Medicinrådet

Bilag til Medicinrådets anbefaling vedr. daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason til behandling af nydiagnosticeret systemisk AL amyloidose

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason
2. Amgros' forhandlingsnotat vedr. daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason
3. Ansøgning vedr. daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason

Janssen-Cilag A/S

Bregnerødvej 133
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19. December 2022

Til Medicinrådet

Janssen-Cilags tilbagemelding på Medicinrådets udkast til anbefaling vedr. daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason til behandling af nydiagnosticeret systemisk AL amyloidose

Datakvalitet
Janssen's ansøgning er baseret på ANDROMEDA studiet, der er et randomiseret fase III studie med en relevant komparator for dansk klinisk praksis, og repræsentere hermed en direkte sammenligning mellem intervention og komparator. Alligevel bruger Medicinrådet relativt meget plads i rapporten på at kritisere datagrundlaget, herunder at der kun er ét studie og det har kort opfølgningstid. Janssen vil her blot bemærke at medmindre en metanalyse der inkluderer flere studier, er tilgængelig, så bliver data ikke meget bedre.

Ekstrapolering af overlevelse
Medicinrådet ændrer de data der anvendes til ekstrapolation af overlevelse i den sundhedsøkonomiske model. Modellen indeholder tre forskellige datagrundlag (Palladini 2012, EMN23 og AlCHEMY), og Medicinrådet vælger at anvende AlCHEMY som giver den mest konservative ekstrapolering af overlevelse og resulterer i en inkrementel QALY på 1,4. Både Palladini 2012 (~2,6 inkrementelle QALYs) og EMN23 (~1,7 inkrementelle QALYs) data giver signifikant højere inkrementelle QALYs.

Janssen hæfter sig ved at der trods denne ændring forsat er en stor QALY gevinst ved at bruge daratumumab i kombination med cyclophosphamid, bortezomib og dexamethason (DaraCyBorD) i stedet for bortezomib i kombination med cyclophosphamid og dexamethason (CyBorD).

Budgetkonsekvenser
Medicinrådet har justeret antagelserne vedr. patientoptaget. Vi mener ikke det er realistisk at patientoptaget sker så hurtigt som antaget (~71% af alle første linje patienter i år 1). Denne antagelse har store konsekvenser for budgetkonsekvenserne i 2023 og 2024, og en mere realistisk antagelse vil nedbringe disse signifikant.

Janssen takker for en god dialog i processen og ser frem til afgørelsen d. 25. januar.

Med venlig hilsen
Jeppe S. Christensen

HEMAR manager Denmark

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25. januar 2023
MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25. januar 2023
Leverandør	Janssen-Cilag A/S
Lægemiddel	Darzalex (daratumumab)
Ansøgt indikation	Darzalex (daratumumab) i kombination med cyclophosphamid, bortezomib og dexamethason (DaraCyBorDex) til behandling af voksne med nydiagnosticeret systemisk let-kæde amyloidose (AL amyloidose).

Forhandlingsresultat

Amgros har opnået følgende priser på Darzalex (daratumumab):

Tabel 1: Forhandlingsresultat på Darzalex (daratumumab) [redacted]

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Tilbudt SAIP (DKK)	Rabatprocent ift. AIP
Darzalex (daratumumab)	1800 mg (SC)	1 stk.	38.192,76	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	20 ml.	12.326,81	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	5 ml.	3.147,97	[redacted]	[redacted]	[redacted]

Prisen er betinget af en anbefaling af Darzalex (daratumumab) til behandling af AL amyloidose.

[redacted]

Tabel 2: Forhandlingsresultat på Darzalex (daratumumab)
[redacted]

Lægemiddel	Styrke/form	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Tilbudt SAIP (DKK)	Rabatprocent ift. AIP
Darzalex (daratumumab)	1800 mg (SC)	1 stk.	38.192,76	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	20 ml.	12.326,81	[redacted]	[redacted]	[redacted]
Darzalex (daratumumab)	20 mg/ml (IV)	5 ml.	3.147,97	[redacted]	[redacted]	[redacted]

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Den nuværende standardbehandling til behandling af patienter med AL amyloidose er CyBorDex. [redacted] Behandlingen seponeres efter 24 behandlingscykler svarende til 96 uger. Nedenstående tabel viser de årlige lægemiddeludgifter for behandling med Darzalex (daratumumab) til patienter med AL amyloidose.

Tabel 3: Sammenligning af lægemiddeludgifter

Lægemiddel	Dosis	Pakningsstørrelse	Pakningspris SAIP (DKK)	Antal pakninger/år	Årlig lægemiddeludgift SAIP pr. år (DKK)
Årlige lægemiddeludgifter med en rabat på [redacted] ift. AIP					
Darzalex (daratumumab) – opstarts år	1800 mg*	1 stk.	[redacted]	23	[redacted]
Darzalex (daratumumab) – vedligeholdelses år	1800 mg**	1 stk.	[redacted]	13	[redacted]
Årlige lægemiddeludgifter med en rabat på [redacted] ift. AIP					
Darzalex (daratumumab) – opstarts år	1800 mg*	1 stk.	[redacted]	23	[redacted]
Darzalex (daratumumab) – vedligeholdelses år	1800 mg**	1 stk.	[redacted]	13	[redacted]

*Styrke: 1800 mg. i uge 1-8, hver 2. uge i uge 9-24 efterfulgt af hver 4. uge indtil sygdomsprogression
**Styrke: 1800 mg. hver 4. uge i 44 uger eller indtil sygdomsprogression

Status fra andre lande

Norge: Under vurdering[1].
England: NICE har ikke anbefalet Darzalex (daratumumab), da ICER blev vurderet at være for høj i forhold til deres betalingsvillighed[2].

Konklusion

[redacted]

[1] https://nyemetoder.no/metoder/daratumumab-darzalex-indikasjon-ii
[2] https://www.nice.org.uk/guidance/gid-ta10656/documents/final-appraisal-determination-document

Medicinrådet

Application for the assessment of Daratumumab (Darzalex®) in combination with bortezomib (Velcade®), cyclophosphamide, and dexamethasone for newly diagnosed systemic light chain (AL) amyloidosis

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table of contents

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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1. Basic information

Contact information	
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Overview of the pharmaceutical	
Proprietary name	DARZALEX®
Generic name	Daratumumab
Marketing authorization holder in Denmark	Janssen-Cilag A/S Bregnerødvej 133 Birkerød, 3460 DK
ATC code	L01XC24
Pharmacotherapeutic group	Oncology
Active substance(s)	Daratumumab
Pharmaceutical form(s)	Solution of injection, subcutaneous injection (SC); Concentrate for solution for infusion, intravenous infusion (IV)
Mechanism of action	Monoclonal antibody targeting the CD38 protein, which is found in high amounts on abnormal white blood cells in AL amyloidosis. Daratumumab activates the immune system to kill the abnormal white blood cells.

Overview of the pharmaceutical	
Dosage regimen	1800 mg Weekly for cycles 1-2 weeks (Days 1, 8, 15, 22) Every 2 weeks for cycles 3-6 (Days 1, 15) Every 4 weeks for cycle 7+ (Day 1)
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Newly diagnosed systemic light chain (AL) amyloidosis
Other approved therapeutic indications	Multiple myeloma
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	In combination with bortezomib, cyclophosphamide and dexamethasone.
Packaging – types, sizes/number of units, and concentrations	1 vial solution for injection, 1800 mg
Orphan drug designation	Yes

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2. Abbreviations

Abbreviation	Description of abbreviation
AE	Adverse events
AL	Amyloid light chain
ASCT	Autologous stem cell transplant
CI	Confidence interval
CR	Complete response
CUA	Cost utility analysis
DKK	Danish Krone
DRG	Diagnosis related group
D-VCd	Daratumumab, bortezomib, cyclophosphamide and dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMN	European Myeloma Network
EORTC QLQ-	European Organisation for Research and Treatment of Cancer Quality of Life
EQ-5D-5L	European Quality of Life Questionnaire - 5 Dimension – 5 Level
HRQoL	Health related quality of life
ICER	Incremental cost-effectiveness ratio
IPD	Individual patient data
IV	Intravenous
kg	Kilogram
LYG	Life-years gained
mg	Milligram
mL	Millilitre
m^2	Meter squared
NR	No response
OS	Overall survival

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Abbreviation	Description of abbreviation
PO	Oral administration
PR	Partial response
PPP	Pharmacy purchase price
QALY	Quality-associated life years
QoL	Quality of life
RCT	Randomized controlled trial
SC	Subcutaneous
SE	Standard error
TEAE	Treatment-emergent adverse event
Tx	Treatment
VAT	Value-added tax
VCd	Bortezomib, cyclophosphamide and dexamethasone
VGPR	Very good partial response

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3. Tables and Figures

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4. Summary

This technology assessment investigates the cost-utility of Daratumumab (Darzalex®) in combination with bortezomib, cyclophosphamide and dexamethasone (D-VCd) in newly diagnosed adults systemic light chain (AL) amyloidosis. Based on the phase III ANDROMEDA trial, Janssen was granted market authorization for D-VCd in June 2021 as the first treatment to receive market authorization for this patient population. Both the primary analysis and the latest 18-month landmark results from the on-going ANDROMEDA trial are included in this application.

