD)†	• Increase of 25% from lowest response value in any one of the following: • Serum M-component (absolute increase must be ≥0.5 g/dL), • Urine M-component (absolute increase must be ≥200 mg/24 hours), • Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) • Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels, bone marrow PC percentage (absolute percentage must be ≥10%) • Bone marrow plasma cell percentage: the absolute percentage must be >10% • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion. • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the PC proliferative disorder
EBMT = European Group for Blood and Marrow Transplantation; FLC = free light chain; PC = plasma cell	
All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.	

*Clarifications to IMWG criteria for coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a >90% decrease in the difference between involved and uninvolved FLC levels.

†Clarifications to IMWG criteria for coding PD: Bone marrow criteria for PD are to be used only in subjects without measurable disease by M protein and by FLC levels; "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia and the "lowest response value" does not need to be a confirmed value.

[a] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.

Clinical Relapse

Clinical relapse is defined using the definition of clinical relapse in the IMWG criteria (Durie 2007, Rajkumar 2011).[4,13] In the IMWG criteria, clinical relapse is defined as requiring one or more of the following direct indicators of increasing disease or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder:

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging
2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L)
4. Decrease in hemoglobin of more than 2 g/dL (1.25 mM) or to less than 10 g/dL
5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥77 mM/L)
6. Hyperviscosity

In some subjects, bone pain may be the initial symptom of relapse in the absence of any of the above features. However, bone pain without imaging confirmation is not adequate to meet these criteria in studies.

Sample size

Up to 90 subjects were to be enrolled in Part 1, in which Phase 2 drug product was to be used. This part utilized a Simon's randomized 2-stage Phase 2 design to identify the treatment group for Part 2, in which Phase 3 drug product was used. Within each randomized treatment group, a 2-stage design was employed. The null hypothesis was that the ORR was at most 15%, and the alternative hypothesis was that the ORR was at least 40%. With a one-sided α of 2.5%, and a power of 85%, the total sample size within each randomized treatment group in Part 1 was 36 response-evaluable subjects. Assuming a non-evaluable rate of 10%, up to 40 subjects were to be enrolled within each randomized treatment group. The Stage 1 analysis was to be performed when approximately 15 subjects were enrolled in each treatment group and had sufficient data (i.e. up to 8 weeks of treatment) to be evaluable for response. Future enrolment into each treatment group was to be terminated if it was determined during the first stage that the treatment group was considered as ineffective or not well-tolerated. If a treatment group proceeded to the second stage with a total of 36 evaluable subjects with 2 stages combined, the null hypothesis was to be rejected if 11 or more responses were observed.

If it was determined at the end of Part 1 that a treatment group was to be further evaluated in Part 2, then up to an additional 60 subjects were to be enrolled in Part 2 and treated with Phase 3 drug product. This would bring the total number of subjects treated during the study up to approximately 100 for the selected treatment group. The purpose of Part 2 was to characterize the 2 different drug products with respect to pharmacokinetics, pharmacodynamics, efficacy, and safety.

Randomisation

Central randomization was implemented in Part 1 Stage 1 using an interactive web response system (IWRS).

Patients were randomly assigned to one of two treatment groups (daratumumab dosed at 8 mg/kg or 16 mg/kg). The randomization was stratified by International Staging System (I, II, or III) and refractory status (none, refractory to either a PI or IMiD, or refractory to both a PI and IMiD).

Blinding (masking)

This was an open-label study.

Statistical methods

Subject Populations Analyzed

All treated Analysis Set: All subjects who received at least 1 dose of daratumumab were used for all efficacy and safety analyses.

Per-Protocol Analysis Set: The per-protocol analysis set excluded all treated subjects who have had major protocol deviations due to not meeting all inclusion/exclusion criteria.

Pharmacokinetic Analysis Set: All treated subjects with at least 1 post-infusion sample were used for all pharmacokinetic analyses.

Immunogenicity Analysis Set: All treated subjects with appropriate samples for detection of antibodies to daratumumab.

No formal statistical hypothesis testing was planned. For each observed response category, a 2-sided 95% exact confidence interval (CI) was presented. For the calculation of ORR, those patients who were not evaluable for response, were to be considered non-responders.

No statistical comparison was performed. The Kaplan-Meier curve was provided for subjects in the 16 mg/kg group only and by responder vs. non-responder based on computerized IMWG algorithm.

As an exploratory analysis, the same PFS analyses were repeated based on investigator assessment, where progressive disease was determined by study investigators.

Additionally, in Part 2, descriptive statistics (mean, standard deviation, median, and range) were provided to summarize time to first response and time to best response for responders in each treatment group. A waterfall plot was generated for maximum percent reduction from baseline in serum/urine M-protein or FLC, based on the measurable type at baseline. Among responders, a shift table of bone marrow percent plasma cells from baseline value to first value post-baseline was provided and a figure was generated to display the percent change from baseline. No inferential analysis was performed.

The primary analysis sets for efficacy results were all treated patients. Two interim analyses were performed as specified in the protocol.

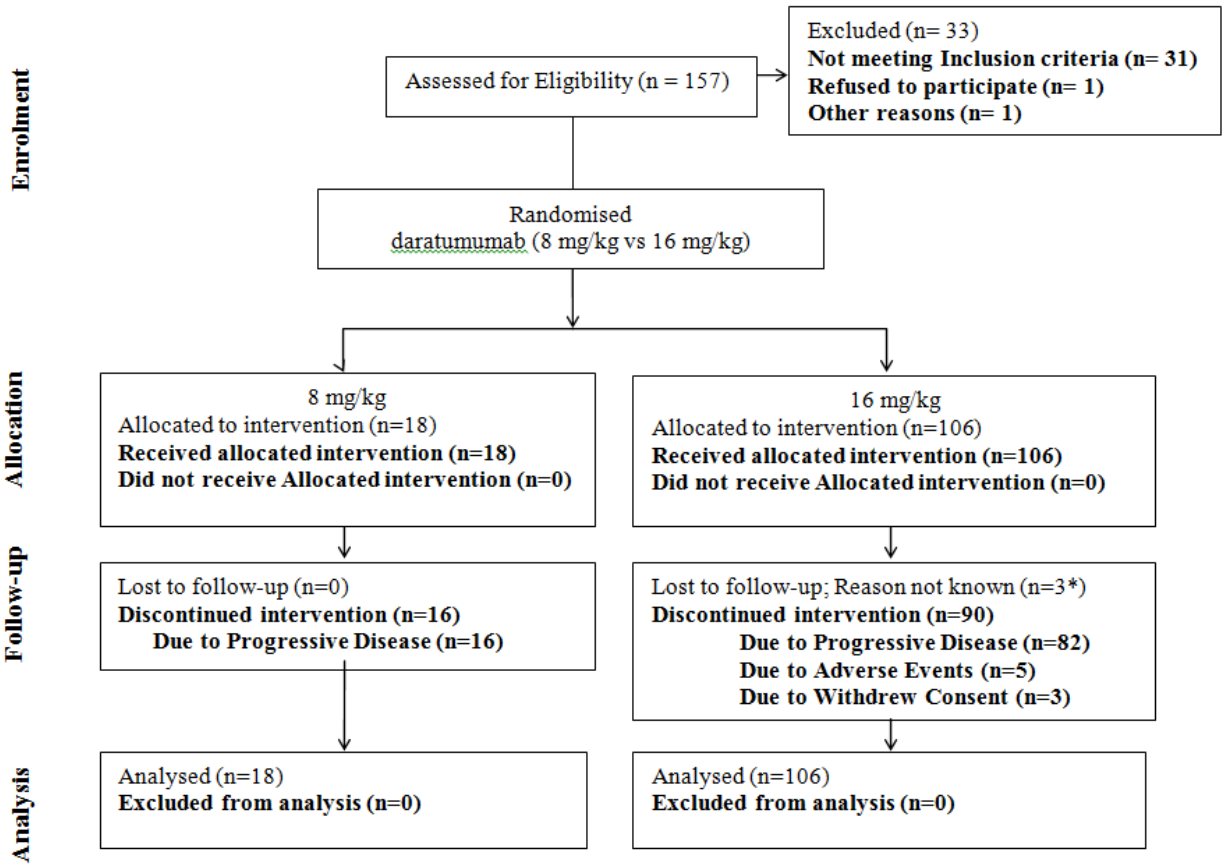
The first interim analysis also referred to as a futility analysis, occurred in March 2014, with a data cut-off 8 weeks after the last patient in Part 1 Stage 1 was dosed. Thirty-four (34) patients who were treated in Part 1 Stage 1 (18 from the 8 mg/kg group and 16 from the 16 mg/kg group), were included in the first interim analysis.

The second interim analysis had a data cut-off 8 weeks after the last patient in Part 1 Stage 2 was dosed, and occurred in June and July 2014. An additional 25 patients were treated in the 16 mg/kg group in Part 1 Stage 2. Based on the cumulative response data observed in Part 1, 11 patients (27%) achieved response in the 16 mg/kg group and this group was further expanded in Part 2.

Three subjects crossed over during the study from the 8 mg/kg to 16 mg/kg but were included in the 8 mg/kg group in all analyses, unless otherwise specified.

Results

Participant flow



*Three patients were lost to follow-up during study MMY2002 for which no reason can be given. As indicated in the study protocol every effort was made by study personnel to contact the subject and determine the reason for discontinuation/withdrawal.

Recruitment

The study was conducted at 26 sites in 3 countries (Canada, Spain, and the United States). Most of the subjects (72%) were enrolled at sites in the United States (16 sites), 18% in Canada (6 sites), and 10% in Spain (4 sites).

The first subject started treatment on 08 October 2013, and the last subject started treatment on 20 May 2014.

Conduct of the study

The original protocol, dated 11 July 2013, was amended 3 times. The original platelet count criteria was <75 x109/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count <50 x109/L.

- Amendment INT-1 (26 November 2013): included the following changes: the sample size was increased to approximately 20 subjects per treatment group in Part 1 Stage 1 from an original 15 subjects, the study agent administration guidelines were changed from mg/hr to mL/hr, and

minor additional changes were made for clarification throughout the protocol. An alternative treatment group (Group C; at the discretion of the Sponsor) was permitted to be added in Part 1, Stage 2, if either or both of the existing Treatment Groups A or B were considered as ineffective and/or not well tolerated. The platelet count criteria was revised to <75 x10^9/L for subjects in whom >50% of bone marrow nucleated cells are plasma cells; otherwise platelet count <50 x10^9/L in subjects with bone marrow plasma cells ≤ 50%.

- Amendment INT-2 (07 February 2014): included the following changes: following the discontinuation of the dose schedule of 8 mg/kg every 4 weeks (Treatment Group B) at the end of Stage 1, the number of subjects in Part 2 was increased to approximately 60 subjects, biomarker sampling time points were modified, and subjects in Group B were allowed to crossover to Group A. The platelet count criteria was modified to <50 x10^9/L (transfusion support within 7 days before the laboratory test is not permitted).
- Amendment INT-3 (09 July 2014): changed the timing of the on treatment bone marrow biopsy.

Table 17: Subjects with major protocol deviations (All treated analysis set; Study MMY2002)

	8 mg/kg	16 mg/kg	Total
Analysis set: all treated	18	106	124
Subjects with major protocol deviation	**2 (11.1%)**	**9 (8.5%)**	**11 (8.9%)**
Received wrong treatment or incorrect dose	0	3 (2.8%)	3 (2.4%)
Received a disallowed concomitant treatment	0	0	0
Entered but did not satisfy criteria	2 (11.1%)	5 (4.7%)	7 (5.6%)
Developed withdrawal criteria but not withdrawn	0	0	0
Efficacy assessment deviation	0	0	0
Safety assessment deviation	0	0	0
Other*	0	1 (0.9%)	1 (0.8%)

* Screening ECG was not done for this subject.
Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TSIPD01

Baseline data

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

Table 18: Demographic characteristics (All Treated Analysis Set; Study MMY2002)

		16 mg/kg			
	8 mg/kg	Part 1	Part 2	Total	Total
Analysis set: all treated	18	41	65	106	124
Age (years)					
N	18	41	65	106	124
Category, n (%)					
18 - < 65	8 (44.4%)	23 (56.1%)	35 (53.8%)	58 (54.7%)	66 (53.2%)
65 - < 75	8 (44.4%)	13 (31.7%)	23 (35.4%)	36 (34.0%)	44 (35.5%)
≥ 75	2 (11.1%)	5 (12.2%)	7 (10.8%)	12 (11.3%)	14 (11.3%)
Mean (SD)	64.2 (7.72)	62.6 (10.39)	63.1 (9.82)	62.9 (10.00)	63.1 (9.68)
Median	65.5	63.0	64.0	63.5	64.0
Range	(49; 76)	(31; 84)	(32; 84)	(31; 84)	(31; 84)
Sex, n (%)					
N	18	41	65	106	124
Male	12 (66.7%)	25 (61.0%)	27 (41.5%)	52 (49.1%)	64 (51.6%)
Female	6 (33.3%)	16 (39.0%)	38 (58.5%)	54 (50.9%)	60 (48.4%)
Race, n (%)					
N	18	41	65	106	124
White	17 (94.4%)	33 (80.5%)	51 (78.5%)	84 (79.2%)	101 (81.5%)
Black or African American	0	4 (9.8%)	11 (16.9%)	15 (14.2%)	15 (12.1%)
Asian	0	1 (2.4%)	3 (4.6%)	4 (3.8%)	4 (3.2%)
Other	0	1 (2.4%)	0	1 (0.9%)	1 (0.8%)
Unknown	0	1 (2.4%)	0	1 (0.9%)	1 (0.8%)
Not reported	1 (5.6%)	1 (2.4%)	0	1 (0.9%)	2 (1.6%)
Height (cm)					
N	18	40	64	104	122
Mean (SD)	168.44 (15.366)	170.75 (9.449)	165.70 (10.858)	167.64 (10.584)	167.76 (11.341)
Median	167.55	171.35	165.05	167.60	167.60
Range	(137.4; 198.0)	(152.0; 190.5)	(139.0; 196.0)	(139.0; 196.0)	(137.4; 198.0)
Weight (kg)					
N	18	41	65	106	124
Mean (SD)	81.95 (28.290)	78.42 (17.505)	74.09 (19.731)	75.77 (18.935)	76.66 (20.529)
Median	78.80	78.00	73.00	75.50	76.00
Range	(46.2; 160.2)	(41.0; 116.0)	(38.4; 140.0)	(38.4; 140.0)	(38.4; 160.2)
Baseline ECOG score, n (%)					
N	18	41	65	106	124
0	7 (38.9%)	9 (22.0%)	20 (30.8%)	29 (27.4%)	36 (29.0%)
1	9 (50.0%)	30 (73.2%)	39 (60.0%)	69 (65.1%)	78 (62.9%)
2	2 (11.1%)	2 (4.9%)	6 (9.2%)	8 (7.5%)	10 (8.1%)

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

[TSIDEM01.rtf] [JNJ-54767414\MMY2002\DBR_CSR\RE_CSR\tsidem01.sas] 13FEB2015, 14:05

Table 19: Baseline disease characteristics (All Treated Analysis Set; Study MMY2002)

		16 mg/kg			
	8 mg/kg	Part 1	Part 2	Total	Total
Analysis set: all treated	18	41	65	106	124
Type of myeloma by immunofixation, n (%)					
N	18	41	65	106	124
IgG	11 (61.1%)	19 (46.3%)	30 (46.2%)	49 (46.2%)	60 (48.4%)
IgA	3 (16.7%)	9 (22.0%)	13 (20.0%)	22 (20.8%)	25 (20.2%)
IgM	0	0	0	0	0
IgD	0	2 (4.9%)	1 (1.5%)	3 (2.8%)	3 (2.4%)
IgE	0	0	0	0	0
Light chain	4 (22.2%)	10 (24.4%)	20 (30.8%)	30 (28.3%)	34 (27.4%)
Kappa	2 (11.1%)	6 (14.6%)	11 (16.9%)	17 (16.0%)	19 (15.3%)
Lambda	2 (11.1%)	4 (9.8%)	9 (13.8%)	13 (12.3%)	15 (12.1%)
Biclonal	0	0	0	0	0
Serum free light chain only[a]	0	1 (2.4%)	1 (1.5%)	2 (1.9%)	2 (1.6%)
ISS Staging, n (%)					
N	18	41	65	106	124
I	2 (11.1%)	11 (26.8%)	15 (23.1%)	26 (24.5%)	28 (22.6%)
II	8 (44.4%)	17 (41.5%)	23 (35.4%)	40 (37.7%)	48 (38.7%)
III	8 (44.4%)	13 (31.7%)	27 (41.5%)	40 (37.7%)	48 (38.7%)
Cytogenetics profile[b]					
N[c]	17	37	58	95	112
T (4; 14)	2 (11.8%)	3 (8.1%)	6 (10.3%)	9 (9.5%)	11 (9.8%)
Del17p	6 (35.3%)	4 (10.8%)	12 (20.7%)	16 (16.8%)	22 (19.6%)
Del13q	4 (23.5%)	15 (40.5%)	15 (25.9%)	30 (31.6%)	34 (30.4%)
Amp1q21	3 (17.6%)	7 (18.9%)	16 (27.6%)	23 (24.2%)	26 (23.2%)
Other[d]	5 (29.4%)	17 (45.9%)	26 (44.8%)	43 (45.3%)	48 (42.9%)
Number of lines of prior therapy, n (%)					
N	18	41	65	106	124
≤ 3 Lines	6 (33.3%)	8 (19.5%)	11 (16.9%)	19 (17.9%)	25 (20.2%)
> 3 Lines	12 (66.7%)	33 (80.5%)	54 (83.1%)	87 (82.1%)	99 (79.8%)
Mean (SD)	5.1 (2.35)	5.3 (2.10)	5.7 (2.50)	5.6 (2.35)	5.5 (2.35)
Median	5.0	5.0	5.0	5.0	5.0
Range	(2; 11)	(2; 11)	(2; 14)	(2; 14)	(2; 14)
Time since initial diagnosis (years)					
N	18	41	65	106	124
Mean (SD)	4.45 (2.144)	5.35 (3.099)	6.52 (4.525)	6.06 (4.057)	5.83 (3.875)
Median	4.21	4.62	5.18	4.76	4.69
Range	(1.2; 9.1)	(1.1; 13.4)	(1.2; 23.8)	(1.1; 23.8)	(1.1; 23.8)

		16 mg/kg			
	8 mg/kg	Part 1	Part 2	Total	Total
Number of lytic bone lesions, n (%)					
N	18	41	64	105	123
None	8 (44.4%)	14 (34.1%)	17 (26.6%)	31 (29.5%)	39 (31.7%)
1-3	3 (16.7%)	3 (7.3%)	14 (21.9%)	17 (16.2%)	20 (16.3%)
4-10	2 (11.1%)	7 (17.1%)	13 (20.3%)	20 (19.0%)	22 (17.9%)
More than 10	5 (27.8%)	17 (41.5%)	20 (31.3%)	37 (35.2%)	42 (34.1%)
Presence of diffuse myeloma-related osteopenia, n (%)					
N	18	41	65	106	124
Yes	6 (33.3%)	19 (46.3%)	24 (36.9%)	43 (40.6%)	49 (39.5%)
No	12 (66.7%)	22 (53.7%)	41 (63.1%)	63 (59.4%)	75 (60.5%)
Number of extramedullary plasmacytomas, n (%)					
N	18	41	65	106	124
0	16 (88.9%)	32 (78.0%)	60 (92.3%)	92 (86.8%)	108 (87.1%)
≥ 1	2 (11.1%)	9 (22.0%)	5 (7.7%)	14 (13.2%)	16 (12.9%)
Bone marrow % plasma cells, n (%)					
N	18	41	63	104	122
< 5	1 (5.6%)	3 (7.3%)	6 (9.5%)	9 (8.7%)	10 (8.2%)
≥ 5 - ≤ 10	5 (27.8%)	8 (19.5%)	7 (11.1%)	15 (14.4%)	20 (16.4%)
> 10 - ≤ 30	1 (5.6%)	8 (19.5%)	16 (25.4%)	24 (23.1%)	25 (20.5%)
> 30	11 (61.1%)	22 (53.7%)	34 (54.0%)	56 (53.8%)	67 (54.9%)

Percentages are calculated with the number of subjects in each group with available data as denominator.
[a]not detected by immunofixation, serum free light chain only.
[b]Cytogenetic abnormalities were detected by FISH and/or karyotyping.
[c]Only includes all subjects with cytogenetics data available.
[d]Includes other types of abnormality or normal result.
Note: For bone marrow % plasma cells, the maximum value from either biopsy or aspirate at baseline is summarized.

Modified from Attachment TSIDEM02

Previous multiple myeloma treatments and refractory status in the study population are summarized in the tables below:

Table 20: Type of prior multiple myeloma therapy (All treated analysis set; Study MMY2002)

	8 mg/kg	16 mg/kg Part 1	16 mg/kg Part 2	Total	Total
Analysis set: all treated	18	41	65	106	124
Number of lines of prior therapy, n (%)					
≤ 3	6 (33.3%)	8 (19.5%)	11 (16.9%)	19 (17.9%)	25 (20.2%)
> 3	12 (66.7%)	33 (80.5%)	54 (83.1%)	87 (82.1%)	99 (79.8%)
Mean (SD)	5.1 (2.35)	5.3 (2.10)	5.7 (2.50)	5.6 (2.35)	5.5 (2.35)
Median	5.0	5.0	5.0	5.0	5.0
Range	(2; 11)	(2; 11)	(2; 14)	(2; 14)	(2; 14)
Prior PI	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Bortezomib	18 (100.0%)	41 (100.0%)	64 (98.5%)	105 (99.1%)	123 (99.2%)
Carfilzomib	6 (33.3%)	19 (46.3%)	34 (52.3%)	53 (50.0%)	59 (47.6%)
Prior IMiD	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Lenalidomide	18 (100.0%)	41 (100.0%)	64 (98.5%)	105 (99.1%)	123 (99.2%)
Pomalidomide	9 (50.0%)	26 (63.4%)	41 (63.1%)	67 (63.2%)	76 (61.3%)
Thalidomide	6 (33.3%)	14 (34.1%)	33 (50.8%)	47 (44.3%)	53 (42.7%)
Prior PI+IMiD[a]	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Prior PI+IMiD+ALKY[a]	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Prior BORT+LEN[a]	18 (100.0%)	41 (100.0%)	63 (96.9%)	104 (98.1%)	122 (98.4%)
Prior CARF+POM[a]	3 (16.7%)	15 (36.6%)	24 (36.9%)	39 (36.8%)	42 (33.9%)
Prior BORT+LEN+CARF[a]	6 (33.3%)	19 (46.3%)	33 (50.8%)	52 (49.1%)	58 (46.8%)
Prior BORT+LEN+POM[a]	9 (50.0%)	26 (63.4%)	41 (63.1%)	67 (63.2%)	76 (61.3%)
Prior BORT+LEN+CARF+POM[a]	3 (16.7%)	15 (36.6%)	24 (36.9%)	39 (36.8%)	42 (33.9%)
Prior BORT+LEN+CARF+POM+THAL[a]	3 (16.7%)	6 (14.6%)	12 (18.5%)	18 (17.0%)	21 (16.9%)
Prior steroids	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Dexamethasone	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Prednisone	7 (38.9%)	10 (24.4%)	29 (44.6%)	39 (36.8%)	46 (37.1%)
Prior chemotherapy	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Alkylating agents[b]	18 (100.0%)	41 (100.0%)	65 (100.0%)	106 (100.0%)	124 (100.0%)
Anthracyclines	12 (66.7%)	16 (39.0%)	39 (60.0%)	55 (51.9%)	67 (54.0%)
Prior ASCT	17 (94.4%)	34 (82.9%)	51 (78.5%)	85 (80.2%)	102 (82.3%)
Prior radiotherapy	3 (16.7%)	18 (43.9%)	19 (29.2%)	37 (34.9%)	40 (32.3%)

Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory drug; ASCT = autologous stem cell transplant; BORT = bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant.

[a] Subject may have received these agents in different treatment regimens.

[b] Includes either alkylating agents or autologous stem cell transplant.

Note: PI includes bortezomib, carfilzomib, MLN9708, marizomib, and oprozomib; IMiD includes thalidomide, lenalidomide, and pomalidomide.

Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TSIPM01

Table 21: Refractory status to prior multiple myeloma therapy (All treated analysis set; Study MMY2002)

		16 mg/kg			
	8 mg/kg	Part 1	Part 2	Total	Total
Analysis set: all treated	18	41	65	106	124
Refractory to PI/IMiD					
Both PI and IMiD	15 (83.3%)	39 (95.1%)	62 (95.4%)	101 (95.3%)	116 (93.5%)
PI only	1 (5.6%)	1 (2.4%)	2 (3.1%)	3 (2.8%)	4 (3.2%)
IMiD only	0	1 (2.4%)	0	1 (0.9%)	1 (0.8%)
None	2 (11.1%)	0	1 (1.5%)	1 (0.9%)	3 (2.4%)
Refractory to PI+IMiD+ALKY	13 (72.2%)	29 (70.7%)	50 (76.9%)	79 (74.5%)	92 (74.2%)
Refractory to last line of prior therapy	15 (83.3%)	39 (95.1%)	64 (98.5%)	103 (97.2%)	118 (95.2%)
Refractory to					
BORT	16 (88.9%)	38 (92.7%)	57 (87.7%)	95 (89.6%)	111 (89.5%)
CARF	6 (33.3%)	19 (46.3%)	32 (49.2%)	51 (48.1%)	57 (46.0%)
LEN	16 (88.9%)	40 (97.6%)	53 (81.5%)	93 (87.7%)	109 (87.9%)
POM	9 (50.0%)	26 (63.4%)	41 (63.1%)	67 (63.2%)	76 (61.3%)
THAL	4 (22.2%)	9 (22.0%)	20 (30.8%)	29 (27.4%)	33 (26.6%)
ALKY	13 (72.2%)	30 (73.2%)	52 (80.0%)	82 (77.4%)	95 (76.6%)
Refractory to[a]					
BORT+LEN	15 (83.3%)	38 (92.7%)	49 (75.4%)	87 (82.1%)	102 (82.3%)
CARF+POM	3 (16.7%)	15 (36.6%)	24 (36.9%)	39 (36.8%)	42 (33.9%)
BORT+LEN+CARF	6 (33.3%)	17 (41.5%)	25 (38.5%)	42 (39.6%)	48 (38.7%)
BORT+LEN+POM	8 (44.4%)	24 (58.5%)	33 (50.8%)	57 (53.8%)	65 (52.4%)
BORT+LEN+CARF+POM	3 (16.7%)	14 (34.1%)	19 (29.2%)	33 (31.1%)	36 (29.0%)
BORT+LEN+CARF+POM+THAL	3 (16.7%)	5 (12.2%)	7 (10.8%)	12 (11.3%)	15 (12.1%)

Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT= bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant.