Population

Systemic AL-amyloidosis is a rare and heterogenous disease caused by the accumulation of misfolded proteins within organs, leading to impaired organ function and premature mortality. Approximately 50%-70% of patients with AL amyloidosis have cardiac involvement (Patel 2015, Muchtar 2019b). As heart failure is the leading cause of death in patients with AL amyloidosis, the presence of cardiac involvement is one of the strongest predictors of mortality risk. Renal involvement is observed in up to 70% of patients with AL-amyloidosis and is often the major cause of morbidity. The median age of patients enrolled in ANDROMEDA was 63 years, and 42% female. Most patients had ≥2 affected organs (D-VCd: 66.2%; VCd: 64.8%), most commonly the heart (71.8% and 71.0%, respectively) and the kidneys (59.0% and 59.1%). About 23% of patients had Stage I disease on the Mayo Clinic Cardiac Staging system, 40% Stage II and 35% stage IIIA. Even though patients with IIIB were initially excluded from the study, eight patients with initial Stage IIIa disease progressed to Stage IIIB disease between screening and baseline assessments. The incidence in Denmark relevant for this STA is estimated to be 56 patients in 2026.

Intervention

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to the CD38 antigen with high affinity and specificity (Darzalex FASPRO 2020, Darzalex SPC 2020, Janssen 2020a), and is approved by the EMA and FDA as a monotherapy or in combination regimens for the treatment of patients with MM (U.S. Food and Drug Administration 2018, Darzalex EPAR 2020). It is administered in ANDROMEDA as subcutaneous formulation in combination with bortezomib, cyclophosphamide and dexamethasone for initially 6 months, followed by up to 18-month monotherapy with daratumumab.

Comparator

In Danish clinical practice, both VCd (CyBorDex) is recommended as first-line therapy for most patients (DMSG 2021). As VCd was the comparator in ANDROMEDA, the STA investigates D-VCd as compared to VCd in newly diagnosed adults with systemic AL-amyloidosis. In ANDROMEDA, VCd is administered for 6 months.

Outcomes

In the pivotal Phase III ANDROMEDA trial in newly diagnosed patients with systemic AL amyloidosis, D-VCd provided deeper and more rapid response than VCd alone, with significantly greater achievement of CR and organ response (Janssen 2020a).

At a median follow-up of 20.3 months, achievement of CR remained significantly greater in the D-VCd group than in the VCd group, with a further increase in CR rate observed in the D-VCd group [59.0% versus 19.2% (OR 5.90; 95% CI 3.72-9.37; $P < 0.0001$)]. Achievement of ≥VGPR also remained significantly improved with D-VCd versus VCd [79.0% vs 50.3% (OR 3.74; 95% CI 2.39-5.86; $P < 0.0001$)].

In addition, the 18-month landmark results (median follow-up of 25.8 months) show no additional safety signals and confirmed that hematologic and organ response continue to increase with D-VCd over VCd after over 2 years follow-up. A significantly greater proportion of patients achieved CR in the D-VCd group than in the VCd group [59.5% vs

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19.2%, respectively (P < 0.0001)], with patients in the D-VCd group having a 6-fold greater probability of achieving CR than those treated with VCd alone (OR 6.03; 95% CI 3.80-9.58; P < 0.0001) (Janssen 2021a). Achievement of ≥VGPR was significantly greater in D-VCd than in the VCd group [79.0% vs. 50.3% (OR 3.74; 95% CI 2.39-5.86; P < 0.0001)]. Consistent with these results, the overall response rate (i.e. PR, VGPR, and CR combined) was also higher in the D-VCd group (91.8%) than in the VCd group (77.2%).

Health economic analysis

A decision tree paired with a Markov model was developed to capture all costs and outcomes associated with D-VCd and VCd in the treatment of AL amyloidosis. The results from the cost-effectiveness analysis show that treatment with D-VCd is associated with better health outcomes than VCd with an expected gain of 2.53 quality adjusted life years (QALYs). The treatment is also associated with an expected overall cost increase of DKK 919 845 per patient. The incremental cost-effectiveness ratio (ICER) per QALY gained is estimated to DKK 363 273. The results of the evaluation also need to be considered in the clinical context of the high unmet need for patients with AL amyloidosis, who have a very poor prognosis, especially if not responding to their first line.

The 5 year cumulated budget consequences in case of reimbursement of D-VCd are expected to be 177 million DKK after five years. Within this disease landscape, D-VCd, has the potential to bring significant health benefits to patients in comparison with VCd.

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5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

5.1.1 Disease description

Immunoglobulin (Ig) light-chain (AL) amyloidosis is a rare plasma cell disorders caused by the accumulation of misfolded proteins within organs, leading to impaired organ function and premature mortality (Badar 2018). The majority of patients (93%) with AL amyloidosis have systemic involvement, in which misfolded Ig light-chain proteins are released into the bloodstream and then accumulate throughout the body (Kourelis 2017, Witteless 2019). Systemic AL amyloidosis is a severe and highly heterogeneous disease, yet patients with systemic AL amyloidosis are often stratified, with subgroups based on the type(s) of organ involvement, most commonly the heart and/or kidneys, as well as the presence of cytogenetic abnormalities (Kumar 2012, Bochtler 2016, NCCN 2020b).

Approximately 50%-70% of patients with AL amyloidosis have cardiac involvement (Patel 2015, Muchtar 2019b). As heart failure is the leading cause of death in patients with AL amyloidosis, the presence of cardiac involvement is one of the strongest predictors of mortality risk. Renal involvement is observed in up to 70% of patients with AL amyloidosis and is often the major cause of morbidity and may limit treatment options (Palladini 2014, Kastritis 2017, Li 2019). Overall, patients with renal involvement tend to have a better prognosis than those with cardiac involvement (Dittrich 2017). However, as kidney function deteriorates, morbidity, mortality, and treatment costs all increase substantially (McCausland 2018, Sidiqi 2019, Heybeli 2020). Also, presence of certain cytogenetic abnormalities such as Translocation t(11;14) is the most prevalent cytogenetic aberrations in AL amyloidosis and its presence has been associated with a poor response to standard treatment (Bochtler et al., 2015).

Compared with the general population, patients with AL amyloidosis have substantial impairment across all aspects of their health-related quality of life, and often a poor prognosis, particularly among patients with delayed diagnosis, later-stage disease, or with more affected organs.

While there are treatment guidelines for systemic AL amyloidosis, prior to market authorization of D-VCd, no approved treatment were available.

5.1.2 Natural history of disease

As a highly heterogeneous disease, the course of systemic AL amyloidosis depends on both the extent as well as the severity of organ involvement (Barrett 2019). Common manifestations include infiltrative cardiomyopathy, renal dysfunction, neuropathy, and gastrointestinal dysmotility (Table 1). A study of patients with systemic AL amyloidosis (N = 592) found that just 34% had single-organ involvement, with 25% having involvement in ≥3 organs (Muchtar 2019b).

Table 1: Common affected organs and associated symptoms in patients with systemic AL amyloidosis

Organ	Symptoms
Heart	Dyspnea, peripheral edema, anasarca, pleural effusion, palpitations, irregular heartbeat, syncope, hypotension or regression of arterial hypertension, reduced heart rate variability
Kidney	Edema, foamy urine, proteinuria (to the point of nephrotic syndrome) with predominant albuminuria, renal failure

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Organ	Symptoms
Liver	Hepatomegaly, elevated liver stiffness, ascites, elevated alkaline phosphatase
Gastrointestinal tract	Dysphagia, loss of appetite, weight loss, nausea, postprandial fullness, meteorism, diarrhea, obstipation, gastrointestinal bleeding
Peripheral and autonomic nervous system	Polyneuropathy (progressive, symmetric, axonal/small fiber, overall, very variable), vegetative dysregulation (orthostatic dysregulation), intestinal motility disorder, urinary retention disorder, erectile dysfunction
Eye	Dry eye, vitreous body opacity, glaucoma, retinal angiopathy
Soft tissues and other manifestations	Macroglossia, hoarseness, coagulation disorders, purpura/cutaneous hemorrhage (eg, periorbital), carpal tunnel syndrome, swollen joints, splenomegaly, myasthenia, fatigue, biceps tendon rupture, lumbar spinal stenosis

Abbreviations: AL = amyloid light chain.

Source: Ihne (2020)

In patients with renal involvement, proteinuria associated with nephrotic syndrome and renal insufficiency is associated with significant morbidity. Heart failure related to hypertrophic cardiomyopathy is associated with a high risk of severe arrhythmia, conduction block and sudden death. In addition, clinically significant involvement may include peripheral neuropathy, autonomic neuropathy and gut disorders, whereas liver and spleen enlargement have relatively minor consequences (Guinault 2016).

Patients with severe cardiac involvement have a dismal prognosis (Grogan 2017). If untreated, the median survival is just six months from the onset of heart failure. Heart transplantation is rarely an option for these patients because of multiorgan involvement, rapid clinical decline, and challenges in predicting which patients will respond to treatment. With treatment and hematological response, patients' outcomes vary with organ involvement; however, patients with advanced cardiac involvement may experience sudden cardiac death despite a hematological response.

5.1.3 Morbidity and mortality

Systemic AL amyloidosis is associated with substantial morbidity (Vaxman 2019). The diseases clinical presentation depends on the number and extent of organ involvement (Patel 2015, Muchtar 2019b).

In patients with cardiac involvement, signs and symptoms include small vessel changes as a result of amyloid deposition (eg, periorbital purpura, macroglossia, submandibular gland enlargement, nail dystrophy) (Patel 2015, Muchtar 2019b). In patients with renal involvement, clinical manifestations include albuminuria and nephrotic-range proteinuria, which can lead to end-stage renal failure if diagnosed late (Gupta 2020). Physical signs specific to AL amyloidosis include periorbital purpura and tongue enlargement (Figure 1) (Vaxman 2019). Despite their specificity, these symptoms are found in only 15% of patients.

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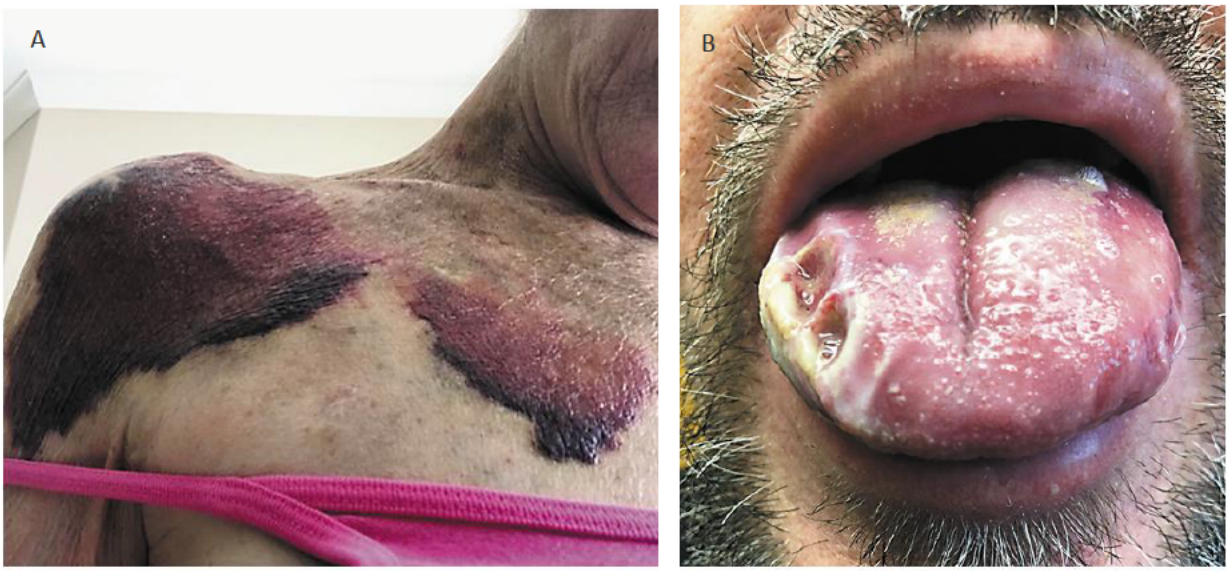
Figure 1: Purpura (panel A) and tongue enlargement (panel B) in patients with systemic AL amyloidosis



Abbreviations: AL = amyloid light chain.

Source: Vaxman (2019).

The survival of patients with systemic AL amyloidosis is generally poor, particularly among patients with delayed diagnosis, later-stage disease, or with more affected organs. Staging systems have been introduced, associated with patient survival prognosis.

The most widely used staging system for systemic AL amyloidosis was developed by the Mayo Clinic group in 2004 and revised in 2012 (Kumar 2012, Wechalekar 2013). The original staging system stratified patients into stages I, II, and III, based on biomarkers N-terminal pro-brain natriuretic peptide (NT-ProBNP) and cardiac troponins T (TnT) levels. These markers have been shown to be independent prognostic factors, with increased levels of both markers being associated with a higher mortality risk. Based on this staging system, the median OS was 26.4 months for patients with stage I, 10.5 months for patients with stage II, and 3.5 months for patients with stage III disease (Wechalekar 2013). The 2012 revision to the Mayo Clinic staging system added dFLC as an additional criterion (Kumar 2012). Revisions were based on a study of 810 patients with systemic AL amyloidosis, which reported that dFLC >180 mg/L, cardiac TnT >0.03 ng/mL, and NT-proBNP >1,800 pg/mL were independent prognostic factors for OS in a multivariate model (Table 2).

Table 2: Prognostic factors for OS in systemic AL amyloidosis

Prognostic factor	Comparison	Prognostic model		
		Univariate RR (*P* value)	Multivariate 1[a] RR (*P* value)	Multivariate 2[b] RR (*P* value)
dFLC, mg/L	>180 vs. ≤180	1.6 (<0.001)	1.4 (0.01)	1.4 (0.002)
Bone marrow plasma cells[c], %	>10 vs. ≤10	1.5 (<0.001)	1.2 (0.2)	NI
PCLI, %	>0 vs. 0	1.3 (0.009)	1.3 (0.09)	NI
β2-microglobulin, mg/dL	>3 vs. ≤3	1.9 (<0.001)	1.5 (<0.01)	NI

Prognostic factor	Comparison	Prognostic model		
		Univariate RR (*P* value)	Multivariate 1[a] RR (*P* value)	Multivariate 2[b] RR (*P* value)
Circulating plasma cells	Yes vs. no	1.5 (0.08)	NI	1.2 (0.1)
cTnT, ng/mL	>0.03 vs. ≤0.03	3.0 (<0.001)	NI	2.4 (<0.001)
NT-proBNP, pg/mL	>1,800 vs. ≤1,800	2.3 (<0.001)	NI	1.4 (0.004)

[a] Model examining plasma cell clone-related characteristics.

[b] Model examining FLC and cardiac biomarkers.

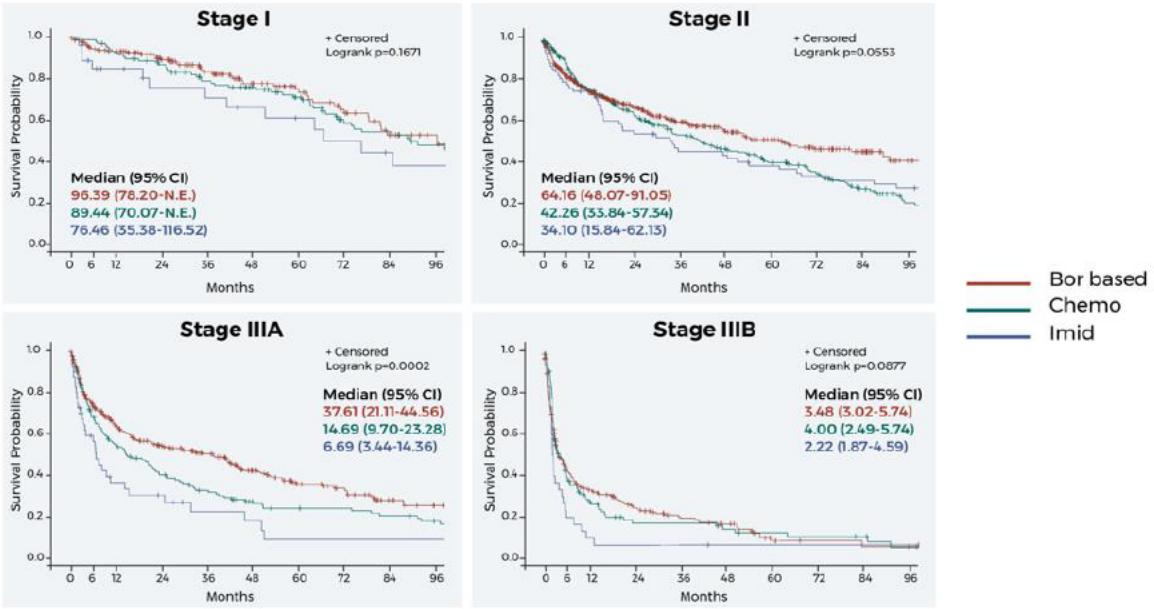
[c] Bone marrow plasma cells ≥10% is a key diagnostic criterion for MM. Therefore, some of the mortality risk could have been driven by comorbid MM, although the proportion with formally diagnosed MM was not reported (NCCN 2020a).