[a]Subject may have received these agents in different treatment regimens.
Refractory to each medication refers to refractory to their most recent medication-containing line.
Note: PI includes bortezomib, carfilzomib, MLN9708, marizomib, and oprozomib; IMiD includes thalidomide, lenalidomide, and pomalidomide.
Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TSIPM02

Numbers analysed

All treated Analysis Set: 124 patients

Per-Protocol Analysis Set: 101 patients

Pharmacokinetic Analysis Set: 123 subjects (18 subjects who received 8 mg/kg and 105 subjects who received 16 mg/kg)

Immunogenicity Analysis Set: 111 patients (16 patients who received 8 mg/kg and 95 patients who received 16 mg/kg).

Outcomes and estimation

As of a 30 June 2015 clinical cut-off date, the median duration of follow-up, based on Kaplan-Meier estimate, was 19.1 months for the 8 mg/kg group and 14.7 months for the 16 mg/kg group.

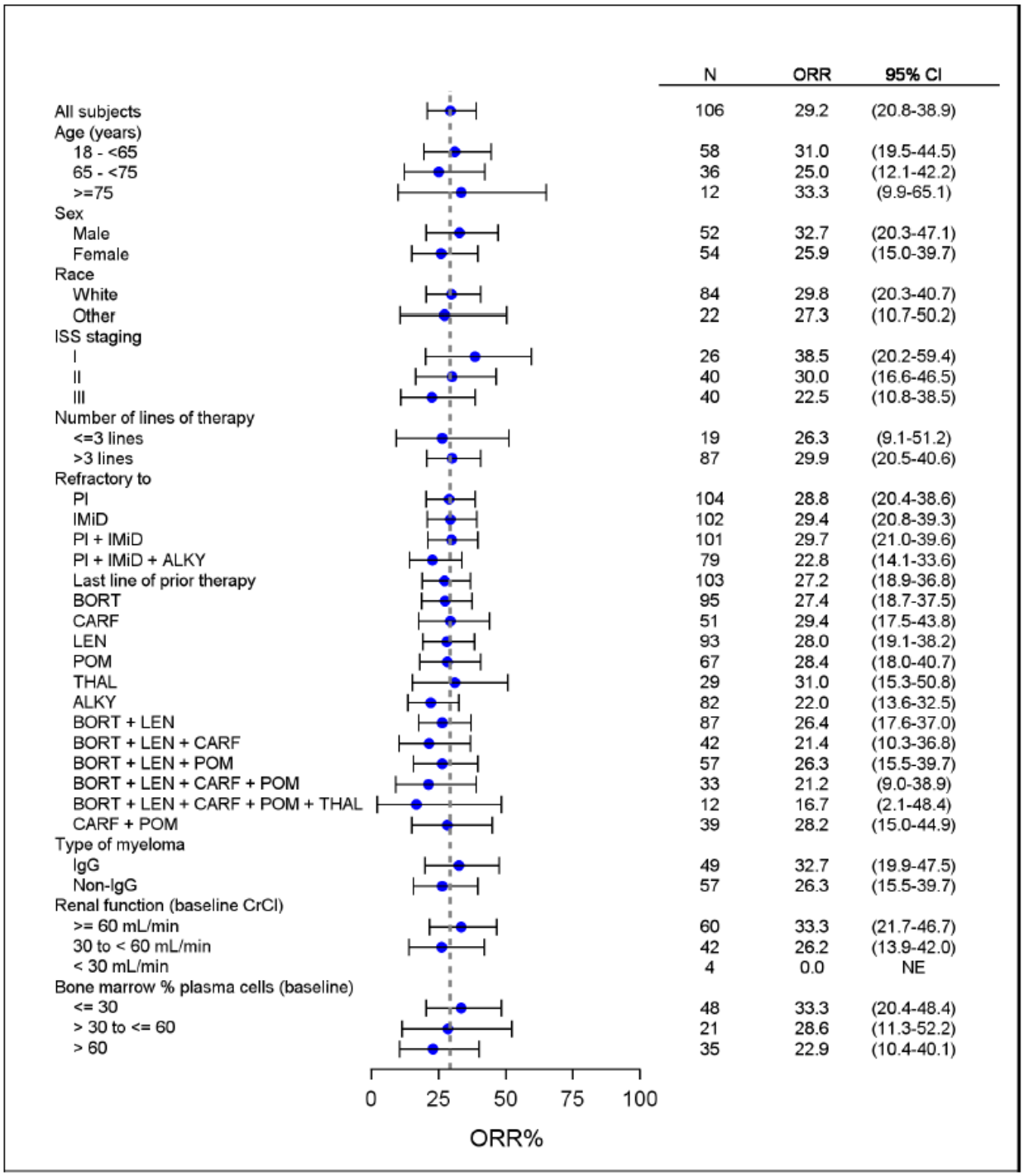
Primary endpoint – ORR

Table 22: Overall best response based on IRC assessment (All treated analysis set; Study MMY2002)

	8 mg/kg		16 mg/kg					
			Part 1		Part 2		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	18	-	41	-	65	-	106	-
Best response								
Stringent complete response (sCR)	0	-	2 (4.9%)	(0.6%, 16.5%)	1 (1.5%)	(0.0%, 8.3%)	3 (2.8%)	(0.6%, 8.0%)
Complete response (CR)	0	-	0	-	0	-	0	-
Very good partial response (VGPR)	1 (5.6%)	(0.1%, 27.3%)	6 (14.6%)	(5.6%, 29.2%)	4 (6.2%)	(1.7%, 15.0%)	10 (9.4%)	(4.6%, 16.7%)
Partial response (PR)	1 (5.6%)	(0.1%, 27.3%)	5 (12.2%)	(4.1%, 26.2%)	13 (20.0%)	(11.1%, 31.8%)	18 (17.0%)	(10.4%, 25.5%)
Minimal response (MR)	2 (11.1%)	(1.4%, 34.7%)	0	-	5 (7.7%)	(2.5%, 17.0%)	5 (4.7%)	(1.5%, 10.7%)
Stable disease (SD)	10 (55.6%)	(30.8%, 78.5%)	16 (39.0%)	(24.2%, 55.5%)	30 (46.2%)	(33.7%, 59.0%)	46 (43.4%)	(33.8%, 53.4%)
Progressive disease (PD)	1 (5.6%)	(0.1%, 27.3%)	9 (22.0%)	(10.6%, 37.6%)	9 (13.8%)	(6.5%, 24.7%)	18 (17.0%)	(10.4%, 25.5%)
Not evaluable (NE)	3 (16.7%)	(3.6%, 41.4%)	3 (7.3%)	(1.5%, 19.9%)	3 (4.6%)	(1.0%, 12.9%)	6 (5.7%)	(2.1%, 11.9%)
Overall response (sCR+CR+VGPR+PR)	2 (11.1%)	(1.4%, 34.7%)	13 (31.7%)	(18.1%, 48.1%)	18 (27.7%)	(17.3%, 40.2%)	31 (29.2%)	(20.8%, 38.9%)
Clinical benefit (Overall response + MR)	4 (22.2%)	(6.4%, 47.6%)	13 (31.7%)	(18.1%, 48.1%)	23 (35.4%)	(23.9%, 48.2%)	36 (34.0%)	(25.0%, 43.8%)
VGPR or better (sCR + CR + VGPR)	1 (5.6%)	(0.1%, 27.3%)	8 (19.5%)	(8.8%, 34.9%)	5 (7.7%)	(2.5%, 17.0%)	13 (12.3%)	(6.7%, 20.1%)
CR or better (sCR + CR)	0	-	2 (4.9%)	(0.6%, 16.5%)	1 (1.5%)	(0.0%, 8.3%)	3 (2.8%)	(0.6%, 8.0%)

Keys: IRC = independent review committee; CI = confidence interval.
Note: Response was assessed by independent review committee, based on international Uniform Response Criteria Consensus Recommendations
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Exact 95% confidence intervals are provided.

Subgroup analysis results are provided in the figure below:



Keys: IRC = independent review committee; CI = confidence interval; PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT= bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant; CrCL = creatinine clearance.
Notes: Subject may have received these agents in different treatment regimens. Exact 95% confidence intervals are provided.

Figure 4: Forest plot of subgroup analyses on overall best response on IRC Assessment (All treated – 16 mg/kg group – Study MMY2002)

Major secondary endpoints

Duration of response

Duration of response based on IRC assessment (median duration of follow-up of 9.3 months) is summarized below:

Table 23: Duration of response based on IRC assessment (Responders in all treated analysis set – Study MMY2002)

	16 mg/kg
Analysis set: responders in all treated	31
Duration of response	
Number of events (%)	17 (54.8%)
Number of censored (%)	14 (45.2%)
Kaplan-Meier estimate (months)	
25% quantile (95% CI)	4.0 (1.9, 5.6)
Median (95% CI)	7.4 (5.5, NE)
75% quantile (95% CI)	NE (7.5, NE)
3-month duration of response rate % (95% CI)	87.1 (69.2, 95.0)
6-month duration of response rate % (95% CI)	59.2 (39.3, 74.5)
12-month duration of response rate % (95% CI)	37.8 (19.6, 55.9)

Keys: IRC = independent review committee; CI = confidence interval; NE = not estimable.
Percentages are calculated with the number of subjects in each group as denominator.

Modified from Attachment TEFDOR01A

Time to response

Table 24: Time to response based on IRC assessment (Responders in all treated analysis set – Study MMY2002)

	8 mg/kg	16 mg/kg
Analysis set: responders in all treated	2	31
Time to first response (months)		
N	2	31
Mean (SD)	0.99 (0.046)	1.67 (1.162)
Median	0.99	0.99
Range	(1.0; 1.0)	(0.9; 5.6)
Time to best response (months)		
N	2	31
Mean (SD)	5.59 (6.551)	2.48 (1.875)
Median	5.59	1.87
Range	(1.0; 10.2)	(0.9; 7.4)
Time to VGPR or better (months)		
N	1	13
Mean (SD)	10.22 (-)	2.49 (2.109)
Median	10.22	1.84
Range	(10.2; 10.2)	(0.9; 7.4)

Keys: IRC = independent review committee; VGPR = very good partial response.

[TEFTTR02A.rtf] [JNJ-54767414\MMY2002\DBR_CSR\RE_CSR\tefttr02a.sas] 04MAR2015, 14:43

Clinical benefit rate (MR or better)

The clinical benefit rate for the 16 mg/kg group, by IRC assessment, was 34% (95% CI: 25%, 44%). Based on the IRC assessment for the per-protocol analysis set, the clinical benefit rate was 35% (95% CI: 26%, 45%) for the 16 mg/kg group (data not shown).

Time to disease progression

Table 25: Time to disease progression based on IRC assessment (All treated analysis set – Study MMY2002)

	8 mg/kg	16 mg/kg
Analysis set: all treated	18	106
Time to disease progression		
Number of events (%)	6 (33.3%)	73 (68.9%)
Number of censored (%)	12 (66.7%)	33 (31.1%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	1.87 (0.99, 4.86)	1.84 (0.95, 2.33)
Median (95% CI)	4.86 (1.84, NE)	3.71 (2.79, 5.39)
75% quantile (95% CI)	NE (3.32, NE)	7.66 (6.51, NE)
3-month disease progression free rate % (95% CI)	63.5 (28.9, 84.7)	51.2 (40.7, 60.7)
6-month disease progression free rate % (95% CI)	25.4 (1.6, 63.7)	37.4 (27.6, 47.2)
12-month disease progression free rate % (95% CI)	25.4 (1.6, 63.7)	18.7 (11.0, 28.0)

Keys: IRC = independent review committee; CI = confidence interval; NE = not estimable.
Note: Percentages are calculated with the number of subjects in each group as denominator.

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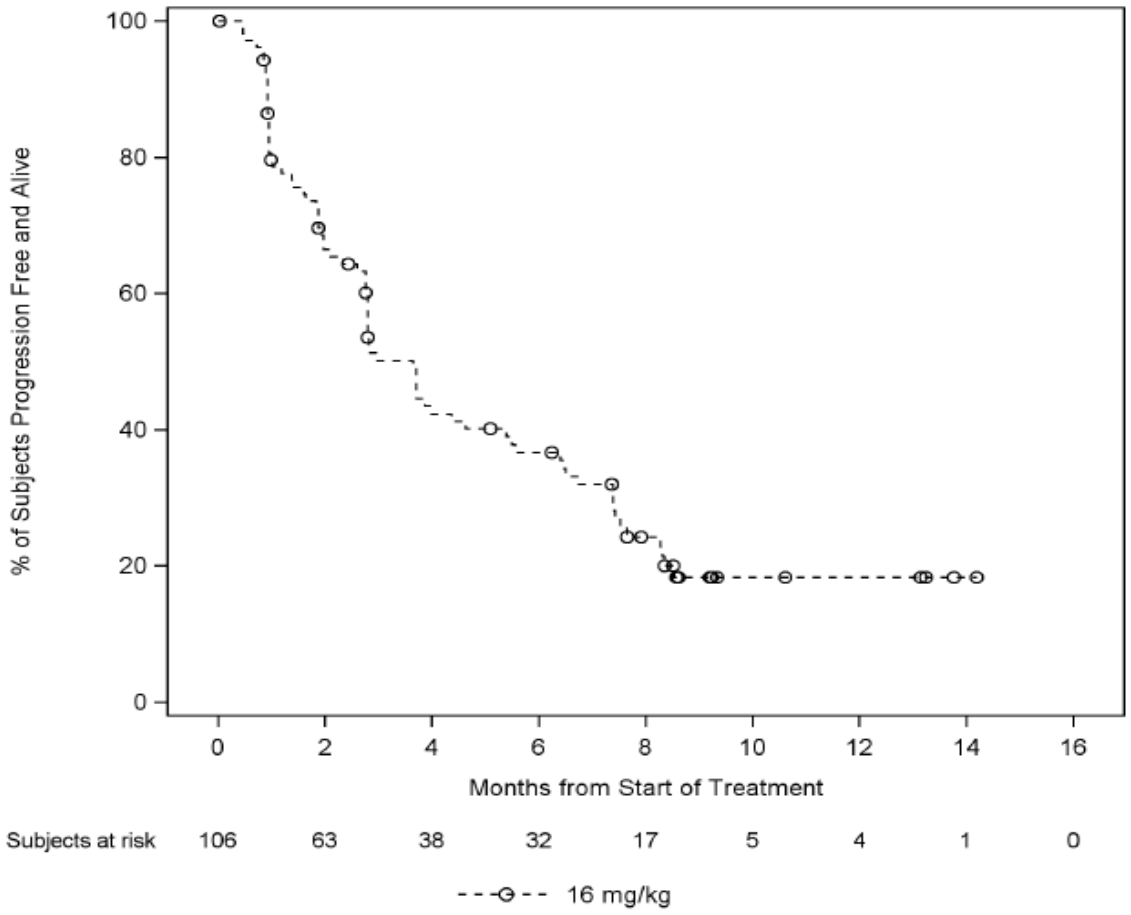
Progression free survival (PFS)

Table 26: PFS based on IRC assessment (All treated analysis set – Study MMY2002)

	8 mg/kg	16 mg/kg
Analysis set: all treated	18	106
Progression-free survival		
Number of events (%)	6 (33.3%)	75 (70.8%)
Number of censored (%)	12 (66.7%)	31 (29.2%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	1.87 (0.99, 4.86)	1.61 (0.95, 1.97)
Median (95% CI)	4.86 (1.84, NE)	3.65 (2.76, 4.63)
75% quantile (95% CI)	NE (3.32, NE)	7.66 (6.47, NE)
3-month progression free survival rate % (95% CI)	63.5 (28.9, 84.7)	50.2 (39.8, 59.6)
6-month progression free survival rate % (95% CI)	25.4 (1.6, 63.7)	36.7 (27.0, 46.4)
12-month progression free survival rate % (95% CI)	25.4 (1.6, 63.7)	18.3 (10.7, 27.5)

Keys: IRC = independent review committee; CI = confidence interval; NE = not estimable.
Note: Percentages are calculated with the number of subjects in each group as denominator.

[TEFPFS01A.rtf] [JNJ-54767414\MMY2002\DBR_CSR\RE_CSR\tefpfs01a.sas] 13FEB2015, 14:39



Keys: IRC = independent review committee.

[GEFPFS01A.rtf] [JNJ-54767414\MMY2002\DBR_CSR\RE_CSR\gefpfs01a.sas] 13FEB2015, 14:39

Figure 5: Kaplan-Meier plot of PFS based on IRC assessment (All treated analysis set – Study MMY2002)

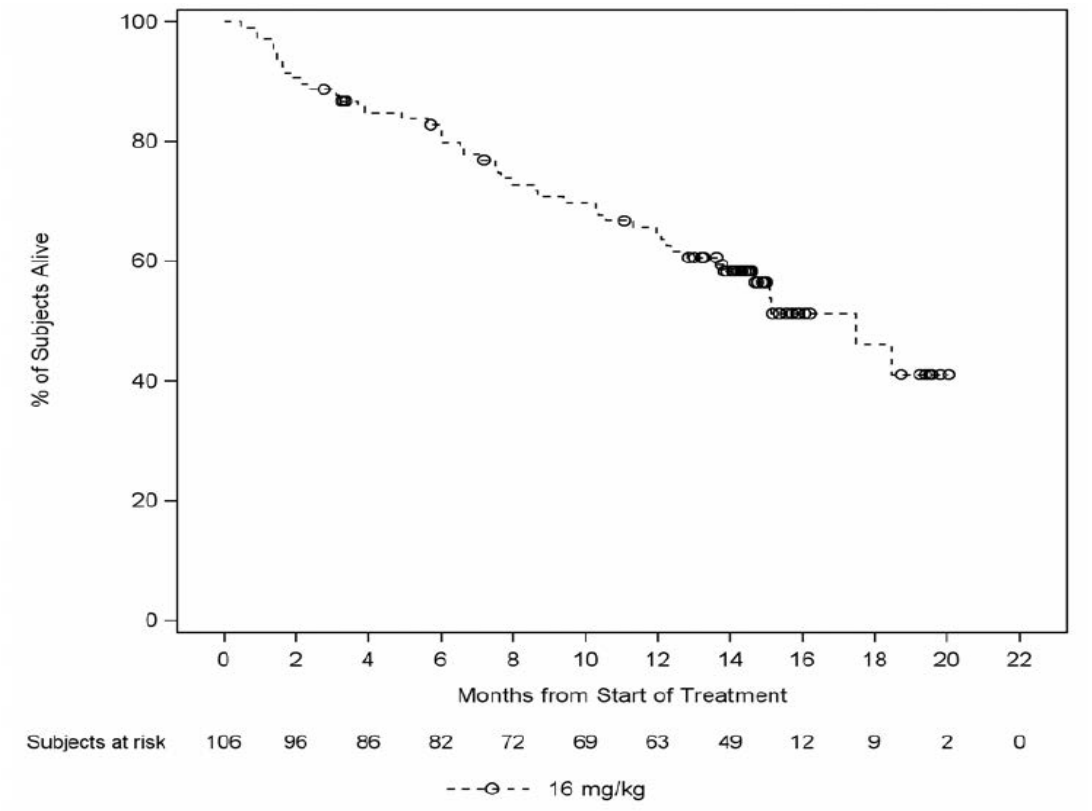
Overall survival (OS)

Table 27: OS (All treated analysis set – Study MMY2002), Data cut-off 30 June 2015

	8 mg/kg	16 mg/kg
Analysis set: all treated	18	106
Overall survival		
Number of events (%)	8 (44.4%)	47 (44.3%)
Number of censored (%)	10 (55.6%)	59 (55.7%)
Kaplan-Meier estimate (months)		
25% quantile (95% CI)	7.79 (3.75, 18.50)	7.59 (5.62, 10.58)
Median (95% CI)	NE (7.72, NE)	17.48 (13.67, NE)
75% quantile (95% CI)	NE (18.50, NE)	NE (NE, NE)
6-month overall survival rate % (95% CI)	87.5 (58.6, 96.7)	81.8 (73.0, 88.0)
12-month overall survival rate % (95% CI)	62.5 (34.9, 81.1)	64.7 (54.5, 73.1)

Keys: CI = confidence interval; NE = not estimable.
Percentages are calculated with the number of subjects in each group as denominator.

[TEFOS01.rtf] [JNJ-54767414\MMY2002\DBR_BLA_2015_4MSU\RE_BLA_2015_4MSU\tefos01.sas] 13AUG2015, 16:36



[GEFOS01.rtf] [JNJ-54767414\MMY2002\DBR_BLA_2015_4MSU\RE_BLA_2015_4MSU\gefos01.sas] 13AUG2015, 16:36

Figure 6: Kaplan-Meier plot of OS (All treated analysis set – Study MMY2002), Data cut-off 30 June 2015

Table 28: Overall Survival; All Treated Analysis Set (Studies: MMY2002 and GEN501 Part 2) Data cut-off 31 December 2015

	16 mg/kg		
	MMY2002	GEN501 Part 2	Total
Analysis set: all treated	106	42	148
Overall survival			
Number of events (%)	57 (53.8%)	16 (38.1%)	73 (49.3%)
Number of censored (%)	49 (46.2%)	26 (61.9%)	75 (50.7%)
Kaplan-Meier estimate (months)			
25% quantile (95% CI)	7.59 (5.62, 10.58)	15.93 (5.95, 22.41)	8.71 (6.05, 12.09)
Median (95% CI)	18.60 (13.67, NE)	NE (18.66, NE)	20.07 (16.62, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
6-month overall survival rate % (95% CI)	81.8 (73.0, 88.0)	88.1 (73.7, 94.9)	83.6 (76.5, 88.7)
12-month overall survival rate % (95% CI)	64.7 (54.5, 73.1)	78.6 (62.9, 88.2)	68.7 (60.5, 75.6)
18-month overall survival rate % (95% CI)	51.3 (41.1, 60.6)	69.0 (52.7, 80.7)	56.5 (47.9, 64.2)
24-month overall survival rate % (95% CI)	41.3 (31.0, 51.2)	57.4 (38.7, 72.3)	45.0 (35.5, 54.1)

Keys: CI = confidence interval; NE = not evaluable.
Percentages are calculated with the number of subjects in each group as denominator.
Cutoff for survival and subsequent therapy data was 31DEC2015

Other efficacy analyses reported that 40 patients (38%) had a >50% reduction in paraprotein from baseline, and 17 (16%) patients having > 90% reduction (data not shown).

Among 12 subjects in the 16 mg/kg group with baseline bone marrow plasma cell involvement greater than 30%, 5 patients (42%) had post baseline bone marrow plasma cell involvement normalized to less than 5%, and an additional 4 patients (33%) had post-baseline bone marrow plasma cell involvement improved to between 5 to 10% (data not shown).

Ancillary analyses

Summary of study MMY2002

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).

Title: An open-label, multicentre, phase 2 trial investigating the efficacy and safety of daratumumab in subjects with multiple myeloma who have received at least 3 prior lines of therapy (including a proteasome inhibitor and IMiD) or are double refractory to a proteasome inhibitor and an IMiD			
Study identifier	MMY2002		
Design	Open-label, multicenter, 2-arm study		
	Initiation of study		30 September 2013
	Data cut-off		9 January 2015
	Updated OS		30 June 2015
Hypothesis	Treatment with daratumumab would result in an ORR of > 15% in patients with relapsed and refractory MM as described.		
Treatments groups	daratumumab 8 mg/kg		Q 4 weeks
	daratumumab 16 mg/kg		Weekly for 8 W, then Q 2 week for 16W, then Q 4 weeks
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	Proportions of patients who achieved PR or better
	Secondary endpoint	Duration of response (DOR)	Time from the date of the initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease
	Secondary endpoint	12-month DOR rate	Percentage of responders without progression at 12 months
	Secondary endpoint	Overall Survival/12 months survival	Time from date of first dose of daratumumab to the date of death/at 12 months
Data cut-off	9 January 2015 (updated OS: 30 June 2015)		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	ITT			
Descriptive statistics and estimate variability	Treatment group	8 mg/kg daratumumab	16 mg/kg daratumumab	
	Number of patients	18	106	
	ORR (%)	11.1	29.2	

	95% CI	1,4; 34,7	20.8; 38.9	
	Median DOR (months)	NE	7.4 (N=31 responders)	
	Kaplan-Meier estimate median 95% CI		5.5;NE	
	12 months DOR rate (%)	NA	37.8 (N= 31 responders)	
	95% CI		19.6;55.9	
	12 months OS (update 30 june-2015)	63%	65%	
	95% CI	34.9; 81,1	54.5; 73.1	

GEN 501

Study GEN501 was a Phase 1/2, open-label, multicentre, safety study divided into 2 parts. Part 1 was a dose-escalation phase; Part 2 was a single-arm phase with multiple cohorts, based on the dose levels established in Part 1. Part 2 was one of the main studies described below.

Methods

Study Participants

The key inclusion criteria were the following:

1. Documented diagnosis of multiple myeloma requiring systemic therapy. Diagnosis of myeloma must have been made following the established criteria at the time of diagnosis (Durie 2006):
    - Presence of a measurable M-protein in serum and/or urine. Measurable M-protein was defined as:
        - Serum M-protein level ≥1.0 g/dL or urine M-protein level ≥200 mg/24 hours; or
        - Light chain multiple myeloma: Serum immunoglobulin free light chain (FLC) ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
    - and clonal plasma cells in the bone marrow or >1 clonal plasmacytoma, but no bone marrow involvement
    - and at time of diagnosis, 1 or more of the following (attributable to underlying plasma cell disorder):
        - Calcium elevation (>11.5 mg/dL [>2.65 mmol/L])
        - Renal insufficiency (creatinine >2 mg/dL [177 µmol/L or more])
        - Anaemia (hemoglobin <10 g/dL [<6.2 mmol/L] or 2 g/dL [1.25 mmol/L] <normal)
        - Bone disease (lytic lesions or osteopenia)
2. Eastern Cooperative Oncology Group (ECOG) Performance Status Score of 0, 1, 2
3. Life expectancy >3 months
4. Relapsed from or refractory to 2 or more different prior therapies, including IMiDs (eg, thalidomide, lenalidomide) and proteasome inhibitors, chemotherapy-based regimens, or autologous stem cell transplantation (ASCT) and without further established treatment options

The key exclusion criteria were the following:

1. Other chemotherapy that is or may be active against multiple myeloma

2. Previously received an allogeneic stem cell transplant
3. Laboratory values: absolute neutrophil counts <1000/mm3; platelet count <75x109/L; serum creatinine >2x the upper limit of normal (ULN) hemoglobin <7.5 g/dL (4.7 mmol/L); alanine aminotransferase (ALT) >3.5 times the ULN; alkaline phosphatase >3.5xULN; bilirubin >2.5xULN; hypokalemia (serum potassium <3.0 mEq/L)
4. Concomitant corticosteroid use of >10 mg prednisone or equivalent
5. Past or current malignancy, except for cervical carcinoma Stage 1B or less; noninvasive basal cell and squamous cell skin carcinoma; malignant melanoma with a complete response (CR) of a duration of >10 years; curable cancer diagnosis with a CR of a duration of >5 years
6. Clinical signs of meningeal involvement of multiple myeloma; history of significant cerebrovascular disease
7. Known severe chronic obstructive pulmonary disease or asthma (forced expiratory volume in 1 second [FEV1] <60% of expected); sensory or motor neuropathy of ≥ Grade 3
8. Chronic or ongoing active infectious disease; positive serology for hepatitis B; known human immunodeficiency virus seropositivity
9. Clinically significant cardiac disease; baseline QTcF >470 msec (women) or >450 msec (men) or complete left bundle branch block (LBBB) (QRS interval ≥120 msec)

Treatments

The summary of the study design is presented in the figure below:

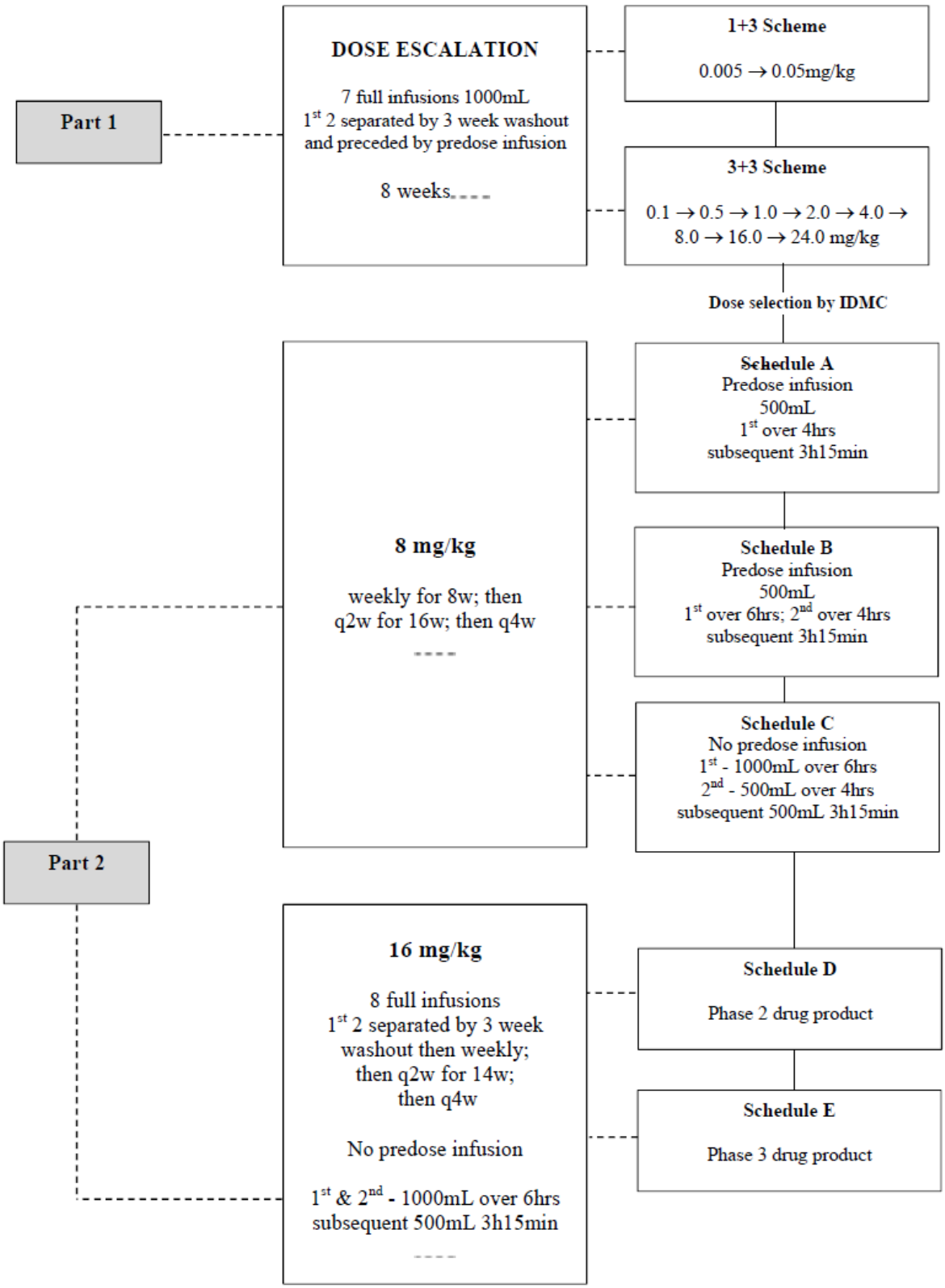


Figure 7: Schematic overview of Study GEN501

During Part 2 of the study, 4 additional amendments (11-14) were issued. Based on pharmacokinetic and efficacy data, the 8 mg/kg dose was chosen as the Part 2 dose (Amendment 11). Additionally, to minimize IRRs, particularly at the first full-dose infusion, different combinations of predose infusions, infusion volumes, and infusion rates were evaluated (Amendment 12). During Part 2, it was determined that the

8 mg/kg dose might not saturate a majority of the target (CD38) throughout dosing, as indicated by the high intersubject variability in pharmacokinetic parameters. Therefore, the 8 mg/kg dose in Cohort D was changed to 16 mg/kg to assess whether high-dose intensity, leading to high levels of systemic exposure and consistent saturation of the CD38 target, was needed to optimize the efficacy of daratumumab (Amendment 13). Further, Amendment 14 made a change in the study design to include Cohort E to evaluate a Phase 3 drug product (commercial product) that is produced with a larger scale manufacturing process.

The dosing schedule used in the study is summarized in the following figure:

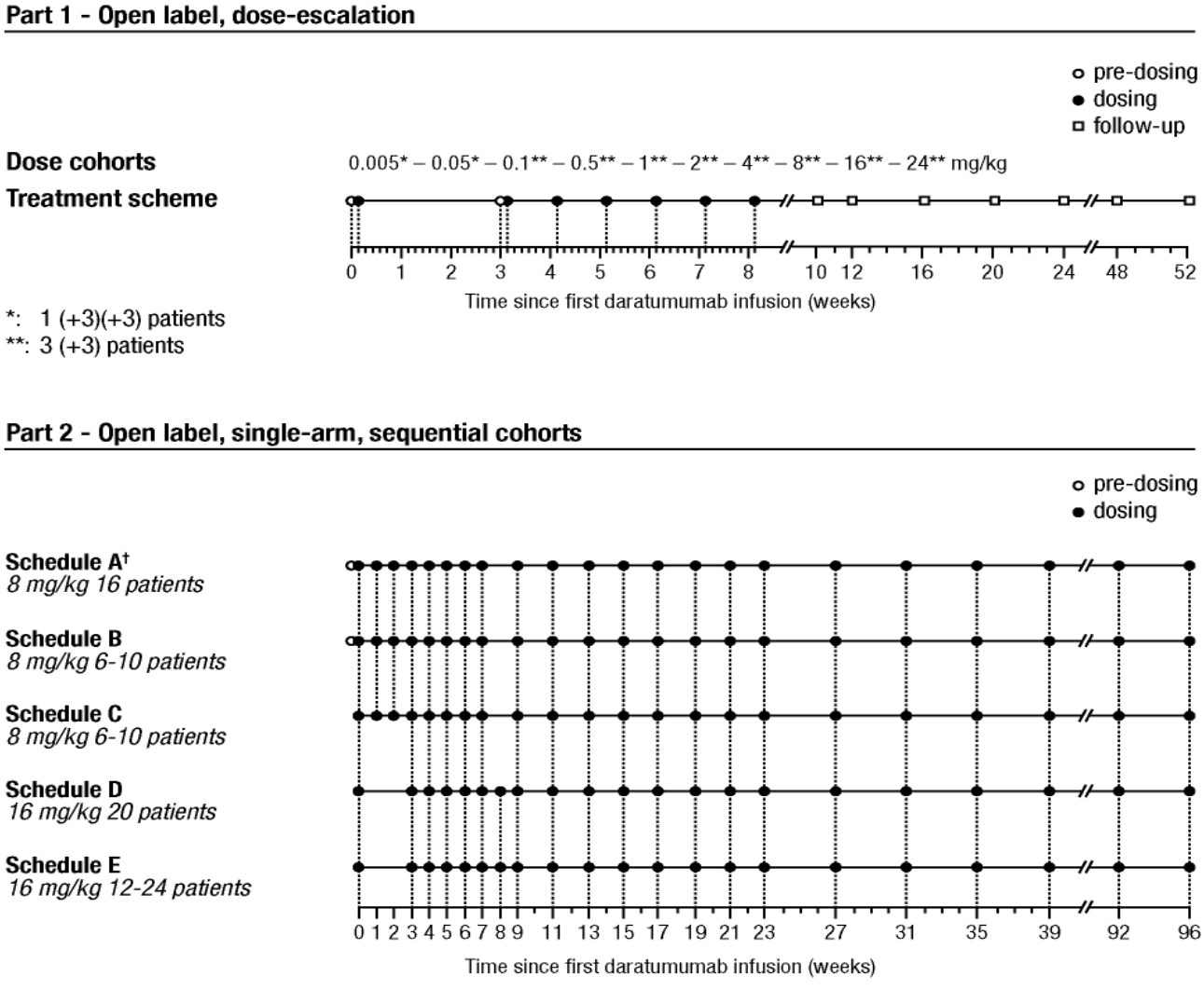


Figure 8: Dosing schedules: Study GEN501 (Part 1 and Part 2)

Pre-infusion medication

In Parts 1 and 2, subjects were to receive:

- 1 g paracetamol (acetaminophen) PO
- antihistamine (clemastine 1 mg IV, cetirizine 10 mg PO, or equivalent)

- glucocorticoids (methylprednisolone 100mg IV before the first 2 pre-doses and before the first 2 full daratumumab infusions and since amendment 4 (April 2010) before every subsequent infusion. The dose could be decreased to 50 mg following Visit 4 in Part 2 of the study if no significant infusion reactions were noted)

Post-infusion medication

In Part 2, all subjects were to receive 20 to 25 mg methylprednisolone PO, or equivalent, on the first and second days after all full-dose infusions. For subjects with a higher risk of respiratory complications (eg, subjects with FEV1 <75%), the following post-infusion medications were permitted:

- antihistamine (clemastine 1 mg IV, cetirizine 10 mg PO, or equivalent) on the first and second days after all full-dose infusions
- salbutamol aerosol
- controller medications (eg, inhaled corticosteroids ± long-acting beta agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salmeterol ± inhaled corticosteroids for subjects with chronic obstructive pulmonary disease)

Objectives

The primary objective of this study was to establish the safety profile of daratumumab given as monotherapy in patients with relapsed or refractory multiple myeloma to at least 2 different cytoreductive therapies and without further established treatment options.

The secondary objectives were:

- To establish the pharmacokinetic profile of daratumumab after single and multiple infusions for both phase 2 and phase 3 drug products.
- To evaluate the efficacy of monotherapy daratumumab in the proposed patient population.
- To establish safe dose levels for future studies with daratumumab.
- To optimize pre-infusion medication and infusion parameters for daratumumab.
- To evaluate the immunogenicity of the drug and biomarkers of daratumumab's mechanism of action, infusion reactions and clinical response.

Outcomes/endpoints

The primary efficacy endpoint was overall response rate (ORR), which was defined as the proportion of patients who achieved a partial response (PR) or better. Objective response evaluations were made based on assessments from a computerized algorithm using the International Multiple Myeloma Working Group (IMWG) Response Criteria for Multiple Myeloma (Durie 2006, Rajkumar 2011).

The secondary endpoints were:

- Time to response, defined as the time from the date of first dose of daratumumab to the date of initial documentation of a response (PR or better)
- Time to best response, defined as the time between the date of first dose of daratumumab and the date of the initial evaluation of the best response (PR or better) to treatment
- Reduction of serum/urine M-protein or free light-chain reduction, defined as the percent change from baseline at each post-baseline assessment visit in the quantification of the corresponding serum/urine M-protein or FLC, according to the measurable type at baseline.

- Change in bone marrow % plasma cells, based on results from either biopsy or aspirate.
- Clinical benefit rate, defined as the proportion of patients with best response of minor response (MR) or better (including PR, VGPR, CR and sCR).
- Time to progression (TTP), defined as the number of days from the date of the first infusion to the date of the first record of disease progression (IMWG criteria), confirmed by 2 consecutive assessments.
- Progression-free survival (PFS), defined as the time between the date of first dose of daratumumab and either disease progression or death, whichever occurred first.
- Duration of response (DOR), calculated from the date of the initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease (IMWG criteria).
- Overall survival (OS), defined as the number of days from administration of the first infusion (day 1) to the date of death.

Sample size

For Part 2, up to 80 subjects could be enrolled, for a maximum of 112 subjects enrolled across both parts. With the descriptive statistics methodology for the primary endpoint in mind, the impact of different sample sizes on the descriptive statistics is presented by the probability of making at least one observation of an event with rare incidence.

In addition, 2 sets of safety stopping rules were defined for Part 2: a set defined per cohort (N ≤30) and another set for all cohorts combined (N ≤80). A stopping rule was triggered if the number of subjects experiencing a CAE (critical adverse event) was greater than or equal to the number shown in the Study Protocol for the indicated number of subjects enrolled. A CAE was defined as s study drug-related serious TEAEs with an onset within 48 hours after the start of the daratumumab infusion that corresponded to CTCAE Grade 3 or higher, did not respond to symptomatic therapy, and did not resolve within 6 hours from onset of the event.

Randomisation

Not applicable.

Blinding (masking)

This was an open label study.

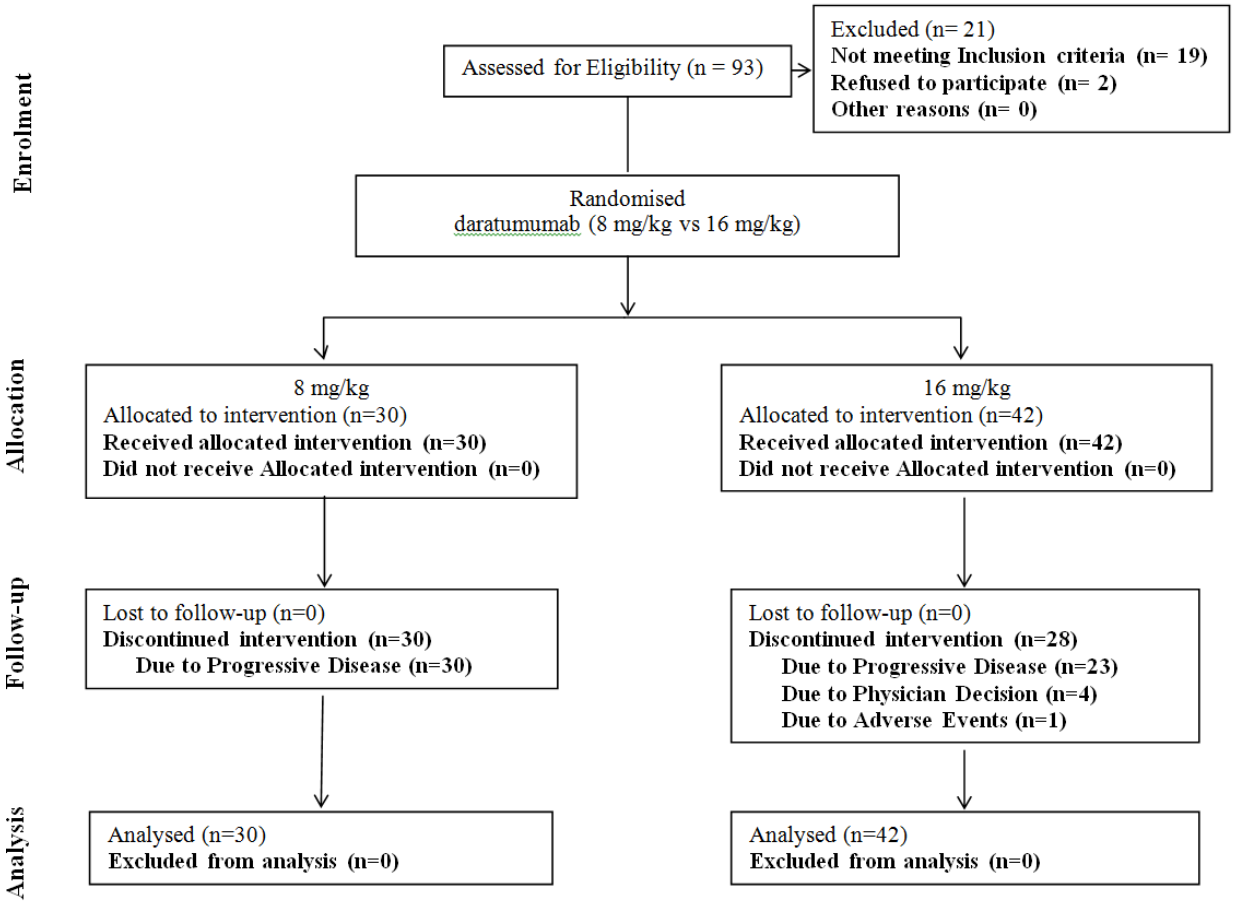
Statistical methods

No formal statistical hypothesis testing was planned. For each observed response category, a 2-sided 95% exact confidence interval (CI) was presented. For the calculation of ORR, those patients who were not evaluable for response were to be considered non-responders. The clinical benefit rate would be analysed similarly to the primary endpoint.

Additionally, in Part 2, descriptive statistics (mean, standard deviation, median, and range) were provided to summarize time to first response and time to best response for responders in each treatment group. No inferential analysis was performed.

Results

Participant flow



Recruitment

A total of 72 patients participated in the study. The study sites for Part 2 were in Denmark (2 sites), Sweden (2 sites), Netherlands (1 site), and the United States (1 site).

Conduct of the study

The original protocol was amended 14 times, this included change of pre- and post-infusion medication, predose and infusion rate. The key amendments were the following:

- 9th amendment (27 June 2011): the dosing period was expanded to 8 weeks with weekly infusions followed by bi-weekly infusions for additional 16 weeks.
- 11th amendment (19 October 2012): the dose chosen for Part 2 was 8 mg/kg, and the treatment duration was increased up to 96 weeks or until disease progression or unmanageable toxicity.
- 13th amendment (28 June 2013): schedule D changes to 16 mg/kg daratumumab to assess whether high levels of systemic exposure and consistent saturation of the CD38 target was needed to optimize efficacy of daratumumab.
- 14th amendment (02-dec-2013): the study design was changed to include Schedule E to evaluate the Phase 3 drug product.

The major protocol violations in the study are summarized in the tables below.

Table 29: Subjects with major protocol violations (Study GEN501 Part 2)

Treatment Group	Deviation Coded Term	Deviation Term
SCHEDULE A - 8 mg/kg	Entered but did not satisfy criteria	Patient had a drop in platelets from screening to <75 x10^9/l at Visit 1.
SCHEDULE B - 8 mg/kg	Entered but did not satisfy criteria	Patient had a drop in platelets from screening to <75 x10^9/l at Visit 1
	Entered but did not satisfy criteria	Patient had a drop in platelets from screening to <75 x10^9/l at Visit 1
SCHEDULE C - 8 mg/kg	Received wrong treatment or incorrect dose	The subject's last treatment was given on 21 Aug 2013 at Visit 9 due to the site's drug shipment being held by US customs. This delayed Visit 10 treatment to 20 Sep 2013
	Received wrong treatment or incorrect dose	The subject's last treatment was given on 27 Aug 2013 at Visit 6 due to the site's drug shipment being held by US customs. This delayed Visit 7 to 20 Sep 2013
	Received wrong treatment or incorrect dose	The subject's last treatment was given on 03 Sep 2013 at Visit 5 due the site's drug shipment being held by US customs. This delayed Visit 6 to 23 Sep 2013
SCHEDULE D - 16 mg/kg	Received wrong treatment or incorrect dose	Subject received only 835 mL versus 1000mL at Visit 2 due to IRRs prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given
SCHEDULE E - 16 mg/kg	Entered but did not satisfy criteria	Patient had a drop in platelets from screening to <75 x10^9/l at Visit 2
	Received wrong treatment or incorrect dose	Visit 8 was expected on 16 Jun 2014 but occurred on 23 Jun 2014 due to delayed receipt of drug
	Received wrong treatment or incorrect dose	Subject only received 747 mL versus 1000 mL at Visit 2 due to IRRs prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given
	Received wrong treatment or incorrect dose	Visit 8 was expected on 18 Jun 2014 but occurred on 25 Jun 2014 due to delayed receipt of drug
	Received wrong treatment or incorrect dose	Subject only received 700 mL versus 1,000 mL at Visit 2 and 777 mL versus 1,000 mL at Visit 5 due to IRRs prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given
	Received wrong treatment or incorrect dose	Subject only received 153 mL mg versus 1000 mL at Visit 2 and 460 mL versus 1,000 mL at Visit 5 due to IRRs prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given
	Received wrong treatment or incorrect dose	Visit 7 was expected on 17 Jun 2014 but occurred on 24 Jun 2014 due to delayed receipt of drug
	Received wrong treatment or incorrect dose	Subject only received 316 mL versus 1,000 mL at Visit 2 due to IRRs prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given
	Received wrong treatment or incorrect dose	Subject only received 242 mL versus 1,000 mL at Visit 2 due to an IRR prolonging the infusion time beyond the site clinic closing time. Therefore the full dose was not given

Baseline data

Table 30: Demographics (All Treated Analysis Set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg	Total
Analysis set: all treated	30	42	72
Age (years)			
N	30	42	72
Category, n (%)			
18 - < 65	21 (70.0%)	22 (52.4%)	43 (59.7%)
65 - < 75	8 (26.7%)	16 (38.1%)	24 (33.3%)
≥ 75	1 (3.3%)	4 (9.5%)	5 (6.9%)
Mean (SD)	58.6 (10.05)	63.8 (8.27)	61.6 (9.34)
Median	58.5	64.0	61.0
Range	(38; 76)	(44; 76)	(38; 76)
Sex, n (%)			
N	30	42	72
Male	21 (70.0%)	27 (64.3%)	48 (66.7%)
Female	9 (30.0%)	15 (35.7%)	24 (33.3%)
Race, n (%)			
N	30	42	72
White	15 (50.0%)	32 (76.2%)	47 (65.3%)
Black or African American	1 (3.3%)	1 (2.4%)	2 (2.8%)
Asian	0	0	0
Other	0	1 (2.4%)	1 (1.4%)
Not Reported	14 (46.7%)	8 (19.0%)	22 (30.6%)
Ethnicity, n (%)			
N	30	42	72
Hispanic or latino	0	1 (2.4%)	1 (1.4%)
Not hispanic or latino	16 (53.3%)	33 (78.6%)	49 (68.1%)
Not Reported	14 (46.7%)	8 (19.0%)	22 (30.6%)
Height (cm)			
N	30	42	72
Mean (SD)	175.23 (9.100)	169.47 (9.910)	171.87 (9.936)
Median	174.50	170.50	172.75
Range	(153.5; 188.0)	(142.0; 189.5)	(142.0; 189.5)
Weight (kg)			
N	30	42	72
Mean (SD)	80.58 (12.479)	77.94 (21.510)	79.04 (18.235)
Median	81.05	78.50	79.70
Range	(56.0; 106.3)	(43.0; 141.8)	(43.0; 141.8)
ECOG Score, n (%)			
N	30	42	72
0	6 (20.0%)	12 (28.6%)	18 (25.0%)
1	23 (76.7%)	28 (66.7%)	51 (70.8%)
2	1 (3.3%)	2 (4.8%)	3 (4.2%)

Percentages are calculated with the number of subjects in each group with available data as denominator.
Modified from Attachment TSIDEM01

Table 31: Baseline Disease Characteristics (All Treated Analysis Set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg	Total
Analysis set: all treated	30	42	72
Type of myeloma by immunofixation, n (%)			
N	30	42	72
IgG	11 (36.7%)	24 (57.1%)	35 (48.6%)
IgA	11 (36.7%)	4 (9.5%)	15 (20.8%)
IgM	0	1 (2.4%)	1 (1.4%)
IgD	0	1 (2.4%)	1 (1.4%)
IgE	0	0	0
Light chain	4 (13.3%)	9 (21.4%)	13 (18.1%)
Kappa	4 (13.3%)	5 (11.9%)	9 (12.5%)
Lambda	0	4 (9.5%)	4 (5.6%)
Biclonal	4 (13.3%)	3 (7.1%)	7 (9.7%)
Serum free light chain only[a]	0	0	0
Number of lines of prior therapy, n (%)			
N	30	42	72
≤ 3 Lines	6 (20.0%)	16 (38.1%)	22 (30.6%)
> 3 Lines	24 (80.0%)	26 (61.9%)	50 (69.4%)
Mean (SD)	4.9 (2.02)	4.9 (2.61)	4.9 (2.37)
Median	4.0	4.0	4.0
Range	(3; 10)	(2; 12)	(2; 12)
Time since initial diagnosis of multiple myeloma (months)			
N	30	42	72
Mean (SD)	79.27 (43.367)	84.64 (53.486)	82.40 (49.267)
Median	66.22	69.04	68.12
Range	(25.8; 183.1)	(9.2; 284.5)	(9.2; 284.5)
Number of lytic bone lesions, n (%)			
N	30	42	72
None	3 (10.0%)	6 (14.3%)	9 (12.5%)
1-3	2 (6.7%)	1 (2.4%)	3 (4.2%)
4-10	3 (10.0%)	13 (31.0%)	16 (22.2%)
More than 10	22 (73.3%)	22 (52.4%)	44 (61.1%)
Number of extramedullary plasmacytomas, n (%)			
N	30	42	72
0	26 (86.7%)	38 (90.5%)	64 (88.9%)
≥ 1	4 (13.3%)	4 (9.5%)	8 (11.1%)
Bone marrow % plasma cells, n (%)			
N	27	42	69
< 5	12 (44.4%)	21 (50.0%)	33 (47.8%)
≥ 5 - ≤ 10	4 (14.8%)	9 (21.4%)	13 (18.8%)
> 10 - ≤ 30	6 (22.2%)	7 (16.7%)	13 (18.8%)
> 30	5 (18.5%)	5 (11.9%)	10 (14.5%)

Percentages are calculated with the number of subjects in each group with available data as denominator.
[a]not detected by immunofixation, serum free light chain only.