Abbreviations: cTnT = cardiac troponin T; dFLC = difference between uninvolved and involved free light chains; mg/dL = milligrams per deciliter; MM = multiple myeloma; ng/mL = nanograms per milliliter; NI = not included in the model; NT-proBNP = N-terminal pro-brain natriuretic peptide; OS = overall survival; PCLI = plasma cell labelling index; pg/mL = picograms per milliliter; RR = risk ratio. Source: Kumar (2012).

In a retrospective analysis of real-world treatment outcomes conducted by the European Myeloma Network (EMN), Mayo Stage at diagnosis was a key determinant of long-term survival among patients with systemic AL amyloidosis (N = 2,787) (Palladini 2020b, Palladini 2020a, Palladini 2020d, Palladini 2020c). Consistent with diagnostic delays, many patients had advanced disease at diagnosis during the 2004-2018 study period, including 17% with Mayo Stage I disease, 35% with Stage II disease, 22% with Stage IIIA disease, and 16% with and Stage IIIB[1] disease. When stratified by Mayo Stage, hematologic response rates and survival both worsened with advancing disease stage, with median OS ranging from 96.4 months for Stage I disease to just 3.5 months for Stage IIIB disease (
Figure 2). Although the introduction of VCd-based regimens substantially improved both hematologic response and survival rates from 2011 onwards, the authors highlighted the need for improved therapies that can provide higher hematologic response rates, as well as the need for earlier diagnosis.

[1] Note: the Mayo Stage was unreported in 10% of patients Palladini, G., Schönland, S., Merlini, G. and et al (2020d). First glimpse on real-world efficacy outcomes for patients with systemic light chain amyloidosis in Europe: a retrospective observational multicenter study by the European Myeloma Network. Oral presentation. Presented at the 62nd ASH Annual Meeting & Exposition. December 5-8, 2020, Palladini, G., Schönland, S., Merlini, G. and et al (2020c). First glimpse on real-world efficacy outcomes for 2000 patients with systemic light chain amyloidosis in Europe: a retrospective observational multicenter study by the European Myeloma Network. Blood 136(Supplement_1): 50-51.. The proportion of patients with advanced Stage IIIB disease remained consistent over time (2004-2010: 15%; 2011-2018: 16%), underscoring the need for earlier diagnosis.

Figure 2: Estimated OS in patients with AL amyloidosis, stratified by Mayo Stage and therapeutic regimen, EMN real-world retrospective analysis (2004-2018)



Note: From 2011 onwards (n = 1,899 of 2,787 patients), VCd was the most common first-line regimen (in 46.1% of patients).

Abbreviations: AL = amyloid light chain; Bor = bortezomib (VELCADE®); Chemo = chemotherapy; EMN = European Myeloma Network; IMID = immunomodulatory; OS = overall survival; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone.

Source: Palladini (2020b).

As highlighted before, advanced heart failure is the most common cause of death in patients with systemic AL amyloidosis. In a study of 194 patients with systemic AL amyloidosis, 82% of patients who died during study period died of cardiac causes (Barrett 2019). Advanced heart failure was the cause of death in 68% of cases and sudden cardiac death in 32% of cases. Further, patients with cardiac involvement had a higher probability of death at 3 years than those with any other organ involvement (
Table 3).

Table 3: Estimated 3-year mortality rates in patients with systemic AL amyloidosis, stratified by organ involvement

Organ	3-year mortality		
	n (%)	HR (95% CI)	*P* value
Cardiac amyloid	162 (83.5)	15.5 (2.130-112.178)	0.007
Renal amyloid	115 (59.3)	0.8 (0.455-1.338)	0.367
Gastrointestinal amyloid	81 (41.8)	0.8 (0.476-1.353)	0.409
Neurologic amyloid	42 (21.6)	1.4 (0.749-2.455)	0.315
Liver amyloid	27 (13.9)	2.0 (1.072-3.818)	0.030
Pulmonary amyloid	11 (5.7)	2.2 (0.866-5.776)	0.097

Organ	3-year mortality		
	n (%)	HR (95% CI)	*P* value
Multiple myeloma	43 (22.2)	1.2 (0.673-2.118)	0.545

Abbreviations: AL = amyloid light chain; CI = confidence interval; HR = hazard ratio. Source: Barrett (2019)

5.1.4 Risk factors

Currently, limited evidence is available regarding specific genetic and environmental risk factors for AL amyloidosis. Multiple myeloma (MM) is one of the strongest risk factors identified to date, with approximately 10-15% of patients with MM eventually developing AL amyloidosis as well (Vela-Ojeda 2009, Grogan 2017). Patients with monoclonal gammopathy of undetermined significance (MGUS) also have an increased risk of developing AL amyloidosis (Merlini 2012, Grogan 2017). Consistent with the increasing prevalence of both MM and MGUS with advanced age, AL amyloidosis risk also increases substantially with age.

Genetic abnormalities are also associated with the increased risk for AL amyloidosis (Bryce 2009). Translocation t(11;14) is present in approximately 39%-57% of patients with AL amyloidosis and is the most common genetic abnormality in this population (Bryce 2009, Milani 2018, Kobayashi 2019). The translocation involves the immunoglobulin heavy chain and genes encoding cyclin D1, which promotes the proliferation of plasma cells (Lakshman 2018).

5.1.5 Comorbidities

Comorbidity evidence is limited in AL amyloidosis, with available studies often focusing on conditions that overlap with amyloidosis-related complications (e.g., heart and kidney failure). Still, available evidence shows that systemic AL amyloidosis is associated with a substantial disease/comorbidity burden, including cardiovascular, renal, and liver disorders, other hematological malignancies, and malnutrition. A US-based study that used the Truven MarketScan® Commercial and Medicare Supplement claims databases from 2007 to 2015 reported that patients with AL amyloidosis experienced a substantial burden of comorbidities (McCausland 2018). The mean Charleston Comorbidity Index (CCI) score was 4.3 (standard deviation [SD] 3.2) among prevalent patients, indicating a high burden of disease. Common comorbidities included renal disease (39.3% of patients), congestive heart failure (33.2%), and moderate-to-severe liver disease (28.6%). Other common comorbidities included MM (38.9%), MGUS (19.6%), and hypothyroidism (17.7%). Given that MM and MGUS are among the risk factors for AL amyloidosis, it is not surprising that these conditions were commonly observed in this cohort.

Comorbidity burden is a key consideration in patients with AL amyloidosis, as it is used to determine eligibility for potentially life-prolonging autologous stem cell transplantation (Gavriatopoulou 2018, NCCN 2020b). Eligibility criteria vary, although patients are typically considered ineligible for ASCT if they have ≥2 affected organs, severe cardiac dysfunction, end-stage renal disease, or high overall disease/comorbidity burden (assessed using the Eastern Cooperative Oncology Group Performance Status [ECOG PS[2]]) (Batalini 2018, Manwani 2018b, Al Saleh 2019, Milani

[2] Note: ECOG PS score cut-offs for determining ASCT eligibility differ across key treatment guidelines. Both the Mayo Clinic mSMART guidelines and the Swiss Amyloidosis Network guidelines recommend restricting ASCT to individuals with an ECOG PS score of <2 (ie, a score of 0 or 1) Mayo Clinic (2020). mSMART. Mayo Consensus on AL Amyloidosis: Diagnosis, Treatment, and Prognosis. v9 October 2020. Available at: https://www.msmart.org/s/Amyloid-Treatment-mSMART-2020-revision-October-2020.pdf, Schwotzer, R., Flammer, A. J., Gerull, S., Pabst, T., Arosio, P., et al. (2020). Expert recommendation from the Swiss Amyloidosis Network (SAN) for systemic AL-amyloidosis. Swiss Med Wkly 150:

2020). Despite ASCT-eligible patients having a lower comorbidity burden than ineligible patients, studies still report a high comorbidity burden in this cohort3 (D'Souza 2015, Gutierrez-Garcia 2019).

5.1.6 Diagnosis of disease

Only in the year 2015, an International Classification of Disease (ICD) diagnostic code became available for AL amyloidosis (Hester 2019). Before, patients with AL amyloidosis would have been classified as having unspecified amyloidosis (eg, ICD-9-CM 277.30) alongside patients with other amyloidosis subtypes, likely reducing the accuracy of claims-based epidemiology and costing analyses. Diagnostic coding for systemic AL amyloidosis was first introduced in October 2015, as part of the ICD-10 (NCHS 2020):

- ICD-10-CM E85 Amyloidosis
    - E85.8 Other amyloidosis
        - E85.81 Light chain (AL) amyloidosis

As systemic AL amyloidosis is a rare disease with nonspecific symptoms, the initial diagnosis is often delayed by several months, or by over a year in some cases (McCausland 2019, Vaxman 2019). A survey from the Amyloid Research Consortium indicated that 37% of patients were diagnosed more than one year from the onset of initial symptoms, with a median of three physician visits before a diagnosis was established (Schulman 2020). In addition, a clinician survey found that there was an average delay of 10 months (range: 1 month to 2 years) between symptom onset and diagnosis (McCausland 2018). Common symptoms include weight loss, fatigue, edema, and shortness of breath. Given that these symptoms are shared with other, more frequent conditions, many patients are initially misdiagnosed (Roccatello 2020).

In a recent United States claims analysis of patients diagnosed with AL over the past two decades (ie, 2001-2019; N = 1,403), the median time from the onset of symptoms/signs to diagnosis was 2.7 years (Hester 2020). When stratified by the type of symptom/sign, nervous symptoms (e.g., peripheral neuropathy), purpura, and malaise/fatigue appeared to be early indicators of AL amyloidosis, occurring a median of approximately 1-2 years before diagnosis (Figure.3). In contrast, symptoms related to more advanced disease progression, such as heart failure and renal impairment, typically occurred a median of <1 year before diagnosis. Notably, most patients were already experiencing disease-related cardiac symptoms (88.1%) and/or renal symptoms (65.1%) at diagnosis, with a meaningful increase in symptom prevalence relative to matched controls[4]. As a result, the authors concluded that

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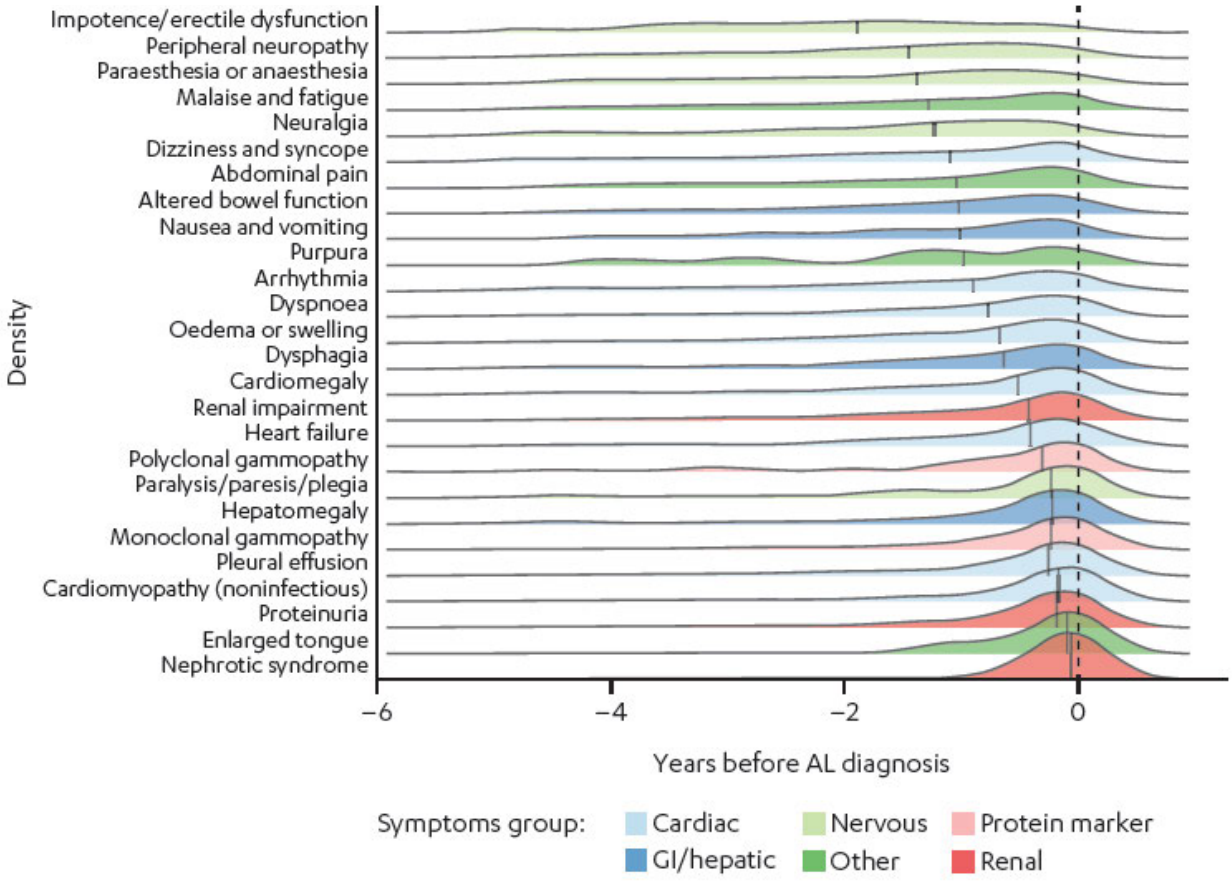
w20364.. In contrast, European Myeloma Network guidelines consider patients eligible for ASCT if they have an ECOG PS a score of ≤2 (ie, a score 0, 1, or 2) Gavriatopoulou, M., Musto, P., Caers, J., Merlini, G., Kastritis, E., et al. (2018). European Myeloma Network recommendations on diagnosis and management of patients with rare plasma cell dyscrasias. Leukemia 32(9): 1883-1898.. National Comprehensive Cancer Network guidelines do not report specific ECOG PS cut-offs for ASCT eligibility NCCN (2020b). NCCN Clinical Practice Guidelines in Oncology (NCCN) Guidelines®: Systemic light chain amyloidosis. Version 1.2020. December 6, 2019., Legeforeningen (2021). "AL-amyloidosis action program 2021." Retrieved 27/09/2021, 2021, from https://www.legeforeningen.no/foreningsledd/fagmed/Norsk-selskap-for-hematologi/handlingsprogram/.

[3] The burden of comorbidities was assessed using the hematopoietic cell transplantation–comorbidity index (HCT-CI), a validated instrument used to assess comorbidities in patients undergoing ASCT Sorror, M. L., Maris, M. B., Storb, R., Baron, F., Sandmaier, B. M., et al. (2005). Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106(8): 2912-2919.. The HCT-CI stratifies patients into three risk groups, with 0 indicating low risk (ie, low comorbidity burden), 1-2 indicating intermediate risk, and 3 or more indicating high risk.

[4] Note: as malaise/fatigue claims data were poorly captured, its relevance as an early disease indicator is unclear Hester, L. L., Gifkins, D. M., Bellew, K. M. and et al (2020). Diagnostic delay and characterisation of the clinical prodrome in AL amyloidosis: data from 1,403 patients between 2001-2019. Poster presentation (number PT016). Presented at the XVII International Symposium on Amyloidosis (ISA). September 14-18, 2020..

there was an opportunity to diagnose patients earlier based on the presence of early symptoms (ie, peripheral neuropathy and purpura[5]), prior to further disease progression and organ damage.

Figure.3: Distribution of common AL amyloidosis symptoms/signs prior to diagnosis, arranged in order of median time from occurrence to diagnosis



Note: the vertical grey lines indicate the median time from symptom/sign occurrence to subsequent AL amyloidosis diagnosis.