Table 32: Prior Multiple Myeloma Therapy (All Treated Analysis Set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg	Total
	Total	Total	
Analysis set: all treated	30	42	72
Number of lines of prior therapy, n (%)			
N	30	42	72
≤ 3	6 (20.0%)	16 (38.1%)	22 (30.6%)
> 3	24 (80.0%)	26 (61.9%)	50 (69.4%)
Mean (SD)	4.9 (2.02)	4.9 (2.61)	4.9 (2.37)
Median	4.0	4.0	4.0
Range	(3; 10)	(2; 12)	(2; 12)
Prior PI	30 (100.0%)	42 (100.0%)	72 (100.0%)
Bortezomib	30 (100.0%)	42 (100.0%)	72 (100.0%)
Carfilzomib	2 (6.7%)	8 (19.0%)	10 (13.9%)
Prior IMiD	29 (96.7%)	40 (95.2%)	69 (95.8%)
Lenalidomide	29 (96.7%)	40 (95.2%)	69 (95.8%)
Pomalidomide	2 (6.7%)	15 (35.7%)	17 (23.6%)
Thalidomide	20 (66.7%)	19 (45.2%)	39 (54.2%)
Prior PI+IMiD[a]	29 (96.7%)	40 (95.2%)	69 (95.8%)
Prior PI+IMiD+ALKY[a]	29 (96.7%)	37 (88.1%)	66 (91.7%)
Prior BORT+LEN[a]	29 (96.7%)	40 (95.2%)	69 (95.8%)
Prior CARF+POM[a]	1 (3.3%)	6 (14.3%)	7 (9.7%)
Prior BORT+LEN+CARF[a]	2 (6.7%)	8 (19.0%)	10 (13.9%)
Prior BORT+LEN+POM[a]	2 (6.7%)	15 (35.7%)	17 (23.6%)
Prior BORT+LEN+CARF+POM[a]	1 (3.3%)	6 (14.3%)	7 (9.7%)
Prior BORT+LEN+CARF+POM+THAL[a]	1 (3.3%)	5 (11.9%)	6 (8.3%)
Prior steroids	30 (100.0%)	42 (100.0%)	72 (100.0%)
Prior chemotherapy	30 (100.0%)	37 (88.1%)	67 (93.1%)
Alkylating agents[b]	30 (100.0%)	39 (92.9%)	69 (95.8%)
Anthracyclines	19 (63.3%)	19 (45.2%)	38 (52.8%)
Prior Autologous Stem Cell Transplant	24 (80.0%)	31 (73.8%)	55 (76.4%)
Prior Allogeneic Stem Cell Transplant	9 (30.0%)	0	9 (12.5%)
Prior radiotherapy	5 (16.7%)	7 (16.7%)	12 (16.7%)

Keys: PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT = bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant.
[a]Subject may have received these agents in different treatment regimens.
[b]Includes either alkylating agents or autologous stem cell transplant.
Note: PI includes bortezomib, carfilzomib, MLN9708, marizomib, and oprozomib; IMiD includes thalidomide, lenalidomide, and pomalidomide.
Percentages are calculated with the number of subjects in each group as denominator.

Numbers analysed

The following populations were:

- All-Treated Analysis Set included all enrolled subjects who received at least 1 dose of study drug. This population was used for all efficacy and safety analyses. For Part 1, only subjects treated with ≥4 mg/kg daratumumab were used for all efficacy analyses since the other doses in Part 1 were under the therapeutic level (12 patients in Part 1 and 72 patients in Part 2, 84 patients in total).
- Pharmacokinetic Analysis Set consisted of all treated subjects with at least 1 baseline and 1 post-baseline pharmacokinetic assessment: 32 patients in Part 1 and 72 patients in Part 2 (104 patients in total)

- Immunogenicity Analysis Set consisted of all treated subjects with at least 1 baseline and 1 post-baseline immunogenicity assessment: 22 patients in Part 1 and 66 patients in Part 2 (88 patients in total).

Outcomes and estimation

Primary endpoint – ORR

The efficacy results in terms of the primary endpoint of ORR (cut-off date 09 January 2015) are summarized in the tables below.

Table 33: Overall Best Response based on Computerized Algorithm (All Treated Analysis Set; Study GEN501 Part 2)

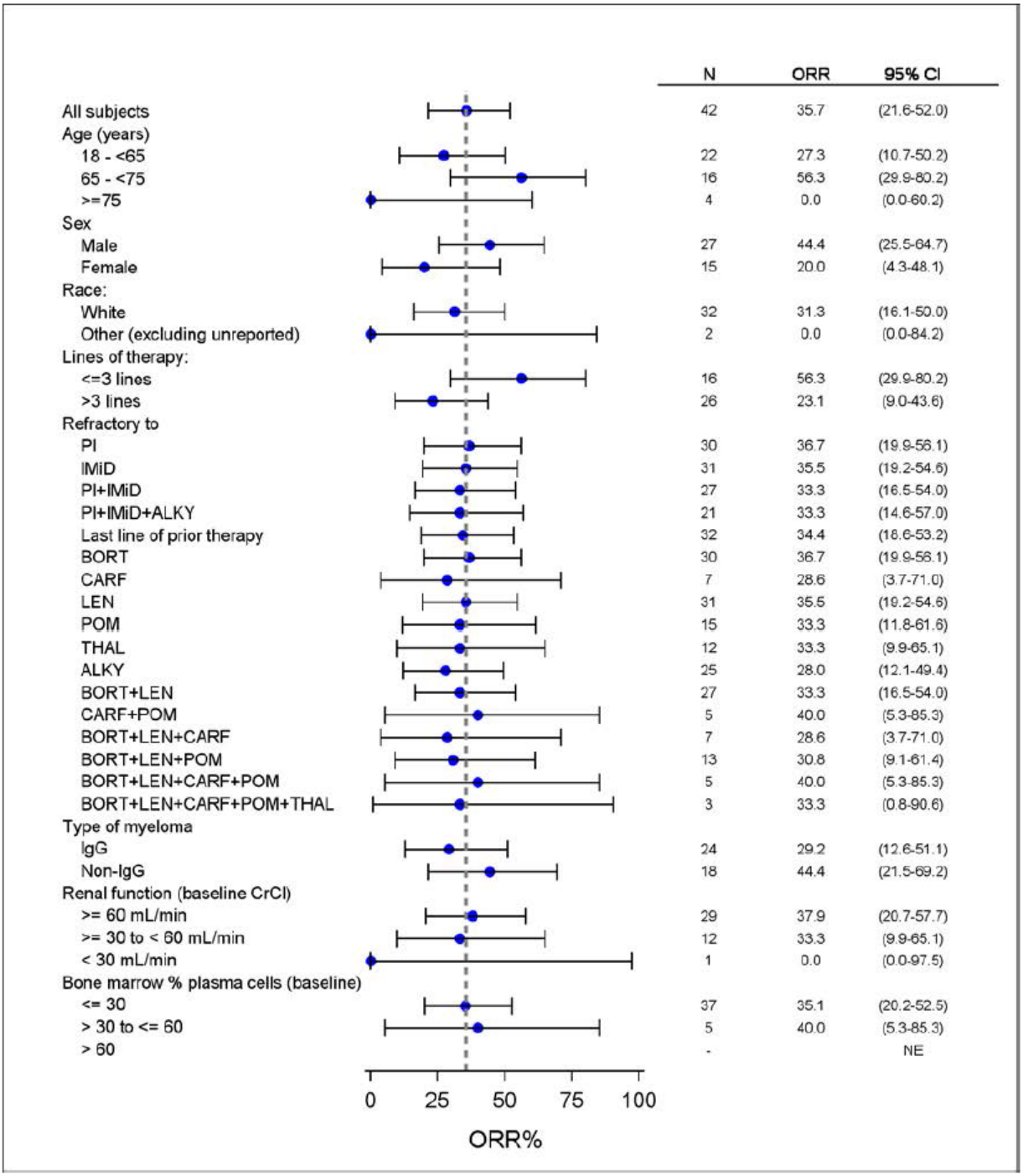
			16 mg/kg - Cohort					
	8 mg/kg		D		E		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	30	-	20	-	22	-	42	-
Best response								
Stringent complete response (sCR)	0	-	0	-	0	-	0	-
Complete response (CR)	0	-	2 (10.0%)	(1.2%, 31.7%)	0	-	2 (4.8%)	(0.6%, 16.2%)
Very good partial response (VGPR)	0	-	1 (5.0%)	(0.1%, 24.9%)	1 (4.5%)	(0.1%, 22.8%)	2 (4.8%)	(0.6%, 16.2%)
Partial response (PR)	3 (10.0%)	(2.1%, 26.5%)	5 (25.0%)	(8.7%, 49.1%)	6 (27.3%)	(10.7%, 50.2%)	11 (26.2%)	(13.9%, 42.0%)
Minimal response (MR)	6 (20.0%)	(7.7%, 38.6%)	0	-	4 (18.2%)	(5.2%, 40.3%)	4 (9.5%)	(2.7%, 22.6%)
Stable disease (SD)	14 (46.7%)	(28.3%, 65.7%)	12 (60.0%)	(36.1%, 80.9%)	10 (45.5%)	(24.4%, 67.8%)	22 (52.4%)	(36.4%, 68.0%)
Progressive disease (PD)	6 (20.0%)	(7.7%, 38.6%)	0	-	0	-	0	-
Not evaluable (NE)	1 (3.3%)	(0.1%, 17.2%)	0	-	1 (4.5%)	(0.1%, 22.8%)	1 (2.4%)	(0.1%, 12.6%)
Overall response (sCR+CR+VGPR+PR)	3 (10.0%)	(2.1%, 26.5%)	8 (40.0%)	(19.1%, 63.9%)	7 (31.8%)	(13.9%, 54.9%)	15 (35.7%)	(21.6%, 52.0%)
Clinical benefit (Overall response + MR)	9 (30.0%)	(14.7%, 49.4%)	8 (40.0%)	(19.1%, 63.9%)	11 (50.0%)	(28.2%, 71.8%)	19 (45.2%)	(29.8%, 61.3%)
VGPR or better (sCR + CR + VGPR)	0	-	3 (15.0%)	(3.2%, 37.9%)	1 (4.5%)	(0.1%, 22.8%)	4 (9.5%)	(2.7%, 22.6%)
CR or better (sCR + CR)	0	-	2 (10.0%)	(1.2%, 31.7%)	0	-	2 (4.8%)	(0.6%, 16.2%)

Keys: CI = exact confidence interval.
Note: Percentages are calculated with the number of subjects in each group as denominator.

Table 34: Subgroup Analysis on Overall Best Response based on Computerized Algorithm (All Treated - 16 mg/kg Group; Study GEN501 Part 2)

		16 mg/kg		
		N	n (%)	95% CI for %
Analysis set:	All subjects	42	15 (35.7%)	(21.6%, 52.0%)
Age:	18 - <65 years	22	6 (27.3%)	(10.7%, 50.2%)
	65 - <75 years	16	9 (56.3%)	(29.9%, 80.2%)
	≥75 years	4	0	(0.0%, 60.2%)
Sex:	Male	27	12 (44.4%)	(25.5%, 64.7%)
	Female	15	3 (20.0%)	(4.3%, 48.1%)
Race:	White	32	10 (31.3%)	(16.1%, 50.0%)
	Other (excluding unreported)	2	0	(0.0%, 84.2%)
Lines of therapy:	≤3 lines	16	9 (56.3%)	(29.9%, 80.2%)
	>3 lines	26	6 (23.1%)	(9.0%, 43.6%)
Refractory to	PI	30	11 (36.7%)	(19.9%, 56.1%)
	IMiD	31	11 (35.5%)	(19.2%, 54.6%)
	PI+IMiD	27	9 (33.3%)	(16.5%, 54.0%)
	PI+IMiD+ALKY	21	7 (33.3%)	(14.6%, 57.0%)
	Last line of prior therapy	32	11 (34.4%)	(18.6%, 53.2%)
	BORT	30	11 (36.7%)	(19.9%, 56.1%)
	CARF	7	2 (28.6%)	(3.7%, 71.0%)
	LEN	31	11 (35.5%)	(19.2%, 54.6%)
	POM	15	5 (33.3%)	(11.8%, 61.6%)
	THAL	12	4 (33.3%)	(9.9%, 65.1%)
	ALKY	25	7 (28.0%)	(12.1%, 49.4%)
	BORT+LEN	27	9 (33.3%)	(16.5%, 54.0%)
	CARF+POM	5	2 (40.0%)	(5.3%, 85.3%)
	BORT+LEN+CARF	7	2 (28.6%)	(3.7%, 71.0%)
	BORT+LEN+POM	13	4 (30.8%)	(9.1%, 61.4%)
	BORT+LEN+CARF+POM	5	2 (40.0%)	(5.3%, 85.3%)
	BORT+LEN+CARF+POM+THAL	3	1 (33.3%)	(0.8%, 90.6%)
Type of myeloma:	IgG	24	7 (29.2%)	(12.6%, 51.1%)
	Non-IgG	18	8 (44.4%)	(21.5%, 69.2%)
Renal function (baseline CrCl):	≥ 60 mL/min	29	11 (37.9%)	(20.7%, 57.7%)
	≥ 30 to < 60 mL/min	12	4 (33.3%)	(9.9%, 65.1%)
	< 30 mL/min	1	0	(0.0%, 97.5%)
Bone marrow % plasma cells (baseline):	≤ 30	37	13 (35.1%)	(20.2%, 52.5%)
	> 30 to ≤ 60	5	2 (40.0%)	(5.3%, 85.3%)
	> 60	-	-	

Keys: CI = exact confidence interval; PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT = bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant.
Note: Response was assessed by computerized algorithm, based on International Uniform Response Criteria Consensus Recommendations.
Note: Percentages are calculated with the number of subjects in each subgroup with available data as denominator.



Keys: CI = exact confidence interval; PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT = bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant.

Figure 9: Forest Plot of Subgroup Analysis on Overall Best Response based on Computerized Algorithm Assessment (All Treated - 16 mg/kg Group; Study GEN501 Part 2)

Secondary endpoint – duration of response (DOR)

The table below summarizes the efficacy results regarding the secondary endpoint (DOR) in Part 2 of the study (cut-off date 09 January 2015).

Table 35: Duration of Response (All Treated Analysis Set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg - Cohort		
		D	E	Total
Analysis set: responders in all treated	3	8	7	15
Duration of response (months)				
Number of events (%)	3 (100.0%)	3 (37.5%)	1 (14.3%)	4 (26.7%)
Number of censored (%)	0	5 (62.5%)	6 (85.7%)	11 (73.3%)
Kaplan-Meier estimate				
25% quartile (95% CI)	6.2 (6.2, 10.6)	6.6 (2.2, NE)	NE (2.8, NE)	7.6 (2.2, NE)
Median (95% CI)	6.9 (6.2, 10.6)	NE (2.2, NE)	NE (2.8, NE)	NE (5.6, NE)
75% quartile (95% CI)	10.6 (6.2, 10.6)	NE (7.6, NE)	NE (NE, NE)	NE (NE, NE)
3-month disease progression-free rate % (95% CI)	100.0 (100.0, 100.0)	87.5 (38.7, 98.1)	83.3 (27.3, 97.5)	86.2 (55.0, 96.4)
6-month disease progression-free rate % (95% CI)	100.0 (100.0, 100.0)	75.0 (31.5, 93.1)	83.3 (27.3, 97.5)	77.5 (44.8, 92.3)
12-month disease progression-free rate % (95% CI)	0.0 (NE, NE)	60.0 (19.5, 85.2)	NE (NE, NE)	64.6 (28.4, 85.9)

Keys: CI = confidence interval; NE=not estimable.
Percentages are calculated with the number of subjects in each group as denominator.

Secondary endpoint – overall survival (OS)

The applicant submitted an updated OS analysis for Part 2 of the study with a data cut-off of 30 June 2015, corresponding to a follow-up time of 15.2 months for the 16 mg/kg group and 27.6 months for the 8 mg/kg group.

Table: 36: Summary of OS (All Treated Analysis Set; Study GEN501 Part 2)

	8 mg/kg	16 mg/kg
Analysis set: all treated	30	42
Overall survival (months)		
Number of events (%)	22 (73.3%)	11 (26.2%)
Number of censored (%)	8 (26.7%)	31 (73.8%)
Kaplan-Meier estimate		
25% quartile (95% CI)	7.2 (2.5, 9.3)	15.9 (5.9, NE)
Median (95% CI)	18.2 (7.5, 23.4)	NE (19.9, NE)
75% quartile (95% CI)	27.0 (20.4, NE)	NE (19.9, NE)
6-month overall survival rate % (95% CI)	76.7 (57.2, 88.1)	88.1 (73.7, 94.9)
12-month overall survival rate % (95% CI)	56.3 (36.8, 71.8)	78.6 (62.9, 88.2)

Keys: CI = confidence interval; NE=not estimable.
Percentages are calculated with the number of subjects in each group as denominator.

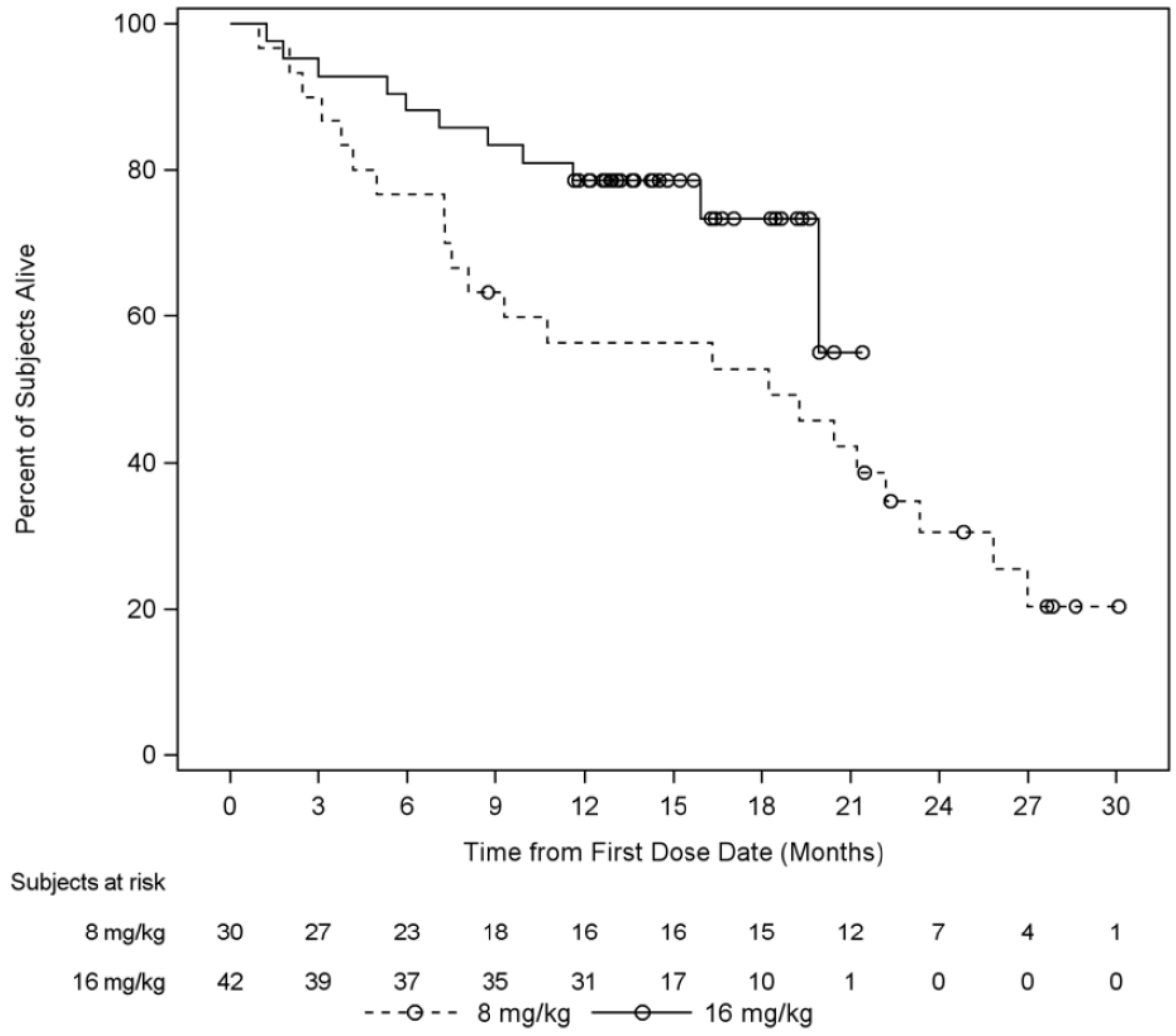


Figure 10: Kaplan-Meier Plot of OS (All Treated Analysis Set; Study GEN501 Part 2)

Ancillary analyses

N/A

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 37: Summary of Efficacy for trial GEN501

Title: **Daratumumab (HuMax-CD38) safety study in multiple myeloma – open-label, single-arm study**			
Study identifier	GEN501		
Design	Open-label, single-arm study		
Hypothesis	Exploratory		
Treatments groups	Daratumumab 8 mg/kg		Weekly for 8 w; then q2w for 16 w, then monthly for up to 72 weeks or until progressive disease or unmanageable toxicity
	Dartumumab 16 mg/kg		The first infusion within a 3 week resting period, followed by weekly for 7 w, then q2w for 14 additional weeks, then monthly for up to 72 weeks or until progressive disease or unmamageable toxicity.
Endpoints and definitions	Primary endpoint	Overall response rate (ORR)	Proportions of patients who achieved a partial response (PR) or better
	Secondary endpoint	Duration of response (DOR)	Time from the date of the initial documentation of a response (PR or better) to the date of first documented evidence of progressive disease.
	Secondary endpoint	Overall survival (OS)	Time from date of first dose of daratumumab to the date of death
Database lock	Part 2 – Database lock: 06 February 2015 OS update: 30 June 2015		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT – Part 2		
Descriptive statistics and estimate variability	Treatment group	8 mg/kg	16 mg/kg
	Number of subjects	30	42
	ORR (%)	10	35.7
	95% CI	2.1, 26.5	21.6, 52.0
	Median DOR (mo)	6.9	NE
	95% CI	6.2, 10.6	5.6, NE
	OS (mo) 95% CI	18.2 7.5, 23.4	NE 19.9, NE

Analysis performed across trials (pooled analyses and meta-analysis)

Table 38: Overall Best Response: All Treated patients Analysis Set (Studies: MMY2002 and GEN501 Part 2)

	16 mg/kg					
	MMY2002		GEN501 Part 2		Total	
	n (%)	95% CI for %	n (%)	95% CI for %	n (%)	95% CI for %
Analysis set: all treated	106	-	42	-	148	-
Best response						
Stringent complete response (sCR)	3 (2.8%)	(0.6%, 8.0%)	0	-	3 (2.0%)	(0.4%, 5.8%)
Complete response (CR)	0	-	2 (4.8%)	(0.6%, 16.2%)	2 (1.4%)	(0.2%, 4.8%)
Very good partial response (VGPR)	10 (9.4%)	(4.6%, 16.7%)	2 (4.8%)	(0.6%, 16.2%)	12 (8.1%)	(4.3%, 13.7%)
Partial response (PR)	18 (17.0%)	(10.4%, 25.5%)	11 (26.2%)	(13.9%, 42.0%)	29 (19.6%)	(13.5%, 26.9%)
Minimal response (MR)	5 (4.7%)	(1.5%, 10.7%)	4 (9.5%)	(2.7%, 22.6%)	9 (6.1%)	(2.8%, 11.2%)
Stable disease (SD)	46 (43.4%)	(33.8%, 53.4%)	22 (52.4%)	(36.4%, 68.0%)	68 (45.9%)	(37.7%, 54.3%)
Progressive disease (PD)	18 (17.0%)	(10.4%, 25.5%)	0	-	18 (12.2%)	(7.4%, 18.5%)
Not evaluable (NE)	6 (5.7%)	(2.1%, 11.9%)	1 (2.4%)	(0.1%, 12.6%)	7 (4.7%)	(1.9%, 9.5%)
Overall response (sCR+CR+VGPR+PR)	31 (29.2%)	(20.8%, 38.9%)	15 (35.7%)	(21.6%, 52.0%)	46 (31.1%)	(23.7%, 39.2%)
Clinical benefit (Overall response + MR)	36 (34.0%)	(25.0%, 43.8%)	19 (45.2%)	(29.8%, 61.3%)	55 (37.2%)	(29.4%, 45.5%)
VGPR or better (sCR + CR + VGPR)	13 (12.3%)	(6.7%, 20.1%)	4 (9.5%)	(2.7%, 22.6%)	17 (11.5%)	(6.8%, 17.8%)
CR or better (sCR + CR)	3 (2.8%)	(0.6%, 8.0%)	2 (4.8%)	(0.6%, 16.2%)	5 (3.4%)	(1.1%, 7.7%)

Keys: CI = confidence interval.
Note: Percentages are calculated with the number of subjects in each group as denominator.
Note: Exact 95% confidence intervals are provided.