Abbreviations: AL = amyloid light chain; GI = gastrointestinal.

Source: Hester (2020).

Specific physical signs of AL amyloidosis include tongue enlargement or periorbital purpura (Roccatello 2020). However, these signs are found in only 15% of patients and therefore of limited diagnostic relevance for most patients. After symptom onset, most diagnoses typically require at least three physician visits or referrals (McCausland 2018).

The workup for patients with suspected systemic AL amyloidosis includes a medical history, physical examination, evaluation of orthostatic vital signs, and complete blood counts (CBC) with differential, including platelet counts, blood urea nitrogen (BUN) content, serum creatinine, coagulation studies, and electrolytes (Gavriatopoulou 2018, NCCN 2020b).

[5] Note: cardiac and renal symptom prevalence was compared versus age/sex/year-matched general population controls using standardized proportion difference analysis (ie, where a difference of >0.10 indicates a meaningful increase in symptom prevalence among patients). The standardized proportion difference was 0.86 for cardiac symptoms and 1.00 for renal symptoms ibid..

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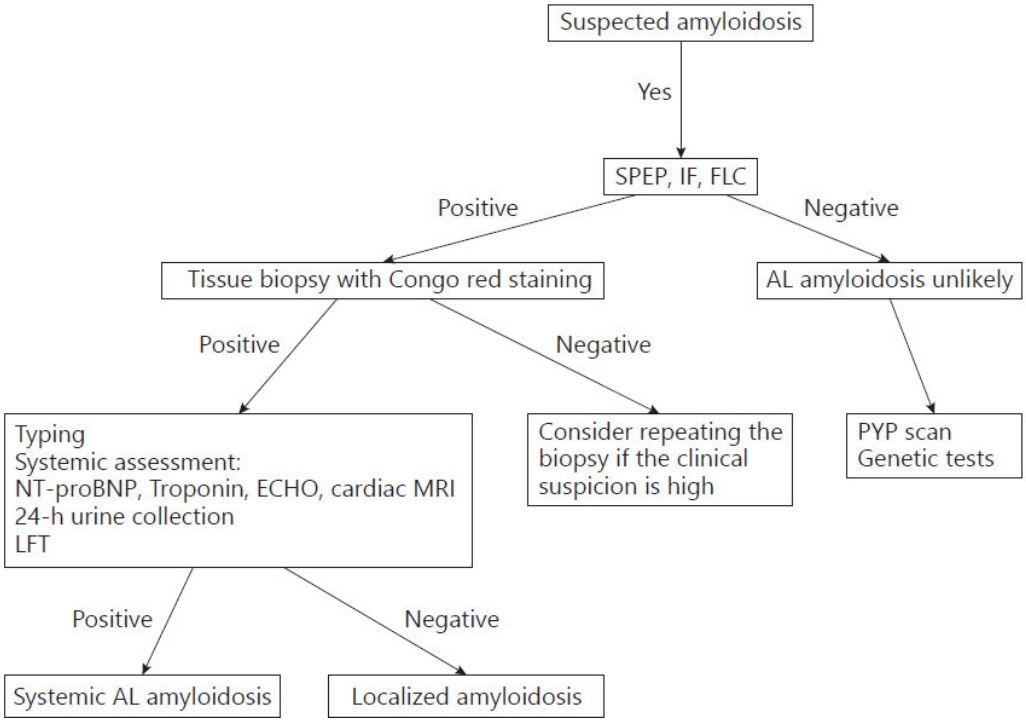
Screening should be performed using serum electrophoresis, immunofixation electrophoresis of serum and urine, and serum free light chain (FLC) assay (Vaxman 2019, NCCN 2020b). As highlighted previously, the λ light-chain isotype is over-expressed relative to the κ isotype in patients with AL amyloidosis, resulting in a κ:λ ratio of approximately 1:3 (Gertz 2002, Sanchorawala 2006, NCCN 2020b). In comparison, the κ:λ ratio is approximately 2:1 in healthy individuals. Thus, the FLC ratio can help diagnosing patients, while the absolute difference in concentration (mg/L) between involved and uninvolved FLC (dFLC) is the standard parameter to diagnose and monitor patients.
The diagnosis of AL amyloidosis requires the demonstration of amyloid fibrils in a tissue sample taken from the suspected affected organ (e.g., heart, kidney, liver) or from a surrogate site (eg, abdominal fat pad, bone marrow), followed by Congo red staining (Vaxman 2019, NCCN 2020b). Congo red staining by experiences laboratories of the subcutaneous fat aspirate is a reliable and noninvasive test that identifies amyloid deposits in approximately 90% of patients (NCCN 2020b). Hereafter, it is essential to confirm that the amyloid deposits are composed of light chains by immunohistochemistry, electron microscopy, or mass spectrometry. Identification of light chains in the serum or urine without confirmation and typing of the amyloid composition in tissue is not adequate, as patients with other types of amyloidosis may have an unrelated MGUS. In addition, the monoclonal plasma cell population can be detected in bone marrow aspirates by immunohistochemical staining of κ and λ chains (NCCN 2020b).

If the tissue biopsy tests are positive, classification of AL amyloidosis into systemic or localized disease is done by demonstrating organ involvement using assessments of cardiac biomarkers N-terminal pro-brain natriuretic peptide (NT-proBNP) and TnT and troponins I, respectively, echocardiology, cardiac magnetic resonance imaging (MRI), renal function test, and liver function tests. A schematic summary of the suggested approach for evaluating a patient with suspected amyloidosis is presented in Figure 4.

Figure 4: Overview of the suggested approach for evaluating a patient with suspected amyloidosis



Note: the above schematic is a suggested approach (included for illustrative purpose only); please see **Chapter 4** for diagnostic recommendations from key treatment guidelines.

Abbreviations: AL = amyloid light chain; ECHO = echocardiology; FLC = free light chains; IF = immunofixation; LFT = liver function tests; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro-brain natriuretic peptide; PYP = pyrophosphate; SPEP = serum protein electrophoresis.

Source: Vaxman (2019).

If AL amyloidosis is still suspected in the setting of negative surrogate site biopsies, the affected organ should be biopsied (Vaxman 2019). Specialized tests that are performed based on organ involvement are outlined in Table 4.

Table 4: Specialized tests based on organ involvement in AL amyloidosis

Organ involvement	Diagnostic tests
Heart	EKG
	Echocardiogram
	Chest x-ray
	Cardiovascular MRI (in certain circumstances)
	Cardiac biomarkers in the serum:
	Cardiac dysfunction: troponin I or T
	Cardiac stress: BNP or NT-proBNP
Liver and GI tract	Elevated serum alkaline phosphatase levels and bilirubin
	Fecal occult blood test
	Gastric emptying scan if gastroparesis is present
	Ultrasound or CT scan to determine craniocaudal liver span
Peripheral nervous system	EMG or nerve conduction testing
Endocrine system or lungs	Thyroid-stimulating hormone levels
	Cortisol levels
Lungs	Pulmonary function tests

Abbreviations: BNP = brain natriuretic peptide; CT = computed tomography; EKG = echocardiography; EMG = electromyogram; MRI = magnetic resonance imaging; NT-proBNP = N-terminal pro B-type natriuretic peptide.

Source: NCCN (2020b).

5.1.7 Incidence and prevalence in Denmark

Systemic AL-amyloidosis is a relatively rare disease with only rough estimates on incidence. The incidence of AL amyloidosis in Denmark is unknown but is estimated to be similar to estimates from the North American population, approximately 12 cases / million (Kyle 2019) (Table 5).

There are no known estimates for prevalence. Clinical experts Janssen contacted considered that while incidence numbers seem realistic, estimates on prevalence are extremely uncertain, and therefore not presented.

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Table 5: Incidence of AL amyloidosis in the past 5 years

Year	2017	2018	2019	2020	2021
Population Denmark	5 748 769	5 781 190	5 806 081	5 822 763	5 840 045
Incidence in Denmark	69.0	69.4	69.6	69.8	70.1

Source: (Kyle 2019, Statistics Denmark 2022b)

Table 6: Estimated number of patients eligible for treatment

Year	2022	2023	2024	2025	2026
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	55	55	56	56	56

Source: (Kyle 2019, DMSG 2021) (Estimation based on market and population growth)

5.1.8 Patient populations relevant for this application

Adult patients with systemic AL amyloidosis.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

There are currently no approved medicines for the treatment of systemic AL-amyloidosis. Recent clinical guidelines from the Danish Multidisciplinary Cancer Groups (DMCG) recommend VCd as a first-line regimen for patients with AL amyloidosis, and daratumumab-containing regimens for second-line (Table 7) (DMSG 2021).