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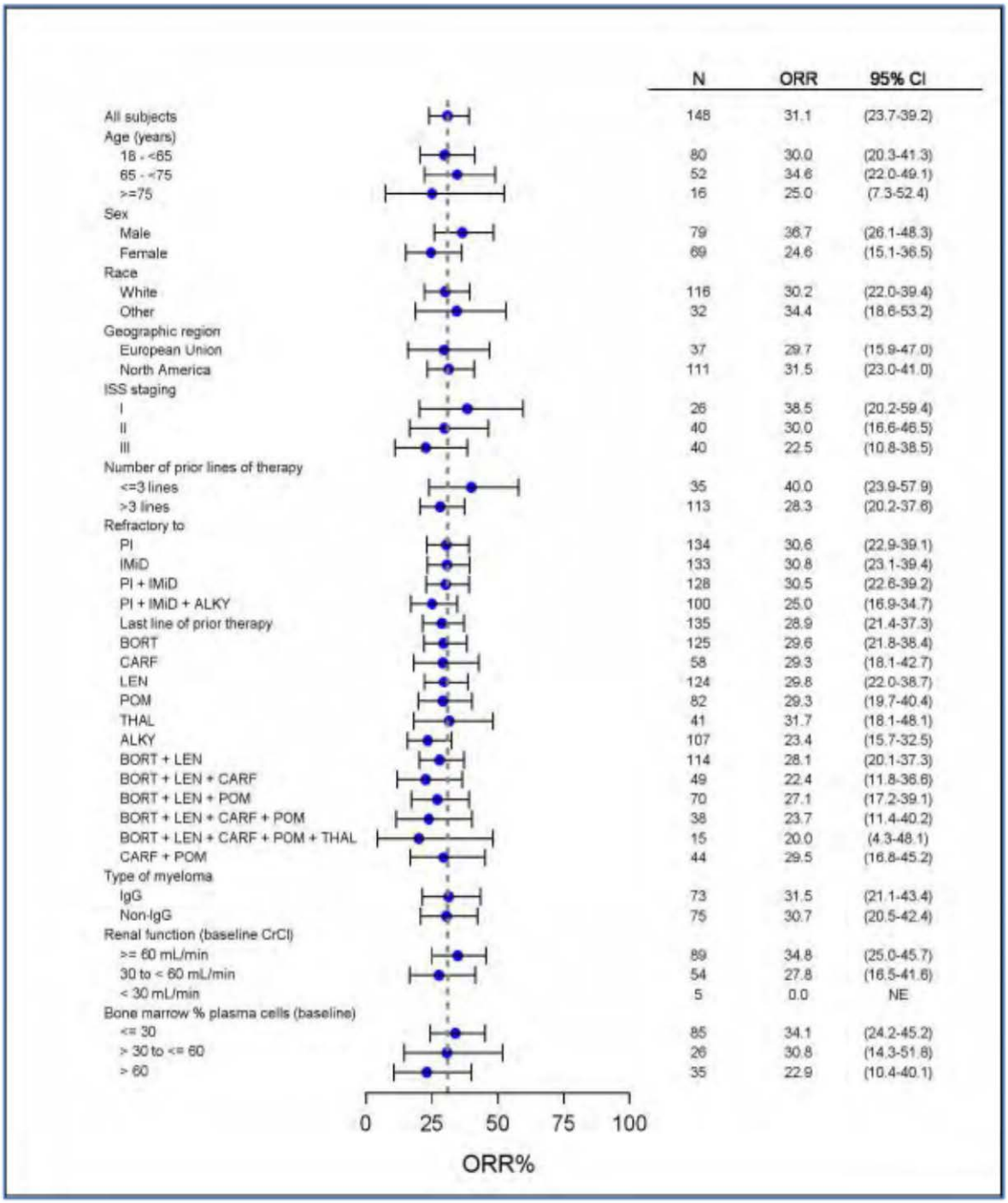


Keys: CI = confidence interval; PI = proteasome inhibitor; IMiD = Immunomodulatory drug; BORT= bortezomib; LEN = lenalidomide; CARF = carfilzomib; POM = pomalidomide; THAL = thalidomide; ALKY = alkylating agents, including autologous stem cell transplant; CrCL = creatinine clearance.
Note: Exact 95% confidence intervals are provided.
ISS staging data is not available in GEN501 Part 2.
'+' indicates that subject may have received these agents in different treatment regimens.

Figure 11: Forest Plot of Subgroup Analyses on Overall Best Response; All Treated Analysis Set (Studies: MMY2002 and GEN501 Part 2)

Table 39: Overall Survival; All Treated Analysis Set (Studies: MMY2002 and GEN501 Part 2)- Data cut-off 31 December 2015

	16 mg/kg		
	MMY2002	GEN501 Part 2	Total
Analysis set: all treated	106	42	148
Overall survival			
Number of events (%)	57 (53.8%)	16 (38.1%)	73 (49.3%)
Number of censored (%)	49 (46.2%)	26 (61.9%)	75 (50.7%)
Kaplan-Meier estimate (months)			
25% quantile (95% CI)	7.59 (5.62, 10.58)	15.93 (5.95, 22.41)	8.71 (6.05, 12.09)
Median (95% CI)	18.60 (13.67, NE)	NE (18.66, NE)	20.07 (16.62, NE)
75% quantile (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
6-month overall survival rate % (95% CI)	81.8 (73.0, 88.0)	88.1 (73.7, 94.9)	83.6 (76.5, 88.7)
12-month overall survival rate % (95% CI)	64.7 (54.5, 73.1)	78.6 (62.9, 88.2)	68.7 (60.5, 75.6)
18-month overall survival rate % (95% CI)	51.3 (41.1, 60.6)	69.0 (52.7, 80.7)	56.5 (47.9, 64.2)
24-month overall survival rate % (95% CI)	41.3 (31.0, 51.2)	57.4 (38.7, 72.3)	45.0 (35.5, 54.1)

Keys: CI = confidence interval; NE = not evaluable.
Percentages are calculated with the number of subjects in each group as denominator.
Cutoff for survival and subsequent therapy data was 31DEC2015

In the subset of subjects who were refractory to pomalidomide or carfilzomib, or both, the median OS were 15.2 to 16.5 months (data not shown).

Tables 47 and 48 summarize previously published data for newer anti-MM drugs.

Table 40: Patient Population Characteristics for Daratumumab, Pomalidomide, and Carfilzomib Studies

	Dara (n=106) (16 mg/kg) Phase 2 MMY2002	**Dara (n=42) (16 mg/kg) Phase 1/2 GEN501**	**POM alone (n=108) Phase 2 MM-002[c]**	**POM+ LD-dex (n=113) Phase 2 MM-002[c]**	**POM+ LD-dex (n=302) Phase 3 MM-003[d]**	**Carfilzomib (n=266) Phase 2 PX171-003-A1[e]**	**Carfilzomib (n=157) Phase 3 FOCUS[f]**
Eligibility criteria							
Median age (yrs)	64	64	61	64	64	63	63
Creatinine	CrCl> 20mL/min /1.73m^2	serum creatinine ≤2xULN	serum creatinine ≤3.0mg/dL	serum creatinine ≤3.0mg/dL	CrCl> 45mL/min	CrCl> 30mL/min	CrCl≥ 15mL/min
Hemoglobin	>7.5g/dL	>7.5g/dL	NR	NR	≥8.0 g/dL	≥8.0 g/dL	NR
Platelet count	>50x10^9/L	>75x10^9/L	>75x10^9/L	>75x10^9/L	>75x10^9/L	≥50x10^9/L	≥30x10^9/L
ANC	>1.0x10^9/L	≥1.0x10^9/L	>1.0x10^9/L	>1.0x10^9/L	>1.0x10^9/L	≥1.0x10^9/L	NR
Prior Therapy							
Prior lines of therapy, median	5	4	5	5	5	5	5
Prior ASCT (%)	80%	74%	76%	74%	71%	74%	68%
Refractory Status (%)							
Refractory to last line of therapy	97%	76%	NR	NR	82% [g]	95%	NR
Refractory to:							
PI + IMiD	95%	64%	61%[h]	62% [h]	75% [h]	80% [h]	62% [h]
BORT+LEN	82%	64%	61%	62%	75%	80% [d]	62%
POM	63%	36%	0	0	0	NR	NR
CARF	48%	17%	NR	NR	NR	0	0
ALKY	77%	60%	NR	NR	NR	NR	NR

Abbreviations: ALKY = alkylating agents; ANC=absolute neutrophil count; ASCT=autologous stem cell transplant; BORT=bortezomib; CARF=carfilzomib; CrCl=creatinine clearance; IMiD=immunomodulatory agent; LEN=lenalidomide; NR=not reported; PI=proteasome inhibitor; POM=pomalidomide; POM+LD-dex= pomalidomide+low-dose dexamethasone; SCT=stem cell transplant

[c] Richardson 2014

[d] San Miguel 2013

[e] Siegel 2012

[f] Ludwig 2014

[g] Taken from San Miguel 2013,

[h] refractory or intolerant to BORT and LEN

Table 41: Response Categories for Daratumumab, Pomalidomide, and Carfilzomib

	Dara (n=106) (16 mg/kg) Phase 2 MMY2002[a]	Dara (n=42) (16 mg/kg) Phase 1/2 GEN501[a]	POM alone (n=108) Phase 2 MM-002[b]	POM+ LD-dex (n=113) Phase 2 MM-002[b]	POM+ LD-dex (n=302) Phase 3 MM-003[c]	Carfilzomib (n=257) Phase 2 PX171-003-A1[d]	Carfilzomib (n=157) Phase 3 FOCUS[e]
Response Rate (%)							
ORR	29%	36%	7%	29%	31%	24%	19%
sCR/CR	3%	5%	0	0.9%	1%	0.4%	NR
VGPR or better	12%	10%	NR	NR	6%	5%	4%
ORR in Subgroups (%)							
Refractory to PI/IMiD	30%	33%	6%[f]	28%[g]	28%[h]	15%[i]	NR
Refractory to POM	28%	33%	No patient with prior POM	No patient with prior POM	No patient with prior POM	NR	NR
Refractory to CARF	29%	29%	NR	NR	NR	No patient with prior CARF	No patient with prior CARF

Abbreviations: BORT=bortezomib; CARF=carfilzomib; CR=complete response; LD-dex=low-dose dexamethasone; LEN=lenalidomide; NR=not reported; ORR=overall response rate; POM=pomalidomide; sCR=stringent complete response; VGPR=very good partial response

[b] FDA Medical Review

[c] San Miguel 2013

[d] Siegel 2012, response evaluable population

[e] Ludwig 2014

[f] Based on n=64 subjects who were refractory to BORT and LEN

[g] Based on n=69 subjects who were refractory to BORT and LEN

[h] Based on n=225 subjects who were refractory to BORT and LEN

[i] Based on n=169 subjects who were refractory to BORT and LEN

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled Trials	0/237	0/237	0/237
Non Controlled Trials	84/237	20/237	0/237

Supportive studies

Study GEN503

Study GEN503 was an open label, international, multicenter, dose escalating phase 1/2 trial investigating the safety of daratumumab in combination with lenalidomide (25 mg orally on Days 1 through 21 of each 28 day cycle) and dexamethasone (total dose of approximately 40 mg weekly) in patients with relapsed or relapsed and refractory multiple myeloma. The design of the study is presented in Table 50.

Table 42: Design of study GEN503

Study ID/ First Patient First Visit/ Study Status	Phase / Study Population/ Efficacy Endpoints	Total Number of Subjects Treated	Dose Regimen/ Duration of Treatment
GEN503 20 Jun 2012 Ongoing	Phase: 1/2 Subjects with relapsed/refractory multiple myeloma ORR, TTP, DOR, PFS	Treated: 45 Phase 1: 13 2 mg/kg (n=3) 4 mg/kg (n=3) 8 mg/kg (n=4) 16 mg/kg (n=3) Phase 2: 32 16 mg/kg (n=32)	daratumumab 2 mg/kg to 16 mg/kg, in combination with lenalidomide (25 mg orally on Days 1 through 21 of each cycle) and dexamethasone (40 mg weekly) in 28-day treatment cycles daratumumab administered weekly for 8 weeks, followed by q2w for an additional 16 weeks, and every 4 weeks thereafter Until disease progression or unacceptable toxicity

The first subject started treatment on 17 March 2014, and the last subject started treatment on 13 August 2014. As of the clinical cutoff date 4 subjects from Phase 1 (n=13) and 6 subjects from Phase 2 (n=32) had discontinued treatment.

In Phase 2, 32 subjects were treated with 16 mg/kg daratumumab in combination with LEN/Dex. At the time of clinical cutoff, 81% of subjects received at least 7 treatment cycles (26 of 32 subjects). The median number of treatment cycles was 8 cycles (range of 1.0; 11.0). Twenty-six (26) of 32 subjects were continuing treatment.

The majority of subjects (81%) in Phase 2 were male and all subjects were White. In Phase 2, 66% (21/32 subjects) had received a prior PI and IMiD, and 22% (7/32) were double refractory to the most recent PI and IMiD.

Efficacy analyses from Phase 2 (16 mg/kg daratumumab) showed the following:

- Twenty-eight (28) of 32 subjects (88%) had an ORR of PR or better; 7 subjects had a stringent CR, 1 subject had a CR, and 9 subjects had a VGPR.
- Response to 16 mg/kg daratumumab in combination with lenalidomide/dexamethasone was rapid and durable. The median time to response was approximately 1 month. A median duration of response was not reached at the time of clinical cutoff; however, 93% of responders remained progression-free and alive after 6 months on treatment.
- At the time of clinical cutoff, disease progression had occurred in 5 subjects (16%). The median time to progression and a median PFS rate were not reached; however, 84% of subjects remained progression-free after 6 months.
- All subjects had substantial reductions in paraprotein from baseline; 31 subjects had at least a 50% reduction in paraprotein from baseline and 22 subjects had at least a 90% reduction in paraprotein from baseline.
- All responders who had bone marrow plasma cell data at baseline and first post-baseline measurement (20 subjects) had complete or near complete clearance of malignant plasma cells from their bone marrow (ie, <5% plasma cells remaining).

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The study population included patients who were heavily pre-treated and highly refractory, thus standard treatment options such as alkylating agents, ASCT, bortezomib and lenalidomide were exhausted. The patient population was not only refractory to bortezomib and lenalidomide, but 95% of the study population in the MMY2002study was refractory towards the newer drugs, pomalidomide and carfilzomib. Patients with poor renal function and compromised haematology parameters were allowed to be included in the studies.

The recommended dose of 16 mg/kg was selected on the basis of the part 1 of Study GEN501 and study MMY2002. The dose of 16 mg/kg seems to offer a better antitumor activity than 8 mg/kg with an acceptable safety profile and to some extent comparable toxicity showed by the dose 8 mg/kg. Taking into account the PK data and the target saturation threshold for CD38, the selection of 16 mg/kg appears reasonable.

Efficacy data and additional analyses

The GEN501 and MMY2002 studies showed that the 16 mg/kg dose met the protocol-specified criteria for continuation of an ORR of 15%. At 16 mg/kg, daratumumab, the response was rapid and durable, a total of 31 patients achieved response of PR or better based on IRC assessment; the ORR was 29% (95% CI: 21%, 39%). The responses were rapid with a median time to response of 1 month and the median duration of response was 7.4 months. The ORR was consistent across different clinically relevant subgroups, including those refractory to newer drugs, such as pomalidomide or carfilzomib. The ORRs of daratumumab in these populations (28% to 33%) were similar to the overall population (29% to 36%).

The data also demonstrated that 3 patients (3%) achieved stringent CR and 13 patients (12%) achieved VGPR or better in the MMY2002 study, while 5% had stringent CR in the GEN501 study. This depth of response, a combined VGPR or better rate of 11% is high for a single-agent therapy, when compared with other recently approved therapies, especially given the refractoriness of the study population. The median OS was 17.5 months for patients who received 16 mg/kg daratumumab. All patients with stringent CR/CR are still on treatment, with longest follow-up of 21.4 months.

Whether daratumumab can change the response of subsequent therapies due to its novel mechanism of action or whether it will be possible to identify potential predictors of response and resistance remains to be elucidated. In the ongoing and future studies as MMY3003 and MMY3004, the Applicant is planning to perform translational biomarker studies, analysis of CD38 expression, subsets of CD38+Tregs and CD38+ Bregs, enzymatic activity of CD38 and T cell clonality, genome sequencing and mRNA sequencing of CD38+ MM cell, and correlate this with clinical response/progression. The CHMP recommended the applicant to provide these data once available.

The Applicant has initiated an Early Access Programme in the U.S. which is being conducted under a clinical trial protocol (54767414MMY3010), this programme will also be expanded to include European countries. The objective of this programme is to provide early access to single agent daratumumab and collect additional data while the medication is not commercially available. By this program, over 600 patients will receive daratumumab. Multiple myeloma patients who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or whose disease is double refractory to both a PI and an IMiD will be eligible for the programme, thus the patient population is similar to the present study group. The CHMP recommended the applicant to provide the results of the US (?) Early Access Programme.

Additional efficacy data needed in the context of a conditional MA

The absence of a control arm and the small number of patients treated with daratumumab in studies MMY2002 and GEN501 impacts on the interpretation of the clinical benefit of daratumumab in the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included

a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

To further support the results obtained in studies MMY2002 and GEN501, the Applicant provided historical previously published data. Although such a comparison should be done cautiously, an ORR of 29%-36% is quite high for monotherapy in this clinical setting and a clinical benefit for daratumumab, can be considered established, but a confirmation from phase III comparative studies is needed in order to better quantify the magnitude of the effect.

The Applicant has proposed to submit the final CSR for Phase 3 studies of daratumumab in combination with lenalidomide/low-dose dexamethasone (MMY3003) and of daratumumab in combination with bortezomib/low dose dexamethasone (MMY3004) in patients with relapsed or refractory multiple myeloma which are currently ongoing to meet this requirement. These studies are expected to generate comprehensive data to confirm the benefit-risk balance in the proposed indication.

Therefore, the CHMP has recommended imposing specific obligations in Annex II to the marketing authorization for the submission of the final results of ongoing Phase 3 studies MMY3003 and MMY3004.

2.5.4. Conclusions on the clinical efficacy

The clinical efficacy data available are adequate to support the efficacy of daratumumab in the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

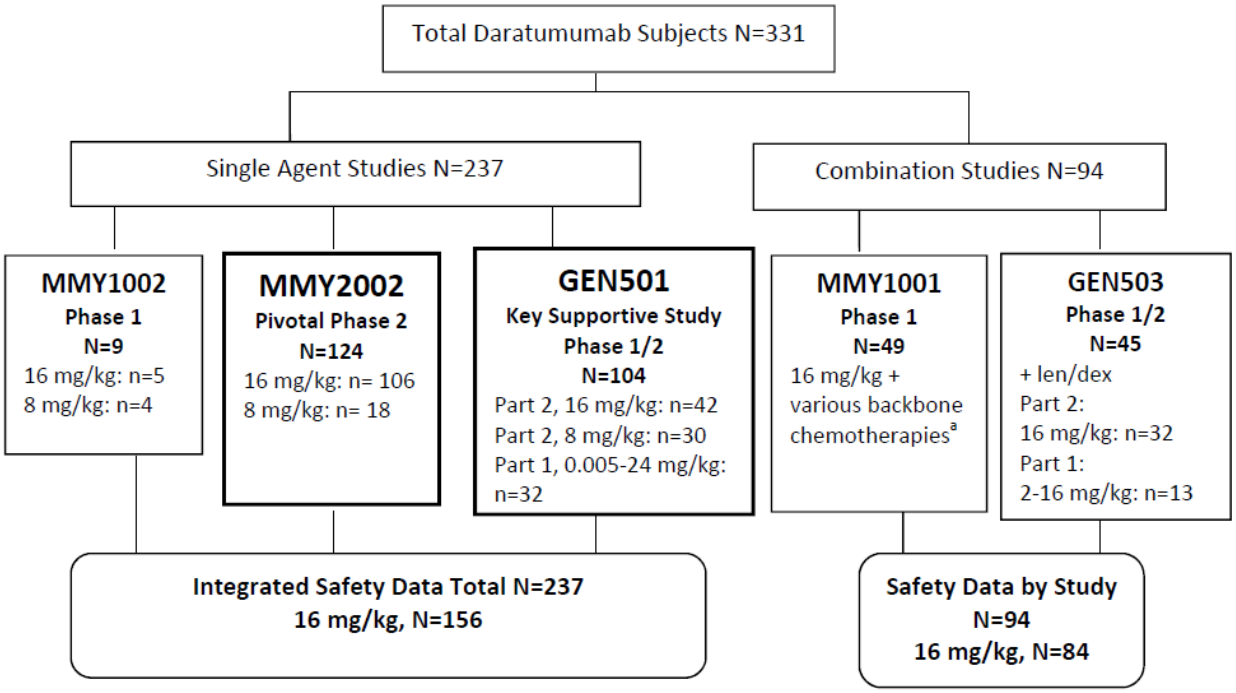
The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.

2.6. Clinical safety

The clinical studies that support the safety of daratumumab are presented in the figure below.



len/dex=lenalidomide+dexamethasone
[a] Pom-dex=pomalidomide-dexamethasone; VD=VELCADE-dexamethasone; VMP=VELCADE-melphalan-prednisone; VTD=VELCADE-thalidomide-dexamethasone

Figure 14: Overview of clinical studies supporting safety for daratumumab

The overview of these clinical studies is presented in the tables below.

Table 43: Overview of daratumumab monotherapy clinical studies

Protocol Number Study Dates CCO for Primary Analysis	Study Design/Population	Treatment	Number of Subjects Treated in Safety Population
Monotherapy Studies—Integrated			
54767414MMY2002 30 September 2013 to ongoing CCO: 09 January 2015	Phase 2, open-label, 2-part, multicenter , study to select the optimal dose and assess the efficacy and safety of daratumumab monotherapy Subjects ≥18 years of age with R/R MM after ≥3 prior lines of therapy (≥2 cycles or 2 months of treatment with a PI and IMiD), or MM that was double refractory to a PI and IMiD, and evidence of disease progression on most recent prior treatment regimen; baseline ECOG score ≤2	Part 1 (Randomized OL, Phase 2 DP): Group A: daratumumab 16 mg/kg QW x 8 wks, Q2W x 16 wks, and Q4W thereafter Group B: daratumumab 8 mg/kg Q4W Part 2 (OL, single arm, Phase 3 DP): daratumumab 16 mg/kg QW x 8 wks, Q2W x 16 wks, and Q4W thereafter Treatment continued until disease progression, unacceptable toxicity, or subject withdrawal.	**Total (n=124)** Part 1: n=59 16 mg/kg (n=41) 8 mg/kg (n=18) Part 2: n=65 all 16 mg/kg Of subjects treated with 16 mg/kg: 41 received Phase 2 DP (all in Part 1) 65 received Phase 3 DP (all in Part 2)
GEN501 01 August 2010 to ongoing CCO: 09 January 2015	Phase 1/2, open-label, 2-part, multicenter, dose-escalation study to establish the safety profile of daratumumab as monotherapy Subjects ≥18 years of age with R/R MM after ≥2 prior lines of therapy (including PI, IMiD, chemotherapy, or ASCT); baseline ECOG score ≤2	Part 1: OL, dose escalation daratumumab 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, or 24 mg/kg for up to 8 wks (first infusion at Week 0, with a 3-wk resting period, followed by 6 QW infusions) Part 2: OL, single-arm daratumumab 8 or 16 mg/kg [a]Schedules A-C: 8 mg/kg QW x 8 wks, Q2W x 16 wks, and Q4W thereafter or [a]Schedules D-E: 16 mg/kg first infusion, followed by 3-wk rest, then QW x 7 w, Q2W x 14 w, and Q4W thereafter Treatment continued for up to 96 weeks or until unacceptable toxicity or disease progression)	**Total (n=104)** Part 1 (n=32) ≤4 mg/kg (n=23) 8 mg/kg (n=3) 16 mg/kg, (n=3) 24 mg/kg (n=3) Part 2 (n=72) 8 mg/kg (n=30) 16 mg/kg (n=42) Of subjects treated with 16 mg/kg: 23 received Phase 2 DP (3 subjects from Part 1 and 20 subjects from Cohort D in Part 2) 22 received Phase 3 DP (all from Cohort E of Part 2)

MMY1002 28 April 2014 to ongoing DBL: 06 February 2015	Phase 1, open-label, nonrandomized, dose-escalation study to evaluate the tolerability and safety of daratumumab in Japanese subjects with R/R MM Subjects ≥20 years of age with R/R MM after ≥2 prior lines of therapy (including PI or IMiD); baseline ECOG score ≤2	daratumumab 8 or 16 mg/kg Period 1: (intense dosing regimen) – until the end of Week 9 (first infusion at Week 0, with a 3-wk resting period, followed by 6 QW infusions) Period 2: (less intense dosing regimen) from Week 10 until End of Treatment (28-day cycles) Cycle 1-4: Q2W Cycle 5 on: Q4W Treatment continued until disease progression or unacceptable toxicity.	**Total (n=9)** 8 mg/kg (n= 4) 16 mg/kg (n=5) (all Phase 3 DP)

Table 44: Overview of daratumumab combination clinical studies

Protocol Number Study Dates CCO for Primary Analysis	Study Design/Population	Treatment	Number of Sub Safety P
Combination Studies--Not Integrated			
GEN503 12 June 2012 to ongoing CCO: 09 January 2015	Phase 1/2, open-label, dose-escalation study to establish the safety profile of daratumumab given in combination with Len/Dex in subjects with R/R MM Part 1: Subjects ≥18 years of age with relapsed MM after 2 to 4 prior lines of therapy and eligible for Len/Dex treatment; baseline ECOG score ≤2 Part 2: Subjects ≥18 years of age who received ≥1 prior line of therapy and had achieved a (PR or better) response to at least 1 prior regimen with documented PD; baseline ECOG score ≤2	Part 1: dose escalation daratumumab 2, 4, 8, or 16 mg/kg in combination with Len/Dex daratumumab QW in Cycles 1-2, Q2W in Cycles 3-6; and Q4W from Cycle 7 on Len 25 mg PO daily on Days 1-21 of each cycle Dex 40 mg QW (20 mg QW for subjects >75 years old or underweight) Part 2: single-arm daratumumab 16 mg/kg in combination with Len/Dex as in Phase 1 Each Cycle was 28 days. In both phases, treatment continued until disease progression or unacceptable toxicity.	**Total (n=45)** Part 1 (n=13) 2 mg/kg dara+I 4 mg/kg dara+I 8 mg/kg dara+I 16 mg/kg dara+ Part 2 (n=32) all 16 mg/kg da All subjects rec
54767414MMY1001 10 March 2014 to ongoing DBL: 06 February 2015	Phase 1b,open-label, nonrandomized study to evaluate the safety, tolerability, and dosing of daratumumab given in combination with either VD, VMP, Pom-dex, or VTD in subjects with newly diagnosed or R/R MM Subjects ≥18 years of age with baseline ECOG score ≤2 and either: - newly diagnosed MM regardless of eligibility for transplantation (for the VD or VTD regimens), - newly diagnosed MM and not considered a candidate for high-dose chemotherapy and SCT (for the VMP regimen), or - R/R MM after ≥2 prior lines of therapy (including LEN and VELCADE) (for the Pom-dex regimen)	daratumumab **in the VD and VTD regimens**: daratumumab 16 mg/kg QW IV in Cycles 1-2, and then Q3W for the remaining 16 cycles or until transplantation **in the VMP regimen**: daratumumab16 mg/kg QW IV in Cycle 1, and then Q3W for the remaining 8 cycles **in the Pom-Dex regimen**: daratumumab 16 mg/kg QW in Cycles 1-2, then Q2W in Cycles 3-6, and then Q4W for the remaining cycles (Cycles 7 to 13) or until disease progression Backbone Regimens: **VD and VTD regimens (3-week cycles)**: VELCADE 1.3 mg/m^2 SC twice weekly (Days 1, 4, 8, and 11) in Cycles 1 to 4, followed by QW administrations (Days 1 and 8) for the subsequent 14 cycles (Cycles 5-18) or until transplant, with an option to change the schedule from QW to biweekly if toxicity was encountered; dex 20 mg on Days 1, 2, 4, 5, 8, 9, 15, and 16 in Cycles 1-2; 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 in Cycles 3-4; and 20 mg on Days 1, 2, 8, and 9 of subsequent cycles (on daratumumab dosing days, dex was administered IV 1 hour prior to the daratumumab infusion, and on days when daratumumab was not administered, dex was administered PO); thalidomide 100 mg PO daily for 21 days **VMP regimen (6-week cycles)**: VELCADE 1.3 mg/m^2 SC twice weekly (Days 1, 4, 8, 11, 22, 25, 29, and 32) in Cycle 1, followed by QW (Days 1, 8, 22, and 29) in subsequent cycles (Cycles 2 to 9); melphalan 9 mg/m^2 PO and prednisone 60 mg/m^2 (IV on Day 1, PO Days 2-4) on Days 1 to 4 of each cycle. **Pom-dex regimen (4-week cycles)**: Pom 4 mg PO once daily on Days 1 to 21 during each 28-day cycle; Dex 40 mg (subjects ≤75 years) or 20 mg (subjects >75 years) per wk. Treatment continued for the maximal allowed duration or until disease progression, unacceptable toxicity, or discontinuation of study treatment	**Total (n=49)** 16 mg/kg dara+ 16 mg/kg dara+ (n=11) 16 mg/kg dara+ (n=8) 16 mg/kg dara+ Pom-dex) (n=2 25 subjects ha MM 24 subjects ha All subjects re daratumumab

CCO=clinical cutoff date; DBL=database lock date; Dara=daratumumab; Dex=dexamethasone; DP=drug product; ECOG=Eastern Cooperative Oncolog
IDMC=Independent Data Monitoring Committee; IMiD=immunomodulatory drug; IV=intravenous(ly); Len=lenalidomide; MM=multiple myeloma; OI
PI=proteasome inhibitor; PO=orally; Pom-Dex=pomalidomide-dexamethasone; QW=every week; Q2W=every 2 weeks; Q3W=every 3 weeks; Q4W=ev
R/R=relapsed/refractory; SC=subcutaneous(ly); VD=VELCADE-dexamethasone; VMP=VELCADE-melphalan-prednisone; VTD=VELCADE-thalidon
dexamethasone; wk=week

Note: Studies MMY2002 and GEN501 were integrated for the population pharmacokinetic exposure-response assessment.

[a] In Part 2 of Study GEN501, different predose infusions/medications and infusion rates were evaluated (ie, Schedules A through E) for each dose.

Patient exposure

Table 45: Total Exposure to Daratumumab in Integrated Monotherapy Studies (N=237)

No. subjects treated per daratumumab dose	≤4 mg/kg[a]	8 mg/kg	16 mg/kg			24 mg/kg	Total
			Total	Ph 2 DP	Ph 3 DP		
MMY2002	0	18	106	41	65	0	**124**
GEN501	23	33	45	23	22	3	**104**
MMY1002	0	4	5	0	5	0	**9**
Total Monotherapy	**23**	**55**	**156**	**64**	**92**	**3**	**237**

DP=drug product; Ph=Phase
[a]Includes the following doses: 0.005, 0.05, 0.10, 0.50, 1, 2, and 4 mg/kg

Table 46: Total Exposure to Daratumumab in Combination Therapy Studies (N=94)

No. subjects treated per daratumumab dose	≤4 mg/kg[a]	8 mg/kg	16 mg/kg			Total
			Total	Ph 2 DP	Ph 3 DP	
GEN503	6	4	35	35	0	**45[b]**
MMY1001	0	0	49	0	49	**49[c]**
Total Combination Therapy	**6**	**4**	**84**			**94**

DP=drug product; Ph=Phase
[a]Includes the following doses: 0.005, 0.05, 0.10, 0.50, 1, 2, and 4 mg/kg
[b] All in combination with lenalidomide+dexamethasone (dex)
[c] In combination with VELCADE+dex (n=6) or VELCADE+thalidomide+dex (n=11) or VELCADE+melphalan+prednisone (n=8) or pomalidomide+dex (n=24)

Table 47: Daratumumab Infusions; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Duration of treatment (month)					
N	23	55	156	3	237
Mean (SD)	1.276 (0.6870)	3.692 (3.5641)	4.469 (3.4808)	1.676 (0.6085)	3.943 (3.4450)
Median	1.446	2.628	3.253	1.906	2.628
Range	(0.07; 1.94)	(0.03; 14.78)	(0.03; 14.19)	(0.99; 2.14)	(0.03; 14.78)
< 1 month	7 (30.4%)	14 (25.5%)	22 (14.1%)	1 (33.3%)	44 (18.6%)
>=1 - < 3 months	16 (69.6%)	21 (38.2%)	53 (34.0%)	2 (66.7%)	92 (38.8%)
>=3 - < 6 months	0	9 (16.4%)	29 (18.6%)	0	38 (16.0%)
>=6 - < 9 months	0	6 (10.9%)	35 (22.4%)	0	41 (17.3%)
>=9 - < 12 months	0	1 (1.8%)	10 (6.4%)	0	11 (4.6%)
>=12 months	0	4 (7.3%)	7 (4.5%)	0	11 (4.6%)
Total dose received (mg/kg)					
N	23	55	156	3	237
Mean (SD)	6.50 (8.407)	74.98 (54.936)	192.96 (99.623)	144.27 (55.404)	146.87 (108.493)
Median	4.20	70.12	176.72	170.40	136.19
Range	(0.0; 30.4)	(7.7; 222.5)	(1.9; 416.8)	(80.6; 181.8)	(0.0; 416.8)
Total number of Daratumumab infusions					
N	23	55	156	3	237
Mean (SD)	4.6 (2.41)	8.9 (6.07)	12.2 (6.27)	5.7 (2.31)	10.6 (6.41)
Median	5.0	9.0	11.0	7.0	10.0
Range	(1; 7)	(1; 26)	(1; 26)	(3; 7)	(1; 26)
Relative dose intensity (%)					
N	23	55	156	3	237
>= 95%	21 (91.3%)	53 (96.4%)	145 (92.9%)	3 (100.0%)	222 (93.7%)
< 95%	2 (8.7%)	2 (3.6%)	11 (7.1%)	0	15 (6.3%)

Percentages are calculated with the number of subjects in each group as denominator.

Adverse events

An overview of treatment emergent adverse events (TEAEs) observed in daratumumab monotherapy studies is provided in the tables below:

Table 48: Overview of TEAEs; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Any TEAE	22 (95.7%)	55 (100.0%)	154 (98.7%)	3 (100.0%)	234 (98.7%)
Drug-related	21 (91.3%)	48 (87.3%)	120 (76.9%)	3 (100.0%)	192 (81.0%)
Any serious TEAE	7 (30.4%)	20 (36.4%)	50 (32.1%)	2 (66.7%)	79 (33.3%)
Drug-related	4 (17.4%)	0	15 (9.6%)	1 (33.3%)	20 (8.4%)
Maximum severity of any TEAE					
Grade 1	1 (4.3%)	3 (5.5%)	10 (6.4%)	0	14 (5.9%)
Grade 2	12 (52.2%)	21 (38.2%)	56 (35.9%)	2 (66.7%)	91 (38.4%)
Grade 3	7 (30.4%)	21 (38.2%)	59 (37.8%)	1 (33.3%)	88 (37.1%)
Grade 4	1 (4.3%)	10 (18.2%)	19 (12.2%)	0	30 (12.7%)
Grade 5	1 (4.3%)	0	10 (6.4%)	0	11 (4.6%)
Treatment discontinuation due to TEAE[a]	4 (17.4%)	0	6 (3.8%)	1 (33.3%)	11 (4.6%)
Drug-related	4 (17.4%)	0	0	1 (33.3%)	5 (2.1%)
Death due to TEAE[b]	0	0	3 (1.9%)	0	3 (1.3%)
Drug-related	0	0	0	0	0

Keys: TEAE = treatment-emergent adverse event.
[a]Treatment discontinuation due to adverse event on the end of treatment CRF page.
[b]Death due to adverse event on the death CRF page.
Percentages are calculated with the number of subjects in each group as denominator.

The most common TEAEs are summarized in the table below:

Table 49: Most Common (At least 10%) TEAEs by System Organ Class, Preferred Term and Grade 3/4; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg		8 mg/kg		16 mg/kg		24 mg/kg		Total	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Analysis set: all treated	23		55		156		3		237	
Total number of subjects with TEAEs	22 (95.7%)	8 (34.8%)	55 (100.0%)	31 (56.4%)	154 (98.7%)	87 (55.8%)	3 (100.0%)	1 (33.3%)	234 (98.7%)	127 (53.6%)
MedDRA system organ class/Preferred term										
General disorders and administration site conditions	11 (47.8%)	0	36 (65.5%)	6 (10.9%)	106 (67.9%)	10 (6.4%)	0	0	153 (64.6%)	16 (6.8%)
Fatigue	2 (8.7%)	0	20 (36.4%)	1 (1.8%)	59 (37.8%)	3 (1.9%)	0	0	81 (34.2%)	4 (1.7%)
Pyrexia	8 (34.8%)	0	20 (36.4%)	1 (1.8%)	29 (18.6%)	2 (1.3%)	0	0	57 (24.1%)	3 (1.3%)
Chills	0	0	9 (16.4%)	1 (1.8%)	16 (10.3%)	0	0	0	25 (10.5%)	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	8 (34.8%)	1 (4.3%)	32 (58.2%)	1 (1.8%)	95 (60.9%)	8 (5.1%)	2 (66.7%)	0	137 (57.8%)	10 (4.2%)
Cough	5 (21.7%)	0	12 (21.8%)	0	31 (19.9%)	0	1 (33.3%)	0	49 (20.7%)	0
Nasal congestion	0	0	5 (9.1%)	0	25 (16.0%)	0	1 (33.3%)	0	31 (13.1%)	0
Dyspnoea	1 (4.3%)	0	11 (20.0%)	0	22 (14.1%)	1 (0.6%)	0	0	34 (14.3%)	1 (0.4%)
Musculoskeletal and connective tissue disorders	6 (26.1%)	1 (4.3%)	30 (54.5%)	5 (9.1%)	89 (57.1%)	12 (7.7%)	1 (33.3%)	0	126 (53.2%)	18 (7.6%)
Back pain	1 (4.3%)	0	8 (14.5%)	3 (5.5%)	33 (21.2%)	3 (1.9%)	1 (33.3%)	0	43 (18.1%)	6 (2.5%)
Arthralgia	2 (8.7%)	0	5 (9.1%)	0	25 (16.0%)	0	0	0	32 (13.5%)	0
Pain in extremity	1 (4.3%)	0	1 (1.8%)	0	23 (14.7%)	1 (0.6%)	0	0	25 (10.5%)	1 (0.4%)
Musculoskeletal chest pain	0	0	5 (9.1%)	0	16 (10.3%)	2 (1.3%)	0	0	21 (8.9%)	2 (0.8%)
Gastrointestinal disorders	9 (39.1%)	0	27 (49.1%)	1 (1.8%)	85 (54.5%)	3 (1.9%)	2 (66.7%)	0	123 (51.9%)	4 (1.7%)
Nausea	3 (13.0%)	0	10 (18.2%)	1 (1.8%)	40 (25.6%)	0	0	0	53 (22.4%)	1 (0.4%)
Diarrhoea	2 (8.7%)	0	13 (23.6%)	0	24 (15.4%)	0	1 (33.3%)	0	40 (16.9%)	0
Constipation	1 (4.3%)	0	6 (10.9%)	0	22 (14.1%)	0	0	0	29 (12.2%)	0
Vomiting	1 (4.3%)	0	8 (14.5%)	1 (1.8%)	20 (12.8%)	0	1 (33.3%)	0	30 (12.7%)	1 (0.4%)
Infections and infestations	7 (30.4%)	0	32 (58.2%)	4 (7.3%)	85 (54.5%)	15 (9.6%)	1 (33.3%)	1 (33.3%)	125 (52.7%)	20 (8.4%)
Upper respiratory tract infection	0	0	12 (21.8%)	0	27 (17.3%)	1 (0.6%)	0	0	39 (16.5%)	1 (0.4%)
Nasopharyngitis	2 (8.7%)	0	9 (16.4%)	0	18 (11.5%)	0	1 (33.3%)	0	30 (12.7%)	0
Blood and lymphatic system disorders	9 (39.1%)	2 (8.7%)	21 (38.2%)	16 (29.1%)	76 (48.7%)	53 (34.0%)	0	0	106 (44.7%)	71 (30.0%)
Anaemia	4 (17.4%)	1 (4.3%)	12 (21.8%)	6 (10.9%)	39 (25.0%)	27 (17.3%)	0	0	55 (23.2%)	34 (14.3%)
Neutropenia	1 (4.3%)	1 (4.3%)	3 (5.5%)	1 (1.8%)	34 (21.8%)	19 (12.2%)	0	0	38 (16.0%)	21 (8.9%)
Thrombocytopenia	3 (13.0%)	2 (8.7%)	10 (18.2%)	8 (14.5%)	31 (19.9%)	22 (14.1%)	0	0	44 (18.6%)	32 (13.5%)
Metabolism and nutrition disorders	2 (8.7%)	0	16 (29.1%)	7 (12.7%)	64 (41.0%)	13 (8.3%)	0	0	82 (34.6%)	20 (8.4%)
Decreased appetite	1 (4.3%)	0	5 (9.1%)	0	23 (14.7%)	1 (0.6%)	0	0	29 (12.2%)	1 (0.4%)
Hypercalcaemia	0	0	4 (7.3%)	2 (3.6%)	18 (11.5%)	5 (3.2%)	0	0	22 (9.3%)	7 (3.0%)

Keys: TEAE = treatment-emergent adverse event.
Adverse events are reported using MedDRA version 17.0.
Percentages are calculated with the number of subjects in each group as denominator.

The most commonly reported TEAEs in the 16 mg/kg group (daratumumab monotherapy) were:

- fatigue: 59 subjects (38%)
- nausea: 40 subjects (26%)
- anaemia: 39 subjects (25%)
- neutropenia: 34 subjects (22%)
- back pain: 33 subjects (21%)
- cough and thrombocytopenia: each in 31 subjects (20%)

Adverse Reactions

Table 50: Adverse Drug Reactions in Patients With Multiple Myeloma Treated With Daratumumab 16 mg/kg (Cut-off date 9 January 2015)

MedDRA System Organ Class Adverse Reaction (Preferred Term)	Daratumumab 16 mg/kg N=156 Frequency (%) Any Grade	Grade 3	Grade 4
Injury, poisoning and procedural complications			
Infusion related reaction[a]	51	4	0
General disorders and administration site conditions			
Fatigue	37	2	0
Pyrexia	17	1	0
Musculoskeletal and connective tissue disorders			
Back pain	20	2	0
Arthralgia	16	0	0
Pain in extremity	15	1	0
Musculoskeletal chest pain	10	1	0
Infections and infestations			
Upper respiratory tract infection	17	1	0
Nasopharyngitis	12	0	0
Pneumonia[b]	10	6	0
Gastrointestinal disorders			
Nausea	21	0	0
Diarrhea	15	0	0
Constipation	14	0	0
Blood and lymphatic system disorders			
Anemia	25	17	0
Neutropenia	22	10	3
Thrombocytopenia	20	8	6
Metabolism and nutrition disorders			
Decreased appetite	15	1	0
Respiratory, thoracic and mediastinal disorders			
Cough	14	0	0

[a] Infusion-related reactions include but are not limited to, multiple adverse drug reaction terms: nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnea, nausea (all ≥ 5%), bronchospasm (2.6%), hypertension (1.9%) and hypoxia (1.3%).

[b] Pneumonia also includes the terms streptococcal pneumonia and lobar pneumonia

Table 51: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg (Cut-off date 30 June 2015)

System Organ Class	Adverse reaction	Frequency (All grades)	Incidence (%)	
			All grades	Grade 3-4
Infections and infestations	Pneumonia**	Very common	11	6*
	Upper respiratory tract infection		20	1*
	Nasopharyngitis		15	0
Blood and lymphatic system disorders	Anaemia	Very common	27	17*
	Neutropenia		22	12
	Thrombocytopenia		20	14
	Lymphopenia	Common	6	6*
Metabolism and nutrition disorders	Decreased appetite	Very common	15	1*
Nervous system disorders	Headache	Very common	12	1*
Vascular disorders	Hypertension	Very common	10	4*
Respiratory, thoracic and mediastinal disorders	Cough	Very common	21	0
	Nasal Congestion		17	0
	Dyspnoea		15	1*
Gastrointestinal disorders	Nausea	Very common	27	0
	Diarrhoea		16	1*
	Constipation		15	0
	Vomiting		13	0
Musculoskeletal and connective tissue disorders	Back pain	Very common	23	2*
	Arthralgia		17	0
	Pain in extremity		15	1*
	Musculoskeletal chest pain		12	1*
General disorders and administration site conditions	Fatigue	Very common	39	2*
	Pyrexia		21	1*
	Chills		10	0

Injury, poisoning and procedural complications	Infusion-related reaction[a]	Very common	48	3*

* No grade 4

** Pneumonia also includes the terms pneumonia streptococcal and lobar pneumonia

[a] Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Adverse events of special interest

Infusion-related reactions

Infusion-related reactions include but are not limited to the following multiple adverse reaction terms: nasal congestion, cough, chills, allergic rhinitis, throat irritation, dyspnoea, nausea (all ⩾ 5%), bronchospasm (2.6%), hypertension (1.3%) and hypoxia (1.3%). The median time to onset of a reaction was 1.5 hours (range: 0.02 to 9.3 hours). Median durations of infusion for the first, second and subsequent infusions were 7.0, 4.6 and 3.4 hours respectively (SmPC section 4.8).

Table 52: Infusion Related Reactions by System Organ Class, Preferred Term and Toxicity Grade; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg		8 mg/kg		16 mg/kg		24 mg/kg		Total	
	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]
Analysis set: all treated	23		55		156		3		237	
Total number of subjects with infusion related reactions	15 (65.2%)	2 (8.7%)	30 (54.5%)	2 (3.6%)	80 (51.3%)	6 (3.8%)	3 (100.0%)	0	128 (54.0%)	10 (4.2%)
MedDRA system organ class/Preferred term										
Respiratory, thoracic and mediastinal disorders	3 (13.0%)	1 (4.3%)	24 (43.6%)	0	55 (35.3%)	4 (2.6%)	2 (66.7%)	0	84 (35.4%)	5 (2.1%)
Nasal congestion	0	0	3 (5.5%)	0	17 (10.9%)	0	1 (33.3%)	0	21 (8.9%)	0
Cough	0	0	6 (10.9%)	0	12 (7.7%)	0	1 (33.3%)	0	19 (8.0%)	0
Rhinitis allergic	1 (4.3%)	0	12 (21.8%)	0	10 (6.4%)	0	0	0	23 (9.7%)	0
Throat irritation	0	0	0	0	9 (5.8%)	0	0	0	9 (3.8%)	0
Dyspnoea	1 (4.3%)	0	3 (5.5%)	0	8 (5.1%)	1 (0.6%)	0	0	12 (5.1%)	1 (0.4%)
Bronchospasm	1 (4.3%)	1 (4.3%)	1 (1.8%)	0	4 (2.6%)	2 (1.3%)	1 (33.3%)	0	7 (3.0%)	3 (1.3%)
Sneezing	0	0	0	0	3 (1.9%)	0	0	0	3 (1.3%)	0
Throat tightness	0	0	0	0	3 (1.9%)	0	0	0	3 (1.3%)	0
Hypoxia	0	0	0	0	2 (1.3%)	1 (0.6%)	0	0	2 (0.8%)	1 (0.4%)
Oropharyngeal pain	0	0	0	0	2 (1.3%)	0	0	0	2 (0.8%)	0
Wheezing	0	0	1 (1.8%)	0	2 (1.3%)	0	0	0	3 (1.3%)	0
Allergic cough	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Laryngeal oedema	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Laryngitis allergic	0	0	3 (5.5%)	0	1 (0.6%)	0	0	0	4 (1.7%)	0
Nasal disorder	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Dysphonia	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0
General disorders and administration site conditions	9 (39.1%)	0	9 (16.4%)	1 (1.8%)	20 (12.8%)	0	0	0	38 (16.0%)	1 (0.4%)
Chills	0	0	5 (9.1%)	1 (1.8%)	11 (7.1%)	0	0	0	16 (6.8%)	1 (0.4%)
Pyrexia	6 (26.1%)	0	4 (7.3%)	0	5 (3.2%)	0	0	0	15 (6.3%)	0
Chest discomfort	0	0	2 (3.6%)	0	1 (0.6%)	0	0	0	3 (1.3%)	0
Chest pain	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Fatigue	2 (8.7%)	0	0	0	1 (0.6%)	0	0	0	3 (1.3%)	0
Influenza like illness	3 (13.0%)	0	0	0	1 (0.6%)	0	0	0	4 (1.7%)	0
Infusion site bruising	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Pain	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Non-cardiac chest pain	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0

	<=4 mg/kg		8 mg/kg		16 mg/kg		24 mg/kg		Total	
	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]
Gastrointestinal disorders	3 (13.0%)	0	7 (12.7%)	0	11 (7.1%)	0	1 (33.3%)	0	22 (9.3%)	0
Nausea	2 (8.7%)	0	3 (5.5%)	0	8 (5.1%)	0	0	0	13 (5.5%)	0
Vomiting	0	0	5 (9.1%)	0	7 (4.5%)	0	1 (33.3%)	0	13 (5.5%)	0
Abdominal pain upper	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Diarrhoea	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Paraesthesia oral	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Dry mouth	1 (4.3%)	0	0	0	0	0	0	0	1 (0.4%)	0
Dyspepsia	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0
Lip oedema	1 (4.3%)	0	0	0	0	0	0	0	1 (0.4%)	0
Skin and subcutaneous tissue disorders	1 (4.3%)	0	3 (5.5%)	0	6 (3.8%)	0	0	0	10 (4.2%)	0
Pruritus	1 (4.3%)	0	1 (1.8%)	0	3 (1.9%)	0	0	0	5 (2.1%)	0
Rash	1 (4.3%)	0	1 (1.8%)	0	1 (0.6%)	0	0	0	3 (1.3%)	0
Rash macular	0	0	1 (1.8%)	0	1 (0.6%)	0	0	0	2 (0.8%)	0
Urticaria	0	0	1 (1.8%)	0	1 (0.6%)	0	0	0	2 (0.8%)	0
Hyperhidrosis	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0
Eye disorders	0	0	0	0	5 (3.2%)	0	0	0	5 (2.1%)	0
Eye pruritus	0	0	0	0	2 (1.3%)	0	0	0	2 (0.8%)	0
Vision blurred	0	0	0	0	2 (1.3%)	0	0	0	2 (0.8%)	0
Cataract	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Musculoskeletal and connective tissue disorders	0	0	2 (3.6%)	0	4 (2.6%)	0	0	0	6 (2.5%)	0
Back pain	0	0	0	0	2 (1.3%)	0	0	0	2 (0.8%)	0
Groin pain	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Myalgia	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Flank pain	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0
Musculoskeletal pain	0	0	1 (1.8%)	0	0	0	0	0	1 (0.4%)	0
Vascular disorders	4 (17.4%)	0	4 (7.3%)	1 (1.8%)	4 (2.6%)	2 (1.3%)	0	0	12 (5.1%)	3 (1.3%)
Hypertension	1 (4.3%)	0	2 (3.6%)	1 (1.8%)	3 (1.9%)	2 (1.3%)	0	0	6 (2.5%)	3 (1.3%)
Flushing	2 (8.7%)	0	1 (1.8%)	0	1 (0.6%)	0	0	0	4 (1.7%)	0
Hypotension	2 (8.7%)	0	1 (1.8%)	0	0	0	0	0	3 (1.3%)	0
Blood and lymphatic system disorders	0	0	0	0	3 (1.9%)	1 (0.6%)	0	0	3 (1.3%)	1 (0.4%)
Anaemia	0	0	0	0	2 (1.3%)	1 (0.6%)	0	0	2 (0.8%)	1 (0.4%)
Red blood cell agglutination	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Cardiac disorders	3 (13.0%)	0	1 (1.8%)	0	3 (1.9%)	0	0	0	7 (3.0%)	0
Palpitations	1 (4.3%)	0	0	0	1 (0.6%)	0	0	0	2 (0.8%)	0
Sinus tachycardia	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Tachycardia	2 (8.7%)	0	1 (1.8%)	0	1 (0.6%)	0	0	0	4 (1.7%)	0

	<=4 mg/kg		8 mg/kg		16 mg/kg		24 mg/kg		Total	
	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]	Any Grade	Grade 3 or 4[a]
Nervous system disorders	3 (13.0%)	0	1 (1.8%)	0	3 (1.9%)	0	0	0	7 (3.0%)	0
Headache	1 (4.3%)	0	0	0	3 (1.9%)	0	0	0	4 (1.7%)	0
Dizziness	2 (8.7%)	0	1 (1.8%)	0	0	0	0	0	3 (1.3%)	0
Psychiatric disorders	0	0	0	0	3 (1.9%)	0	0	0	3 (1.3%)	0
Anxiety	0	0	0	0	2 (1.3%)	0	0	0	2 (0.8%)	0
Delirium	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Immune system disorders	3 (13.0%)	1 (4.3%)	1 (1.8%)	1 (1.8%)	2 (1.3%)	0	0	0	6 (2.5%)	2 (0.8%)
Cytokine release syndrome	1 (4.3%)	0	1 (1.8%)	1 (1.8%)	1 (0.6%)	0	0	0	3 (1.3%)	1 (0.4%)
Seasonal allergy	0	0	0	0	1 (0.6%)	0	0	0	1 (0.4%)	0
Hypersensitivity	2 (8.7%)	1 (4.3%)	0	0	0	0	0	0	2 (0.8%)	1 (0.4%)
Infections and infestations	0	0	0	0	0	0	1 (33.3%)	0	1 (0.4%)	0
Nasopharyngitis	0	0	0	0	0	0	1 (33.3%)	0	1 (0.4%)	0

[a] Grade 3 only; no Grade 4 infusion-related reactions were reported.
Adverse events are reported using MedDRA version 17.0.
Percentages are calculated with the number of subjects in each group as denominator.