Table 7: Currently recommended treatment options for AL amyloidosis

	DMSG 2021	
First-line	(VCd) Cyclophosphamide Bortezomib Dexamethason	(D-VCd) Cyclophosphamide Bortezomib Dexamethason Daratumumab
Second-line (in case of relapse, in addition to medicines above)	Daratumumab Lenalidomid	Daratumumab Lenalidomid

Source: (DMSG 2021)

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5.2.2 Choice of comparator

In Danish clinical practice, VCd is recommended as a first-line regimen for patients with AL amyloidosis (DMSG 2021). Clinical experience with VCd has shown favorable efficacy (demonstrated by rapid and deep clonal responses and improvements in organ function) with an acceptable toxicity profile (Jaccard 2014, Palladini 2015). Preliminary results from the ongoing, retrospective, European real-world EMN23 study (N =5000) suggest that VCd has replaced the combination of melphalan and dexamethasone (Md) as the most common first-line treatment, used by 46% of patients after 2010 (Palladini 2020a). Thus, VCd is considered as the most suitable comparator regimen.

5.2.3 Description of the comparator

An overview of VCd is presented in Table 8.

Table 8: Description of VCd combination therapy

Product description			
Name of preparation/pharmaceutical	VELCADE®	Cytoxan Endoxan Neosar Procytox Revimmune Cycloblastin	Dextenza Ozurdex Neofordex Decadon
Active ingredient	Bortezomib	Cyclophosphamide	Dexamethasone
Pharmaceutical form	SC	PO	PO
Strength	3.5 mg	50 mg tablet	8 mg tablet
Recommended daily dose	1.3 mg/m2 (Days 1, 8, 15, 22)	300 mg/m2 (Days 1, 8, 15, 22)	40 mg weekly (Days 1, 8, 15, 22)
Should the intervention be used with other drugs?	Yes, in combination with cyclophosphamide and dexamethasone		
Treatment length/criteria for termination of treatment	Maximum 6 cycles	Maximum 6 cycles	Maximum 6 cycles
Required monitoring, under administration or during treatment period	CBC with differential and including platelet counts should be frequently monitored throughout treatment	Refer to the manufacturer's prescribing information for additional details for cyclophosphamide, bortezomib, and dexamethasone.	

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Product description			
Requirements of diagnostics or other tests	Refer to the manufacturer's prescribing information for additional details for cyclophosphamide, bortezomib, and dexamethasone.		
Medically approved indication /-s	Multiple myeloma Mantle cell lymphoma	Treatment of malignant diseases	Multiple myeloma

Abbreviations: CBC = complete blood counts; IV = intravenous; m = meter; mg = milligrams; PO = oral; SC = subcutaneous.

Source: (Cyclophosphamide 2012, Neofordex 2021, Velcade EPAR 2021)

5.3 The intervention

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to the CD38 antigen with high affinity and specificity (Darzalex FASPRO 2020, Darzalex SPC 2020, Janssen 2020b). Daratumumab is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology.

Daratumumab has demonstrated safety and efficacy in numerous clinical studies (Lokhorst 2015, Dimopoulos 2016, Palumbo 2016, Chari 2017, Mateos 2018, Spencer 2018, Facon 2019) and is approved by the EMA and FDA as a monotherapy or in combination regimens for the treatment of patients with MM (U.S. Food and Drug Administration 2018, Darzalex EPAR 2020). It is available in formulations for intravenous (IV) or subcutaneous (SC) administration. The SC formulation uses a higher concentration of daratumumab and reduces the infusion volume to 15 mL, which reduces the risk that patients with cardiac or renal comorbidities will experience signs or symptoms of volume overload (Janssen Research and Development 2018). An overview of D-VCd is presented in Table 9.

Table 9: Product description of daratumumab in combination with VEL, cyclophosphamide and dexamethasone (D-VCd)

Product description				
Name of preparation/pharmaceutical	DARZALEX®	VELCADE®	Cytoxan Endoxan Neosar Procytox Revimmune Cycloblastin	Dextenza Ozurdex Neofordex Decadon
Active ingredient	Daratumumab	Bortezomib	Cyclophosphamide	Dexamethasone
Pharmaceutical form	SC	SC	PO	PO
Strength	1,800 mg	3.5 mg	50 mg tablet	8 mg tablet
Recommended daily dose	1,800 mg Weekly for cycles 1-2 weeks (Days 1, 8, 15, 22) Every 2 weeks for cycles 3-6 (Days 1, 15)	1.3 mg/m^2 (Days 1, 8, 15, 22)	300 mg/m^2 (Days 1, 8, 15, 22)	40 mg weekly (Days 1, 8, 15, 22)

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Product description				
	Every 4 weeks for cycle 7+ (Day 1)			
Should the intervention be used with other drugs?	In combination with bortezomib, cyclophosphamide and dexamethasone.			
Treatment length/criteria for termination of treatment	Maximum 24 cycles	Maximum 6 cycles	Maximum 6 cycles	Maximum 6 cycles
Required monitoring, under administration or during treatment period	Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies.	Refer to the manufacturer's prescribing information for additional details for cyclophosphamide, bortezomib, and dexamethasone.		
Requirements of diagnostics or other tests	Monitor patients with neutropenia for signs of infection.	Refer to the manufacturer's prescribing information for additional details for cyclophosphamide, bortezomib, and dexamethasone.		
Medically approved indication /-s	AL-amyloidosis Multiple myeloma			

Abbreviations: AL = light chain; IV = intravenous; m^2 = meter squared; mg = milligrams; PO = oral; SC = subcutaneous.

Source: (Darzalex EPAR 2021, Kastritis 2021b) Janssen, 2020a

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6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

A systematic literature review was not performed since the ANDROMEDA study contains a direct comparison between D-VCd and the relevant comparator VCd

7. Efficacy and safety

7.1 Efficacy and safety of D-VCd compared to VCd for newly diagnosed AL amyloidosis

7.1.1 Relevant studies

For detailed study characteristics refer to Appendix C. For baseline characteristics of patients included refer to Appendix D.

ANDROMEDA (54767414AMY3001) is an on-going, randomized, open-label, active-controlled, Phase III trial evaluating efficacy and safety of Daratumumab plus VCd as compared to VCd alone in adult patients with newly diagnosed systemic AL amyloidosis (Janssen 2020b). ANDROMEDA is the study supporting EMA approval.

7.1.2 Efficacy and safety – ANDROMEDA

Eligible patients had confirmed AL amyloidosis, involvement in ≥1 organ(s), measurable hematologic disease (i.e. via serum free light chain criteria or serum M-protein) and an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0-2. Patients were excluded if they had advanced Stage IIIb disease on the European Modification of the Mayo Cardiac Staging System, an estimated glomerular filtration rate (eGFR) of <20 mL/min/1.73 m2, a previous or current diagnosis of symptomatic multiple myeloma, evidence of significant cardiovascular conditions or abnormal liver enzyme levels (i.e. alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal), non-AL amyloidosis, or a planned autologous stem cell transplantation (ASCT) during the first six cycles treatment.

Patients were randomly assigned in a 1:1 ratio to receive either subcutaneous daratumumab plus VCd (D-VCd) or VCd alone, after balancing for cardiac stage (i.e. Stage I, II, and IIIa), renal function (i.e. creatine clearance [CrCl] ≥60 or <60 mL/min), and the availability of ASCT (Figure 6). Patients in the D-VCd and VCd groups both received a maximum of six 28 day cycles of VCd therapy, including subcutaneous VELCADE® (bortezomib; 1.3 mg/m2; maximum weekly dose: 500 mg), oral or intravenous (IV) cyclophosphamide (300 mg/m2; maximum weekly dose: 500 mg), and oral or IV dexamethasone (20 or 40 mg weekly) (Figure 6). Patients in the D-VCd group also received a fixed 1,800 mg dose of subcutaneous daratumumab, with weekly therapy (Q1W) during Cycles 1-2 and bi-weekly therapy (Q2W) during cycles 3-6. After Cycle 6, patients in the D-VCd group continued to daratumumab monotherapy every four weeks (Q4W), until experiencing disease progression, starting a subsequent anti-plasma cell therapy, or a maximum of 24 cycles (~2 years) from the first dose of study treatment.