Table 53: Time to Onset of Infusion Related Reaction; All Treated Analysis Set - 16 mg/kg Group (Studies: MMY2002, GEN501 and MMY1002)

		Event Onset		
	Total	1st Infusion	2nd Infusion	Subsequent Infusions
Analysis set: all treated	156			
Total number of subjects with event of infusion related reactions	80	73 (91.3%)	9 (11.3%)	10 (12.5%)
Total number of infusion related reactions	165	135 (81.8%)	13 (7.9%)	17 (10.3%)
Time to onset of infusion related reactions (minutes)				
N[a]	144	128	9	7
Mean (SD)	114.76 (109.128)	102.09 (82.899)	132.11 (93.399)	324.00 (267.927)
Median	90.00	90.00	100.00	495.00[b]
Range	(1.0; 557.0)	(1.0; 540.0)	(60.0; 363.0)	(10.0; 557.0)[b]

[a] Infusion related reactions with no onset time are excluded.

[b] One subject from GEN 501 Part 1 reported Grade 1 fever for 4 consecutive infusions (4th to 7th infusions) with onset times of 495, 544, 555, and 557 minutes after infusion.

Note: Percentage of the number of infusion related reactions in each event onset sub-group are calculated with the number of 'Total' column in each group as denominator.

Note: Time to onset of infusion related reactions in minutes are calculated as the start of the infusion related reaction minus the start of the latest infusion which is prior to this event.

Table 54: Duration of Daratumumab Infusions; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Duration of infusions (hours)					
First infusion					
N	23	55	156	3	237
Mean (SD)	6.20 (2.163)	7.46 (2.662)	7.50 (1.531)	9.65 (1.186)	7.39 (1.955)
Median	6.00	6.92	7.00	9.98	7.00
Range[a]	(-2.1; 9.9)	(3.9; 23.5)	(1.5; 14.3)	(8.3; 10.6)	(-2.1; 23.5)
Second infusion					
N	19	51	149	3	222
Mean (SD)	6.98 (2.050)	4.82 (1.451)	5.40 (1.411)	7.78 (0.347)	5.44 (1.587)
Median	6.00	4.17	4.55	7.67	4.54
Range	(5.6; 13.9)	(2.4; 8.8)	(2.7; 8.5)	(7.5; 8.2)	(2.4; 13.9)
All subsequent infusions					
N	64	383	1599	11	2057
Mean (SD)	6.43 (0.841)	3.64 (0.861)	3.52 (0.551)	7.57 (0.202)	3.66 (0.855)
Median	6.00	3.42	3.40	7.50	3.42
Range	(5.4; 8.3)	(2.8; 8.4)	(1.1; 8.3)	(7.2; 7.9)	(1.1; 8.4)

Note: Duration of infusion includes both actual infusion time and interruption time, if any.

[a] One subject had a data issue where infusion end time was earlier than start time for one infusion. Another subject from Study MMY2002 had an infusion stopped due to an IRR of exacerbated hypertension. The infusion was not restarted until the next morning, thus resulting in a prolonged infusion duration of 23.5 hours.

Of particular clinical concern were IRRs of bronchospasm, which are summarized in the next table:

Table 55: Summary of Subjects who Experienced Bronchospasm IRRs (Studies: MMY2002 and GEN501)

Past Medical History	Treatment Group	Study Day of TEAE	Serious/ Toxicity Grade	Drug Relationship	Action Taken With Study Drug	Pre-Infusion Steroids Y/N	Post-Infusion Steroids Y/N	Start of IRR	Dose Resumed after IRR and Completed?	Subject Received Future Doses?
No h/o of airway disease	16mg/kg	1	N/2	Very likely	Interrupted	Y	Y	60 minutes after start of first dose	Y	Y
No h/o of airway disease	16 mg/kg	1	N/3	Very likely	Interrupted	Y	Y	90 minutes after start of first dose	Y	Y
h/o Grade 1 COPD and Grade 1 asthma	16 mg/kg	1	N/3	Very likely	Interrupted	Y	Y	90 minutes after start of first dose	N	Y
No h/o of airway disease	16 mg/kg	1	N/2	Very likely	Interrupted	Y	Y	90 minutes after start of first dose	N	Y
COPD at study entry	2 mg/kg	2	N/2	Possibly/probably	Interrupted	Y	Y[a]	Approximately 180 minutes after start of first dose	Y	Y
		23	N/2	Possibly/probably	Withdrawn	Y	Y[a]	Approximately 210 minutes after start of first dose	Y	N
		25	Y/3	Possibly/probably	Withdrawn	Y	Y[a]	2 days after d/c from study drug	N/A	N/A
h/o of pneumonia	8 mg/kg	2	N/1	Possibly/probably	Interrupted	Y	Y	45 minutes after the start of 1st full dose	Y	N
h/o asthma at study entry	24 mg/kg	24	Y/2	Possibly/probably	Dose not changed	Y	Y	Approximately 24 hours after the 2nd full dose	N/A	Y
		31	N/2	Possibly/probably	Withdrawn	Y	Y	Approximately 24 hours after the 3rd full dose was administered	N/A	N

COPD=chronic obstructive pulmonary disease; F=female; h/o=history of; IRR=infusion-related reaction; M=male; min=minute(s); N=no; N/A=not applicable; SAE=serious adverse event; TEAE=treatment-emergent adverse event; Y=yes

[a] post-infusion steroids were not mandated as prophylaxis per protocol, but given as treatment for the TEAE.

[b] Subject was assigned to Schedule A, 500 mL for first infusion.

Source: data on file

Infections and Infestations

Table 56: Exposure-Adjusted Incidence Rate of Infections / Infestations; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Total patient-years of treatment	2.44	16.92	58.10	0.42	77.88
Number of adverse events of infection	8	67	152	4	231
Events per patient years	3.27	3.96	2.62	9.55	2.97
Number of adverse events of infection with Grade 3 or 4	0	5	21	2	28
Events per patient years	0	0.30	0.36	4.77	0.36
Number of serious adverse events of infection	0	8	24	2	34
Events per patient years	0	0.47	0.41	4.77	0.44
Number of adverse events of infection leading to treatment discontinuation	0	0	2	0	2
Events per patient years	0	0	0.03	0	0.03
Number of adverse events of infection leading to dose interruption or prolongation	0	0	0	0	0
Events per patient years	0	0	0	0	0
Number of adverse events of infection leading to death	0	0	1	0	1
Events per patient years	0	0	0.02	0	0.01
Number of adverse events of infection leading to death reasonably related to daratumumab	0	0	0	0	0
Events per patient years	0	0	0	0	0

Second Primary Malignancies

One subject on daratumumab monotherapy developed a skin cancer (basal cell carcinoma) during the course of treatment (Study GEN501).

One subject on daratumumab monotherapy was diagnosed with adenocarcinoma with metastases (origin most likely the colon) and was withdrawn from the study (Study GEN501, Part 2).

One subject in combination therapy with daratumumab was reported to have gastric adenocarcinoma (Study GEN503).

Serious adverse event / deaths / other significant events

Serious adverse event

In the 16 mg/kg monotherapy group, 50 subjects (32%) experienced treatment-emergent SAEs. The most common were pneumonia in 9 subjects (6%), general physical health deterioration, pyrexia (each in 5 subjects [3%]), and hypercalcemia in 4 subjects (3%). All other SAEs occurred in 3 or fewer subjects (Table 65).

Table 57: Most Common (At Least 1%) Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Total number of subjects with serious TEAEs	7 (30.4%)	20 (36.4%)	50 (32.1%)	2 (66.7%)	79 (33.3%)
MedDRA system organ class / Preferred term					
Infections and infestations	0	6 (10.9%)	19 (12.2%)	1 (33.3%)	26 (11.0%)
Pneumonia	0	3 (5.5%)	9 (5.8%)	0	12 (5.1%)
Herpes zoster	0	0	2 (1.3%)	0	2 (0.8%)
Lobar pneumonia	0	0	2 (1.3%)	0	2 (0.8%)
Varicella	0	0	2 (1.3%)	0	2 (0.8%)
General disorders and administration site conditions	1 (4.3%)	4 (7.3%)	13 (8.3%)	0	18 (7.6%)
General physical health deterioration	0	1 (1.8%)	5 (3.2%)	0	6 (2.5%)
Pyrexia	1 (4.3%)	2 (3.6%)	5 (3.2%)	0	8 (3.4%)
Metabolism and nutrition disorders	0	1 (1.8%)	6 (3.8%)	0	7 (3.0%)
Hypercalcaemia	0	0	4 (2.6%)	0	4 (1.7%)
Musculoskeletal and connective tissue disorders	0	2 (3.6%)	6 (3.8%)	0	8 (3.4%)
Musculoskeletal chest pain	0	0	2 (1.3%)	0	2 (0.8%)
Investigations	1 (4.3%)	1 (1.8%)	4 (2.6%)	0	6 (2.5%)
Crossmatch incompatible	0	0	3 (1.9%)	0	3 (1.3%)
Blood and lymphatic system disorders	1 (4.3%)	3 (5.5%)	3 (1.9%)	0	7 (3.0%)
Anaemia	1 (4.3%)	1 (1.8%)	2 (1.3%)	0	4 (1.7%)
Injury, poisoning and procedural complications	1 (4.3%)	1 (1.8%)	3 (1.9%)	0	5 (2.1%)
Spinal compression fracture	1 (4.3%)	0	2 (1.3%)	0	3 (1.3%)
Nervous system disorders	0	2 (3.6%)	3 (1.9%)	0	5 (2.1%)
Headache	0	0	2 (1.3%)	0	2 (0.8%)

Keys: TEAE = treatment-emergent adverse event.
Adverse events are reported using MedDRA version 17.0.
Percentages are calculated with the number of subjects in each group as denominator.

Deaths

Fifteen deaths occurred within 30 days of last dose (Table 66).

In the 16 mg/kg monotherapy group, 11 subjects died within 30 days of the last dose of study drug due to progressive disease, and 3 subjects died due to TEAEs not considered related to daratumumab (Table 7). One additional subject (in the 8 mg/kg group) died within 30 days of the last dose of study drug due to progressive disease (Table 10).

In the total population, 15 subjects (6%) died within 30 days of the last dose of study drug. No TEAE with a fatal outcome (in 3 subjects [2%]) was considered by the investigator to be related to daratumumab

(cardiorespiratory arrest due to H1N1 influenza, general physical health deterioration secondary to aspiration pneumonia, and pneumonia).

Across all dose groups, 11 subjects (5%) experienced a Grade 5 TEAE. Ten of these were in the 16 mg/kg group; these were general physical health deterioration in 5 subjects; respiratory failure, pneumonia, cardiorespiratory arrest, hepatic failure, and hypercalcemia (each in 1 subject).

A total of 56 deaths were recorded (24% of the integrated safety population); of these, 46/56 deaths (82%) were due to progression of disease.

Three subjects in the 16 mg/kg group who died due to a TEAE. One subject from Study MMY2002 died of cardiorespiratory arrest due to H1N1 influenza. One subject from Study MMY2002 died due to general physical health deterioration secondary to aspiration pneumonia, and a second subject from Study GEN501 (Part 2) died due to pneumonia. None of the fatal TEAEs were considered related to study drug.

Table 58: Death and Primary Causes of Death; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg	8 mg/kg	16 mg/kg	24 mg/kg	Total
Analysis set: all treated	23	55	156	3	237
Total number of subjects died	1 (4.3%)	15 (27.3%)	40 (25.6%)	0	56 (23.6%)
Adverse event	0	0	3 (1.9%)	0	3 (1.3%)
Progressive disease	1 (4.3%)	10 (18.2%)	35 (22.4%)	0	46 (19.4%)
Other	0	5 (9.1%)	2 (1.3%)	0	7 (3.0%)
Death within 30 days of last dose	0	1 (1.8%)	14 (9.0%)	0	15 (6.3%)
Adverse event	0	0	3 (1.9%)	0	3 (1.3%)
Progressive disease	0	1 (1.8%)	11 (7.1%)	0	12 (5.1%)
Other	0	0	0	0	0

Percentages are calculated with the number of subjects in each group as denominator.

Laboratory findings

Anaemia and Thrombocytopenia

Anaemia and thrombocytopenia are commonly found in patients with Multiple Myeloma; anaemia being included in the CRAB-criteria indicating treatment-requiring Multiple Myeloma. In the 16 mg/kg group of Study MMY2002, 3% of responders had Grade 3 or 4 AEs of anaemia compared to 32% of non-responders. Likewise, in the 16 mg/kg group of Study MMY2002, 7% of responders had Grade 3 or 4 AEs of thrombocytopenia compared to 24% of non-responders.

Leukopenia/Neutropenia

In the 16 mg/kg group, of 154 of subjects with Grade 0-2 leukopenia at baseline, 26% (17%) worsened to Grade 3 and 3 (2%) worsened to Grade 4 during treatment. This pattern was similar to that observed across groups.

In the 16 mg/kg group, of 155 subjects with Grade 0-2 neutropenia at baseline, 25 (16%) worsened to Grade 3 and 6 (4%) worsened to Grade 4 during treatment. Treatment-emergent AEs of neutropenia were reported in 34 (22%) of these subjects, 19 (12%) of which were considered Grade 3-4. This was slightly higher than across dosing groups where treatment-emergent AEs of neutropenia were reported in 38 (16%), 21 (9%) of which were considered Grade 3-4.

No statistically significant trend in the TEAE rate of neutropenia or of neutropenic fever was found with increasing exposure, and no patients discontinued daratumumab due to neutropenia in any of the treatment.

Lymphopenia

In the 16 mg/kg group, of 138 subjects with baseline Grade 0-2 lymphocyte count, 46 (33%) worsened to Grade 3 and 6 (4%) worsened to Grade 4 during treatment. This was similar to the findings across dosing groups.

Natural Killer Cells

Natural Killer Cells counts decreased or remained low in the majority of subjects treated in the daratumumab monotherapy studies. the incidence of TEAEs of infection and infestation did not increase over time (ie, the incidence was 50% during the first 6 months of treatment and 38% after 6 months of treatment.

In the 16 mg/kg group, of 111 subjects with normal NK cell counts at baseline, 108 were low at some time during the study, and 3 remained normal. All of the subjects with low or high NK cells at baseline had low NK cells at some time during the study.

In the total population, 137 of 143 subjects with normal NK cell counts at baseline were low at some time during the study, and 6 remained normal. All of the subjects with low or high NK cell counts at baseline had low NK cell counts during the study.

Chemistry

Chemistry laboratory abnormalities generally occurred with a low incidence, most were grade 1-2 and most were related to underlying Multiple Myeloma. Grade 3-4 changes were infrequent. Across dosing groups, the most common Grade 3-4 chemistry laboratory abnormalities were hypercalcemia (15 subjects (6%), Grade 4 in 7 subjects), and hyponatremia (13 subjects (6%), Grade 4 in 1 subject).

Electrocardiogram Assessment

The clinical and pharmacokinetic/pharmacodynamic data demonstrate that daratumumab does not cause clinically relevant QT prolongation. There were no subjects with QTcF values >500 ms or changes from baseline of >60 ms, and no TEAE of cardiac arrhythmia associated with QT prolongation was reported.

In Study GEN501 Part 1, no new QTcF above 500 msec, no change from baseline >60 msec, and no TEAEs of QT prolongation were reported at doses at 2 mg/kg or higher. No subject had an abnormal U wave or a new QTcF >500 ms. No subject had a >60 ms change from baseline for QTcF. In Study GEN501 Part 2, no subject had an abnormal, clinically significant ECG, based on investigator's overall interpretation, at baseline or at any timepoint during treatment. Based on central review of ECG data, no subject had a QTcF >500 ms or a >60 ms change from baseline. No TEAEs of QT prolongation were reported.

In Study MMY1002, 12-lead triplicate ECGs were digitally recorded at the sites and then transmitted to a central laboratory for measurement of cardiac intervals and morphologic assessment by a central cardiologist. There were no clinically significant changes in ECG data observed in either the 8 mg/kg or 16 mg/kg group during the study (See discussion on clinical pharmacology). Based on central ECG review, no subject had a QTcF value >500 msec or an increase of >60 msec from baseline. No TEAEs of QT prolongation were reported.

Haemolysis Analysis

No subjects in the 16 mg/kg group experienced TEAEs of hemolysis.

In Study GEN501, free haemoglobin, haptoglobin, lactic acid dehydrogenase (LDH), total bilirubin, and haemoglobin levels were performed and analysed at a central laboratory to evaluate haemolysis. In the 32 subjects in Part 1, 3 subjects had TEAEs of haemolysis, 5 subjects had TEAEs of free haemoglobin present, and 1 subject had a TEAE of haptoglobin decreased; all of which were reported in subjects receiving ≤1 mg/kg of daratumumab. All events were Grade 1, events (with the exception of a Grade 2

free haemoglobin present) that resolved; and no event resulted in clinically meaningful decreases in haemoglobin (>1 g/dL decrease in haemoglobin during a daratumumab dosing window pre-dose to 12 hours post dose). One subject had only a decrease in haptoglobin without a concomitant increase in free haemoglobin or elevation of LDH, and 2 subjects had elevations of free haemoglobin without concomitant decreases in haptoglobin or elevations of LDH. Analysis of all laboratory values of free haemoglobin, haptoglobin, LDH, total bilirubin, and haemoglobin in all subjects in Study GEN501 Part 1 showed no consistent pattern of haemolysis.

Direct and Indirect Coomb's Test

The binding of daratumumab to CD38 on RBCs triggers a positive readout on indirect Coombs testing, which interferes with the ability to detect red cell alloantibodies. CD38 is expressed at very low levels on erythrocytes. Data indicate that daratumumab interferes with indirect Coombs testing and will make complete blood typing difficult for subjects receiving treatment.

Transfusion Usage and Red Blood Cell Transfusion-related Reactions

In the 16 mg/kg group, 48 subjects received 208 transfusions; 29% of subjects received RBC transfusions. This was similar to the incidence in the total population; 65 subjects received 270 transfusions (24% of subjects received RBC transfusions). A summary of blood transfusions is presented in Table 67. No TEAEs related to RBC transfusions were reported.

Table 59: Transfusions During Treatment; All Treated Analysis Set (Studies: MMY2002, GEN501 and MMY1002)

	<=4 mg/kg		8 mg/kg		16 mg/kg		24 mg/kg		Total	
	Number of Transfusions	Number(%) of Subjects	Number of Transfusions	Number(%) of Subjects	Number of Transfusions	Number(%) of Subjects	Number of Transfusions	Number(%) of Subjects	Number of Transfusions	Number(%) of Subjects
Analysis set: all treated		23		55		156		3		237
Transfusions during treatment	5	3 (13.0%)	55	13 (23.6%)	208	48 (30.8%)	2	1 (33.3%)	270	65 (27.4%)
Type of Transfusion										
Red Blood Cells[a]	5	3 (13.0%)	28	8 (14.5%)	134	45 (28.8%)	2	1 (33.3%)	169	57 (24.1%)
Platelets	0	0	26	7 (12.7%)	73	15 (9.6%)	0	0	99	22 (9.3%)
Blood, Whole	0	0	1	1 (1.8%)	1	1 (0.6%)	0	0	2	2 (0.8%)

[a]Red blood cells may include concentrated or packed RBC and erythrocytes.
Percentages are calculated with the number of subjects in each group as denominator.

Safety in special populations

Age

Table 60: Treatment-emergent Adverse Events By Age Group; All Treated Analysis Set - 16 mg/kg (Studies: MMY2002, GEN501 and MMY1002)

MedDRA Terms Number (percentage)	Age <65 86 (55.1%)	Age 65-74 54 (34.6%)	Age 75-84 16 (10.3%)	Age ≥85 0 (0%)
Subjects with any TEAEs	86 (100%)	53 (98.1%)	16 (100%)	-
Subjects with serious TEAEs	27 (31.4%)	20 (37.0%)	4 (25.0%)	-
- Fatal	6 (7.0%)	2 (3.7%)	2 (12.5%)	-
- Hospitalization/prolong existing hospitalization	21 (24.4%)	16 (29.6%)	3 (18.8%)	-
- Life-threatening	6 (7.0	%) 5 (9.3%)	3 (18.8%)	-
- Disability/incapacity	0	0	0	-
- Congenital anomaly or birth defect	0	0	0	
- Other (medically significant)	7 (8.1%)	3 (5.6%)	0	-
Subjects with AEs leading to treatment discontinuation	3 (3.5%)	1 (1.9%)	2 (12.5%)	-
Psychiatric disorders	13 (15.1%)	12 (22.2%)	4 (25.0%)	-
Nervous system disorders	24 (27.9%)	23 (42.6%)	9 (56.3%)	-
Accidents and injuries	14 (16.3%)	11 (20.4%)	3 (18.8%)	-
Cardiac disorders	7 (8.1%)	4 (7.4%)	2 (12.5%)	-
Subjects with vascular disorders	11 (12.8%)	14 (25.9%)	4 (25.0%	-
Cerebrovascular disorders	1 (1.2%)	0	0	-
Infections and infestations	51 (59.3%)	30 (55.6%)	11 (68.8%)	-
Anticholinergic syndrome	30 (34.9%)	22 (40.7%)	9 (56.3%)	-
Subjects with general physical health deterioration	3 (3.5%)	1 (1.9%)	1 (6.3%)	-
Subjects with sum of hypotension, fall, black outs (or unconsciousness), syncope, dizziness, ataxia, fracture	9 (10.5%)	12 (22.2%)	3 (18.8%)	-

Sex

In the 16 mg/kg group, 84 (54%) of the subjects were male while 72 (46%) were female. No differences in the rate of AEs between males and females were observed.

Race

There was an overrepresentation of White study participants (76%) in the 16 mg/kg group. No differences in the rate of AEs between races were observed.

Baseline Renal Function

In the 16 mg/kg group, 95 (61%) of subjects had baseline CrCl ≥60 mL/min, 56 (36%) had baseline CrCl between 30 to <60 mL/min while 5 (3%) had baseline CrCl <30 mL/min. In the latter group there were too few subjects to make meaningful comparisons. In the two former groups, the incidences of AEs were similar.

Baseline Hepatic Function

In the 16 mg/kg group, 134 (86%) subjects had normal hepatic function at baseline while 21 (13%) had mildly impaired hepatic function at baseline. Overall, the incidence of AEs by baseline hepatic function was similar to the total 16 mg/kg group. When comparing subjects with mildly impaired hepatic function with all subjects, there was a higher incidence of SAEs (9 subjects (43%) vs. 50 subjects (32%)), Grade

≥3 AEs (15 subjects (71%) vs. 88 subjects (56%)) and AEs leading to treatment discontinuation (4 subjects (19%) vs. 6 subjects (4%)).

Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with daratumumab (see discussion on clinical safety).

Discontinuation due to adverse events

In the 16 mg/kg group in the monotherapy studies, a total of 6 patients discontinued treatment due to AEs. None of these AEs were related to daratumumab as determined by the investigator. Across all treatment groups, a total of 11 subjects discontinued due to AEs. Five were considered drug related. Four of the 5 occurred in the ≤4 mg/kg group and 1 occurred in the 24 mg/kg group. Two of the patients in the ≤4 mg/kg group who discontinued due to AEs did not receive prophylactic post-infusion steroids, as the protocol did not call for it at the time.

In one of the 5 patients who discontinued treatment due to AEs this was due to hepatic function abnormal. The remaining 4 patients discontinued due to infusion related reactions.

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

Safety data from a total of 331 subjects treated with daratumumab (237 as monotherapy, 94 as part of a combination therapy regimen) is considered sufficient to evaluate the safety profile of daratumumab under conditional approval.

The proposed treatment dose applied for (16 mg/kg) corresponds to the treatment dose of the majority of subjects included in the clinical studies (240/331). Long term data (exposure ⩾6 months) has been obtained from 52 subjects however, there is limited data on the long term use >2 years of daratumumab. Long term extension trials are ongoing, and will provide additional safety information when completed. Long term use (>2 years) is included in the RMP under missing information.

The majority of subjects (99%) in the 3 pivotal studies experienced AEs. Most notably, infusion related reactions were common which also justifies the recommendation of both pre- and post-infusion steroid treatment. Other frequently occurring AEs were fatigue, nausea, anaemia, neutropenia, back pain, cough and thrombocytopenia.

In the 16 mg/kg group, the most common infections were upper respiratory tract infections, nasopharyngitis, pneumonia and sinusitis. Infections were most frequent within the first 6 months of treatment. The most common serious infection was pneumonia. No subjects had febrile neutropenia. The overall incidence of infections and infestations was similar to the total population and consistent with underlying Multiple Myeloma. Of note, the incidence of opportunistic infections was low (2% per specified opportunistic infection). No AEs of reactivated HBV or HCV were reported. Infections have been classified as an important potential risk in the RMP.

The most frequently reported adverse reactions were IRRs (48%); see section 4.4. Other frequently reported adverse reactions (⩾ 20%) were fatigue (39%), pyrexia (21%), cough (21%), nausea (27%), back pain (23%), upper respiratory tract infection (20%), anaemia (27%), neutropenia (22%) and thrombocytopenia (20%) (SmPC section 4.8).

Infusion-related reactions (IRRs) were reported in approximately half of all patients treated with daratumumab. Monitor such patients throughout the infusion and the post-infusion period. The majority (95%) of IRRs occurred at the first infusion. Five percent of all patients had an IRR at more than one infusion. Symptoms predominantly included (⩾5%) nasal congestion, chills, cough, allergic rhinitis, throat irritation, dyspnoea, and nausea, and were mild to moderate in severity. Severe IRRs (3%) including bronchospasm (1.3%), hypertension (0.6%), and hypoxia (0.6%) were also reported (SmPC section 4.4).

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with daratumumab. Daratumumab infusion should be interrupted for IRRs of any severity. Medical management/supportive treatment for IRRs should be instituted as needed. The infusion rate should be reduced when re-starting the infusion. For the prevention of delayed IRRs, oral corticosteroids should be administered to all patients the first and second day after all infusions. Additionally the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of obstructive pulmonary disorder to manage respiratory complications should they occur (SmPC sections 4.2 and 4.8). Infusion Related Reactions have been classified as an important identified risk in the RMP.

In study MMY1002, all nine subjects experienced a positive result in indirect Coomb's Test after treatment with daratumumab. Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted. Patients should be typed and screened prior to starting daratumumab treatment (SmPC section 4.4).

However, there was no reported interference with the clinical decision to administer blood transfusions. Moreover, no AEs were reported in relation to blood transfusions.

In the event of a planned transfusion blood transfusion centres should be notified of this interference with indirect antiglobulin tests. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices (SmPC sections 4.4 and 4.5).

An additional risk minimisation measure is considered to be needed to address this safety concern. To make HCPs and Blood banks aware of the risk associated with blood typing, educational materials will be distributed that include an HCP and blood bank brochure and a patient alert card. Survey tools will be used to measure (and increase) the awareness of the risk of interference of blood typing associated with daratumumab. Final results will be presented in the next PSUR/PBRER after the survey has been concluded (see RMP).

Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs (SmPC section 4.5). Interference for blood typing (minor antigen) (Positive Indirect Coombs' test) has been classified as an important identified risk in the RMP.

Daratumumab targets CD38 which is expressed on NK cells. This is evidenced by an expected decrease in the number of NK cells. However, this was not accompanied by an overall increase in infections or infestations and infections did not become more frequent with time on treatment. Prolonged decrease in NK cells has been classified as an important potential risk in the RMP.

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data (SmPC section 4.8). Intravascular haemolysis has been classified as an important potential risk in the RMP.

The immunogenicity of daratumumab has been evaluated in 2 monotherapy daratumumab studies (GEN501 and MMY2002) using validated Charles River ECLIA methods. Limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab cannot be ruled out. Therefore, the Applicant will develop a new method for detecting ADAs (See RMP). Immunogenicity has been classified as an important potential risk in the RMP however until further information are available, the following text is included in section 5.1 of the SmPC: ‘‘Patients (n = 199) were evaluated for anti -therapeutic antibody responses to daratumumab at multiple time points during treatment and up to 8 weeks following the end of treatment. Following the start of daratumumab treatment, none of the patients tested positive for anti-daratumumab antibodies. However, the employed assay has limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab. Therefore, the incidence of antibody development might not have been reliably determined”.

Among AEs of higher grades, haematologic AEs were common, but no clear dose-dependency was noted for grade 5 TEAEs. In the 16 mg/kg group, 6% of the patients had grade 5 TEAEs, 4% of the patients in the < 4 mg/kg group, and none in either the 8 or 24 mg/kg groups. The incidence of grade 3 or 4 TEAE were similar across all dose groups.

Apart from pneumonia, common SAEs were general physical health deterioration, pyrexia and hypercalcemia. Three deaths occurred within 30 days of the last dose of study drug which were caused by adverse events but none were considered related to study drug.

Anaemia and/or thrombocytopenia were experienced by many study subjects. However, anaemia and thrombocytopenia are frequently associated with Multiple Myeloma. It was apparent that higher incidences of anaemia and thrombocytopenia were observed among non-responders to daratumumab as compared with responders, therefore they are more likely due to the underlying disease than to the daratumumab treatment.

Leukopenia and neutropenia were also observed, No statistically significant trend in the TEAE rate of neutropenia or of neutropenic fever was found with increasing exposure, and no patients discontinued daratumumab due to neutropenia in any of the treatment.

Most chemistry laboratory abnormalities occurred with a low incidence, were of low grade and most were related to underlying Multiple Myeloma. There were no safety signals identified in a review of vital signs. No formal QT studies of daratumumab were conducted, but ECGs were systematically collected and reviewed. Although few ECG abnormalities were detected, in Study GEN501 Part 2 a statistically significant QT-prolongation was indeed observed. Although this was not observed in Part 1 of the study and may in part be attributable to an observed increase in heart rate, however, as discussed in Clinical Pharmacology, conflicting results were observed in Study GEN501 Part 1 and Part 2.

No differences in the incidence of AEs were observed with regard to age groups, sex, race, baseline renal or hepatic function, geographical area or drug product. For renal and hepatic function it is noted that some groups contain only few subjects.

Due to the large, overlapping CIs, no statistically significant trend in the TEAE rate was found with increasing drug exposure. IRRs were the most frequently observed TEAEs in all treatment groups, but most of them were grade 1 or 2. In the 16 mg/kg group, IRRs were reported in 48% of the patients and 55% in the 8 mg/kg group; 3% and 4% of patients, respectively, had Grade 3 IRRs, but no grade 4 IRR was noted in the two dose groups. All IRRs were well-managed, and none resulted in discontinuation from treatment.

Women of child-bearing potential should use effective contraception during, and for 3 months after cessation of daratumumab treatment (SmPC section 4.6).

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore

daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus (SmPC section 4.6).

It is not known whether daratumumab is excreted into human or animal milk. Maternal IgG is excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed. The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue daratumumab therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman (SmPC section 4.6). Use in pregnancy and lactation is included in the RMP under missing information.

Due to the small population of patients ⩾75 years (n=18), ''Use in the elderly over 75 years'' is added as missing information in the RMP until Phase 3 trials are completed. Additional analyses of covariates (including age ⩾75 years) will be done with larger sample sizes as current Phase 3 trials reach maturation (see discussion on clinical pharmacology).

There has been no experience of overdosage in clinical studies. Doses up to 24 mg/kg have been administered intravenously in a clinical study. There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately. Daratumumab is not expected to have a potential for abuse (SmPC section 4.9).

Daratumumab has no or negligible influence on the ability to drive and use machines. However fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines (SmPC section 4.7).

No drug-drug interaction studies have been performed. However, as daratumumab is an IgG, renal excretion and hepatic enzyme-mediated metabolism is considered unlikely.

In the group treated with the proposed dose of 16 mg/kg, a total of 6 subjects discontinued treatment due to AEs. None of these were related to daratumumab as determined by the investigator. Across all treatment groups, additionally 5 subjects discontinued treatment due to AEs which were indeed related to daratumumab as determined by the investigator. Four of the 5 AEs were IRRs but 2 of these occurred before the protocol was amended to include post-treatment administration of steroids.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The overall safety profile of daratumumab 16 mg/kg dosing regimen is considered acceptable for use in the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy and appears favourable. The adverse events appeared manageable.

The CHMP also considers the following measure necessary to address the missing safety data in the context of a conditional MA:

The safety data provided based on a single-arm, open-label pivotal study was quite limited. Additional safety data from the ongoing comparative phase III studies assessing lenalidomide and dexamethasone with or without daratumumab (study MMY3003) and bortezomib and dexamethasone with or without daratumumab in patients with relapsed or refractory multiple myeloma (study MMY3004), will be provided to further establish the safety profile of daratumumab.

2.7. Risk Management Plan

The CHMP received the following PRAC advice on the submitted RMP.

The PRAC considered that the RMP version 1.0 (dated 03 September 2015) could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur Updated assessment report.

The CHMP endorsed the PRAC advice with changes.

The applicant implemented the changes in the RMP as requested by PRAC and CHMP.

The CHMP endorsed the RMP version 1.2 (dated 30 March 2016) with the following content:

Table 61: Summary of the Safety concerns

Important Identified Risks	
	Infusion Related Reactions (IRRs) Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)
Important Potential Risks	
	Infections Prolonged decrease in NK cells QTc prolongation Immunogenicity Intravascular haemolysis
Missing Information	
	Use in pregnancy and lactation Reproductive and developmental toxicity Use in the elderly ≥75 years Use in patients with moderate or severe hepatic impairment Long term use (>2 years)

Pharmacovigilance plan

Table 62: Table of Ongoing and Planned Additional Pharmacovigilance Studies/Activities in the Pharmacovigilance Plan

Study / activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Trial MMY 3003 a Phase 3, two arm, Randomised, Parallel-group Trial of Lenalidomide and Dexamethasone with or without Daratumumab in Patients with Previously-treated Multiple Myeloma (category 2)	To compare the safety and efficacy of daratumumab when combined with lenalidomide and dexamethasone to that of lenalidomide and dexamethasone in subjects with relapsed or refractory multiple myeloma.	Overall Safety	Ongoing	30 September 2017
Trial MMY 3004, a Phase 3, two arm, Randomised, Parallel-group Trial of Bortezomib and Dexamethasone with or without Daratumumab in Patients with Previously-treated Multiple Myeloma. (category 2)	To compare the safety and efficacy of daratumumab when combined with VELCADE and dexamethasone to that of VELCADE and dexamethasone, in subjects with relapsed or refractory multiple myeloma.	Overall Safety	Ongoing	31 December 2016
Survey of additional risk minimisation measures for interference of blood typing (category 3)	To measure awareness of blood banks and HCPs on the interference of blood typing	Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)	Protocol to be submitted Initial evaluation Final Report	3 months after EC decision 18 months following the launch of the product. Final results will be presented in the next PSUR/PBRER after the survey has been concluded
Trial SMM2001: A randomised Phase 2 trial to evaluate 3 daratumumab dose schedules in smouldering multiple myeloma. (category 3)	As a secondary objective to determine if daratumumab has an effect on QT interval.	Effect of daratumumab on QT interval.	Started	31 December 2018
Investigate new method for detecting antidrug antibodies (category 3)	Improve the immunogenicity method's ability to detect anti-daratumumab antibodies in the presence of high trough levels of daratumumab	Immunogenicity	Planned	31 December 2018

Risk minimisation measures

Table 63 – Summary Table of the Risk Minimisation Measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important identified risks		
Infusion Related Reactions (IRRs)	Wording in SmPC Section 4.2, 4.4, 4.8	None
Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)	Wording in SmPC Section 4.4.	Educational materials will be distributed to HCPs and blood banks to advice regarding the risk of and solutions for interference for blood typing. Additionally, patient alert cards will be distributed to increase awareness to patients about the interference of blood typing occurring with daratumumab.
Important potential risks		
Infections	Wording in SmPC Section 4.8.	None
Prolonged decrease in NK cells	Wording in SmPC Section 5.1.	None
QTc prolongation	Wording in SmPC Section 5.1.	None
Immunogenicity	Wording in SmPC Section 5.1.	None
Intravascular haemolysis	Wording in SmPC Section 4.8.	None

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Missing information		
Use in pregnancy and lactation	Wording in SmPC Section 4.6.	None
Reproductive and developmental toxicity	Wording in SmPC Section 4.6, 5.2.	None
Use in the elderly ≥75 years	Wording in SmPC Section 4.2, 5.2.	None
Use in patients with moderate or severe hepatic impairment	Wording in SmPC Section 4.2, 5.2.	None
Long term use (>2 years)	None proposed	None

Conclusion

The CHMP and PRAC considered that the RMP version 1.2 (dated 30 March 2016) is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Darzalex (daratumumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU, and is to be approved under conditional marketing authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Daratumumab monotherapy at 16 mg/kg achieved an ORR of 29% in this studied population. The response data were supported by the GEN501 study, which had an ORR of 36% among patients treated with 16 mg/kg daratumumab. The ORR was consistent across different clinically relevant subgroups, such as number of prior lines of therapy, type of myeloma (IgG, non IgG), baseline renal function, refractory status including those refractory to newer drugs, such as pomalidomide or carfilzomib. The ORRs of daratumumab in these populations (28% to 33%) were similar to the overall population (29% to 36%).

The responses were rapid with a median time to response of 1 month and the median duration of response was 7.4 months.

A response of VGPR or better rate of 12% in the MMY2002 study was demonstrated. In the MMY2002 and GEN501, 3% and 5% of the patients respectively achieved stringent CR/CR.

For the combined studies, the median OS was 20.1 months after a median duration of follow-up of 20.77 months. Percentages of events in the MMY2002 and GEN501 were 53.8% and 38.1% respectively, with a 24-month OS rate of 41.3% and 57.4% respectively. The median OS for patients in the MMY2002 study who were refractory to pomalidomide was 13.8 months and 18.7 months in the GEN501 study. For patients refractory to carfilzomib, the median OS in study MMY2002 was 15.2 months and NE in the GEN501. Finally, the median OS in the MMY2002 study who were refractory to both pomalidomide and carfilzomib was 13.8 months and 16.5 months in the GEN501 study.

Uncertainty in the knowledge about the beneficial effects

The design of the study with no comparative arm is of concern because the ORR, PFS, and OS data cannot be directly compared to other treatment results in the same population. To further support the results obtained in studies MMY2002 and GEN501, the Applicant will submit the final CSR for study MMY3003 an ongoing phase 3, two arm, randomized, parallel-group study designed to compare the efficacy of daratumumab when combined with lenalidomide and dexamethasone (DRd) to that of lenalidomide and dexamethasone (Rd) in subjects with relapsed or refractory multiple myeloma and also for study MMY3004, phase 3, two arm, randomized, parallel-group study designed to compare the efficacy of daratumumab when combined with bortezomib and dexamethasone (DVd) to that of bortezomib and dexamethasone (Vd) in subjects with relapsed or refractory multiple myeloma.

Therefore, the CHMP has recommended two specific obligations in Annex II to the marketing authorization for the submission of the final results of ongoing studies MMY3003 and MMY3004.

Risks

Unfavourable effects

The most frequently reported adverse reactions were IRRs (48%); see section 4.4. Other frequently reported adverse reactions (≥ 20%) were fatigue (39%), pyrexia (21%), cough (21%), nausea (27%), back pain (23%), upper respiratory tract infection (20%), anaemia (27%), neutropenia (22%) and thrombocytopenia (20%).

Most AEs were of lower grades. Daratumumab targets CD38 which is expressed on NK cells and consequently the majority of subjects experienced a temporal decrease or had continually low measurements of NK cells. However, the overall incidence of infections and infestations remained comparable to the total population and consistent with underlying Multiple Myeloma. Notably, the incidence of opportunistic infections was low (2%).

While 15% of study subjects experienced AEs leading to infusion delays and 40% of subjects experienced AEs leading to infusion interruptions, the number of patients who permanently discontinued treatment due to AEs was low.

The incidence of death within 30 days of the last dose of study drug was relatively low. While 15 subjects in total died within this period, only 3 of the deaths were caused by AEs and none were considered related to study drug.

In study MMY1002, all 9 subjects experienced a positive result in indirect Coomb's Test after treatment with daratumumab. However, there was no reported interference with the clinical decision to administer blood transfusions and no AEs were reported in relation to blood transfusions.

Uncertainty in the knowledge about the unfavourable effects

The safety data provided based on a single-arm, open-label pivotal study was quite limited. Additional safety data from the ongoing comparative phase III studies assessing daratumumab versus lenalidomide and dexamethasone (study MMY3003) and versus bortezomib and dexamethasone in patients with relapsed or refractory multiple myeloma (study MMY3004), will be provided to further establish the safety profile of daratumumab.

No plausible cause for the findings of the statistically significant QTc prolongation in Study GEN501 Part 2 has been identified. A (thorough) QTc study is not feasible but the Applicant will incorporate more well-controlled data collection in a substudy of the ongoing Study SMM2001 to further evaluate a relationship between daratumumab concentration and QTc (see RMP).

Finally, only 11% of the patients treated with the dose of 16 mg/kg were older than 75 years, though the ORR was in line with the overall population (31% vs 25%). Use in the elderly ≥ 75 years is included in the RMP under missing information (see RMP).

Limitations in detecting anti-daratumumab antibodies in the presence of high concentrations of daratumumab cannot be ruled out (see discussion on clinical pharamacology). Therefore, the Applicant will develop a new method for detecting ADAs (see RMP).

In study MMY1002, all 9 subjects experienced a positive result in indirect Coomb's Test after treatment with daratumumab. However, there was no reported interference with the clinical decision to administer blood transfusions and no AEs were reported in relation to blood transfusions. An additional risk minimisation measure is considered to be needed to address this safety concern (see RMP and Annex II).

Effects Table

Table 64: Effects Table for Daratumumab

Effect	Short Description	Unit	Treatment MMY2002:d GEN501:d	Control None	Uncertainties/Strength of evidence	References
Favourable Effects						
ORR	Overall response rate	Percentage (KM median; 95% CI)	MMY2002: 29% (21%; 39%) GEN501:36% (22%; 52%)	-	Lack of comparator arm	See clinical efficacy AR and discussion
DOR	Duration of response	Months	MMY2002: 7.4 GEN501:NE		Lack of comparator arm	
sCR/CR	Stringent Complete remission/CR	Percentage	MMY2002: 3% GEN501: 5%	-	Lack of comparator arm	
OS	Overall survival	Months (KM median; 95% CI)	MMY2002:17.5 (13.7; NE)	-	Lack of comparator arm	
Unfavourable Effects (MMY2002, GEN501, MMY1002)						
AEs (e.g. fatigue, nausea, anaemia, neutropenia, back pain, cough and thrombocytopenia)	Incidence as percentage of patients involved	Percentage	99%, grade 3-4:56% AE leading to discontinuation: 4%	-	- Use in the elderly ⩾75 years - Immunogenicity - QTc prolongation - limited data	See clinical safety AR and discussion
SAEs (e.g. Infection and infestations, pneumonia,deterioration, pyrexia, hypercalcemia)	Incidence as percentage of patients involved	Percentage	32 Grade 5 AEs: 10/11 pts	-		
IRR	Incidence as percentage of patients involved	Percentage	51, 2 pts discontinued	-		

Abbreviations: AE: adverse event, AR: Assessment Report, CI: confidence interval, CR: complete response, DOR: duration of response, IRR: infusion-related reaction, KM: Kaplan Meier, NE: not estimated, ORR: overall response rate, OS: overall survival, PR: partial response, pts: patients, SAE: serious adverse event, sCR/CR: stringent complete remission/ complete remission.

Benefit-risk balance

Importance of favourable and unfavourable effects

A positive effect on ORR has been demonstrated for daratumumab monotherapy. Furthermore, the safety profile can be acceptable in the context of the stage of the disease.

Benefit-risk balance

Based on the positive clinical effect of daratumumab as a single agent drug that has been demonstrated in a highly refractory/relapsed patient population and that the safety profile is acceptable and manageable, the benefit/risk balance is positive.

Discussion on the benefit-risk balance

Daratumumab, a novel monoclonal antibody that specifically binds to the cell surface molecule CD38, has shown a durable response rate in a heavily pre-treated population with limited treatment options. Given the limitations in the number of patients treated and the design of the studies the applicant has applied for a conditional approval.

The CHMP considered that DARZALEX falls under the scope of Article 2 of Commission Regulation (EC) No. 507/2006 as eligible for a Conditional Marketing Authorisation as it belongs to:

a) Medicinal products designated as orphan medicinal products in accordance with Article 3 of Regulation (EC) No 141/2000;

b) Medicinal products which aim at the treatment, the prevention or the medical diagnosis of seriously debilitating diseases or life-threatening diseases.

Furthermore, the requirements listed in Article 4 of Commission Regulation No 507/2006 apply to daratuzumab on the basis of the following reasons:

a) The benefit/risk balance of the product is positive.

The ORR of 29% obtained with daratumumab in pivotal study MT103-211 is significant and clinically relevant in patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy despite the absence of confirmatory controlled data. Patients were heavily pretreated, and 79.8% and 69.4% had received more than 3 lines of prior therapy in the MMY2002 and GEN501 studies respectively, further 95% and 95.8% respectively were refractory to both PI's and IMiD's.

Together with an acceptable safety-profile in patients in the proposed indication, the benefit-risk balance is considered positive.

b) It is likely that the Applicant will be able to provide comprehensive data

The applicant will provide further comprehensive clinical data to confirm efficacy and safety of daratumumab in the proposed indication. More specifically the Applicant will provide:

- Study MMY 3003 a phase 3, two arm, randomized, parallel-group trial of lenalidomide and dexamethasone with or without daratumumab in patients with previously-treated multiple myeloma.
- Study MMY 3004, a Phase 3, two arm, randomized, parallel-group trial of bortezomib and dexamethasone with or without daratumumab in patients with previously-treated multiple myeloma.

These phase 3 studies of daratumumab in combination with lenalidomide/low-dose dexamethasone (MMY3003) and bortezomib/low dose dexamethasone (MMY3004) in patients with relapsed or refractory multiple myeloma are currently ongoing. A total of 560 and 480 patients respectively are planning to be randomized in these studies. These phase III studies are not in the exact same setting where daratumumab is authorised. It is anticipated that approximately 240 subjects across both studies enrolled will have received 3 or more prior lines of therapy. These studies will therefore provide comparative efficacy and safety data for daratumumab in combination with standard backbone therapies in a population that overlaps that enrolled in MMY2002 and GEN501. In the absence of controlled single-agent data in patients who have exhausted all standard treatments as in MMY2002 and GEN501, these studies can provide controlled data in a larger target population within the same condition which will further define the benefit-risk of daratumumab in the proposed indication. Both studies are ongoing and

the data will be provided by the applicant for study MMY3003 by the September 2017 and for study MMY3004 by December 2016.

c) The product fulfils an unmet medical need.

Daratumumab fulfils an unmet medical need for patients with poor long-term prognosis and limited treatment alternatives. Daratumumab has a new mechanism of action, a manageable safety profile, and treatment with daratumumab was associated with durable response, which provides a major therapeutic advantage.

d) The benefits to the public health of the immediate availability of the product outweigh the risks inherent in the fact that additional data are still required

In view of the high ORR compared to available treatment options, the immediate availability of DARZALEX on the market outweighs the risk inherent in the fact that additional data are still required.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Darzalex is not similar to Thalidomide Celgene, Revlimid, Imnovid, Farydak and Kyprolis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Darzalex in the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed

RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Prior to the launch of DARZALEX (daratumumab) in each Member State (MS) the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational materials, aiming at increasing awareness about the Important Identified Risk of "Interference for blood typing (minor antigen) (Positive Indirect Coombs' test)" and providing guidance on how to manage it.

The MAH shall ensure that in each MS where DARZALEX (daratumumab) is marketed, all HCPs and patients who are expected to prescribe, dispense and receive this product have access to/are provided with the below.

The HCPs and Blood Banks educational materials shall contain the following key elements:

- The guide for HCPs and Blood Banks, to advice about the risk of interference for blood typing and how to minimise it;
- The Patient Alert Card.

The Guide for HCP and Blood Banks shall contain the following key elements:

- All patients should be typed and screened prior to start treatment with daratumumab; alternatively, phenotyping may also be considered;
- Daratumumab-mediated positive indirect Coombs test (interfering with cross-matching of blood) may persist for up to 6 months after the last product's infusion; therefore, the HCP should advise the patient to carry the Patient Alert Card until 6 months after the treatment has ended;
- Daratumumab bound to Red Blood Cells (RBCs) may mask the detection of antibodies to minor antigens in the patient's serum;
- The determination of a patient's ABO and Rh blood type are not impacted;
- The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell Blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, genotyping may also be considered;
- In case of urgent need for transfusion, non-cross matched ABO/RhD compatible RBC units can be administered as per local bank practices;
- In the event of a planned transfusion, the HCPs should notify blood transfusion centres about the interference with indirect antiglobulin tests;
- Reference to the need to consult the Summary of Product Characteristics (SmPC);

- Reference to the need of giving the Patient Alert Card to the patients and to advise them to consult the Package Leaflet (PL).

The Patient Alert Card shall contain the following key elements:

- A warning message for HCPs treating the patient at any time, including in conditions of emergency, that the patient is using DARZALEX (daratumumab), and that this treatment is associated with the Important Identified Risk of Interference for blood typing (minor antigen) (Positive Indirect Coombs' test), which might persist for up to 6 months after the last product's infusion; and a clear reference that the patient should continue to carry this card until 6 months after the treatment has ended;

- Contact details of the DARZALEX (daratumumab) prescriber;

- Reference to the need to consult the Package Leaflet (PL).

- ***Obligation to complete post-authorisation measures for the conditional marketing authorisation***

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3003, a phase III randomised study investigating lenalidomide and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	30 September 2017
In order to address the uncertainties related to the single arm design of the pivotal study supporting the approval of Darzalex, the MAH should submit the results of study MMY3004, a phase III randomised study investigating bortezomib and dexamethasone with or without daratumumab in patients with previously treated multiple myeloma.	31 December 2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that daratumumab is qualified as a new active substance.