The goal was for all subjects to complete 6 cycles of treatment. Patients that did not achieve VGRP or better after 6 cycles were switched to subsequent therapy. However, patients could receive subsequent therapy earlier in case of

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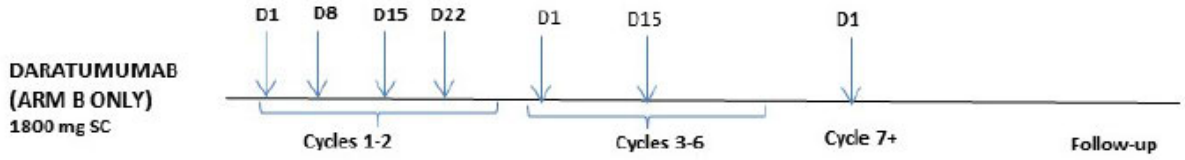
developed major organ deterioration progression-free-survival, or if the best achieved response was PR but in combination with worsening organ function at cycle 4 day 1.

Both preliminary results from February 2020 (median follow-up duration: 11.4 months, median treatment duration: 5.3 month in the VCd group, 9.6 month in the D-VCd group) and the new "18-Month-Landmark" results from May 2021 (median follow-up duration: 25.8 months; median treatment duration: 5.3 month in the VCd group, 21.3 months in the D-VCd group) are presented. Both the D-VCd and VCd regimens remained well tolerated, with no new safety concerns identified, and D-VCd continued to provide deeper and more rapid hematologic response than VCd alone (Janssen 2021a). The study design is described in more detail in Appendix C.

Figure 5: ANDROMEDA daratumumab dosing schedule

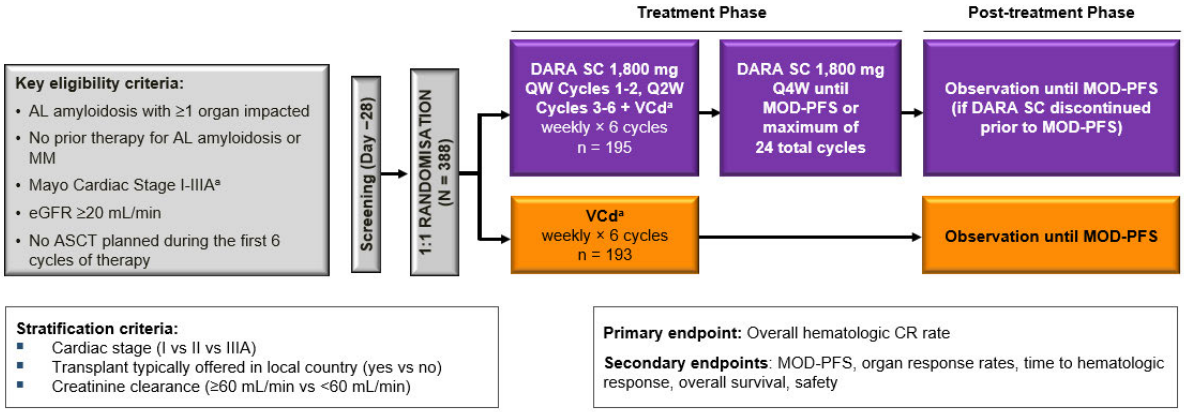


Note: from Cycle 7 onwards, daratumumab is dosed every four weeks until a maximum of 24 total cycles (see Figure 6).

Abbreviations: D = day.

Source: Janssen (2019).

Figure 6: Overview of the ANDROMEDA trial study design



[a]Note: 8 patients with initial Stage IIIa disease progressed to Stage IIIb disease between screening and baseline assessments (D-VCd 1.0%; VCd 3.2%).

Source: Janssen (2020a).

Patient demographics and disease characteristics were well balanced across the two treatment groups and were reflective of the general patient population with newly diagnosed AL amyloidosis (Appendix C). At baseline, patients had a mean age of 63.1 years (median: 64.0 years), with a total of 163 females (42.0%) and 225 males (58.0%). Most patients had ≥2 affected organs (D-VCd: 66.2%; VCd: 64.8%), most commonly the heart (71.8% and 71.0%, respectively) and the kidneys (59.0% and 59.1%). Approximately one-third of patients had Stage IIIa disease on the Mayo Clinic Cardiac Staging System (D-VCd: 35.9%; VCd: 33.2%). Patients with Stage IIIb disease were excluded during screening, although eight patients with initial Stage IIIa disease progressed to stage IIIb disease between screening and baseline assessments (D-VCd: 1.0%; VCd: 3.2%; combined Stage IIIa/IIIb disease: 37.3% and 35.6%, respectively). Fluorescence in situ hybridization (FISH) testing indicated that t(11;14) translocations were present in approximately

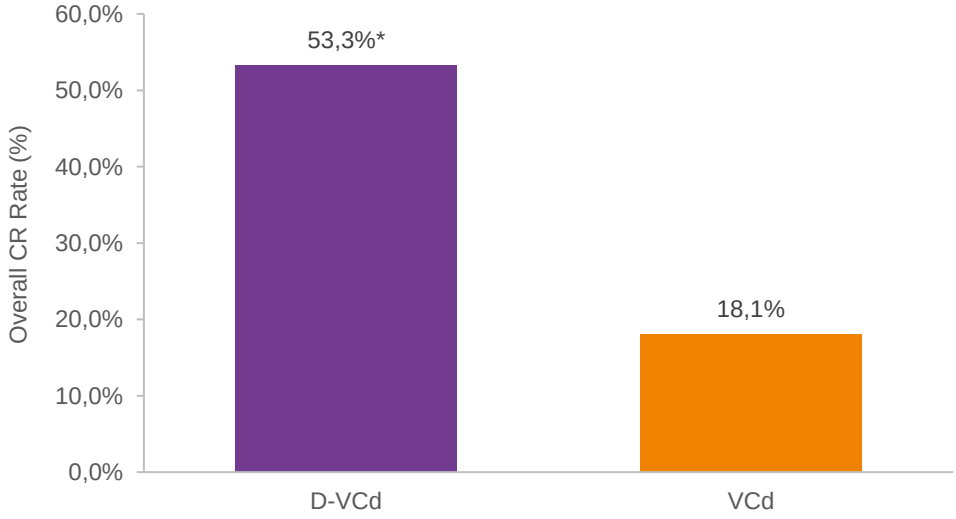
half of evaluable patients (D-VCd: 53.7% [n evaluable = 95]; VCd: 51.4% [n evaluable = 107]). Among randomized patients (n = 388), a total of 381 (98.2%) received study treatment (Appendix C).
The following ANDROMEDA results are presented:

- "Preliminary Results": February 2020 ((median follow-up duration: 11.4 months, median treatment duration: 5.3 month in the VCd group, 9.6 month in the D-VCd group)
- "Updated 18-month Landmark Results": May 2021 (median follow-up duration: 25.8 months; median treatment duration: 5.3 month in the VCd group, 21.3 months in the D-VCd group)

7.1.2.1 Preliminary results (11.4 months follow-up)

7.1.2.1.1 CR rate (primary endpoint)

At a median follow-up duration of 11.4 months, the addition of daratumumab SC to VCd resulted in a statistically significant and clinically meaningful improvement in the overall CR (as per confirmed IRC assessment) compared to VCd alone (53.3% and 18.1%, respectively; P < 0.0001; Figure 7). Compared with VCd, D-VCd was associated with an approximately five-fold greater probability of achieving CR (odds ratio [OR] 5.13; 95% confidence interval [CI] 3.22 8.16).



* P < 0.0001 for D-VCd vs. VCd.

Abbreviations: CR = complete hematologic response; D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; IRC = independent review committee; ITT = intention-to-treat; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone.

Source: Janssen (2020d).

Achievement of CR was consistent across all prespecified patient subgroups, including hard-to-treat patients with Mayo Cardiac Stage III disease or t(11:14) translocation, with higher rates in the D-VCd group than in the VCd group for all analyses (Figure 8 and Figure 9). When stratified by the severity of cardiac involvement at baseline, patients in the D-VCd group had similar rates of CR across each cardiac stage (Stage I: 44.7%; Stage II: 53.9%; Stage IIIa/IIIb: 58.3%). In contrast, achievement of CR declined in the VCd group as cardiac involvement worsened, ranging from 27.9% at Stage I to just 10.0% at Stage IIIa/IIIb. In addition, patients in the D-VCd group had similarly high rates of CR regardless of t(11;14) translocation (i.e. 52.3%-54.9%), whereas the VCd group had lower rates among patients with this translocation (present: 12.7%; absent: 25.0%). However, the interpretation of certain subgroup results may be limited by small sample sizes, including for other race and baseline renal Stage III disease.

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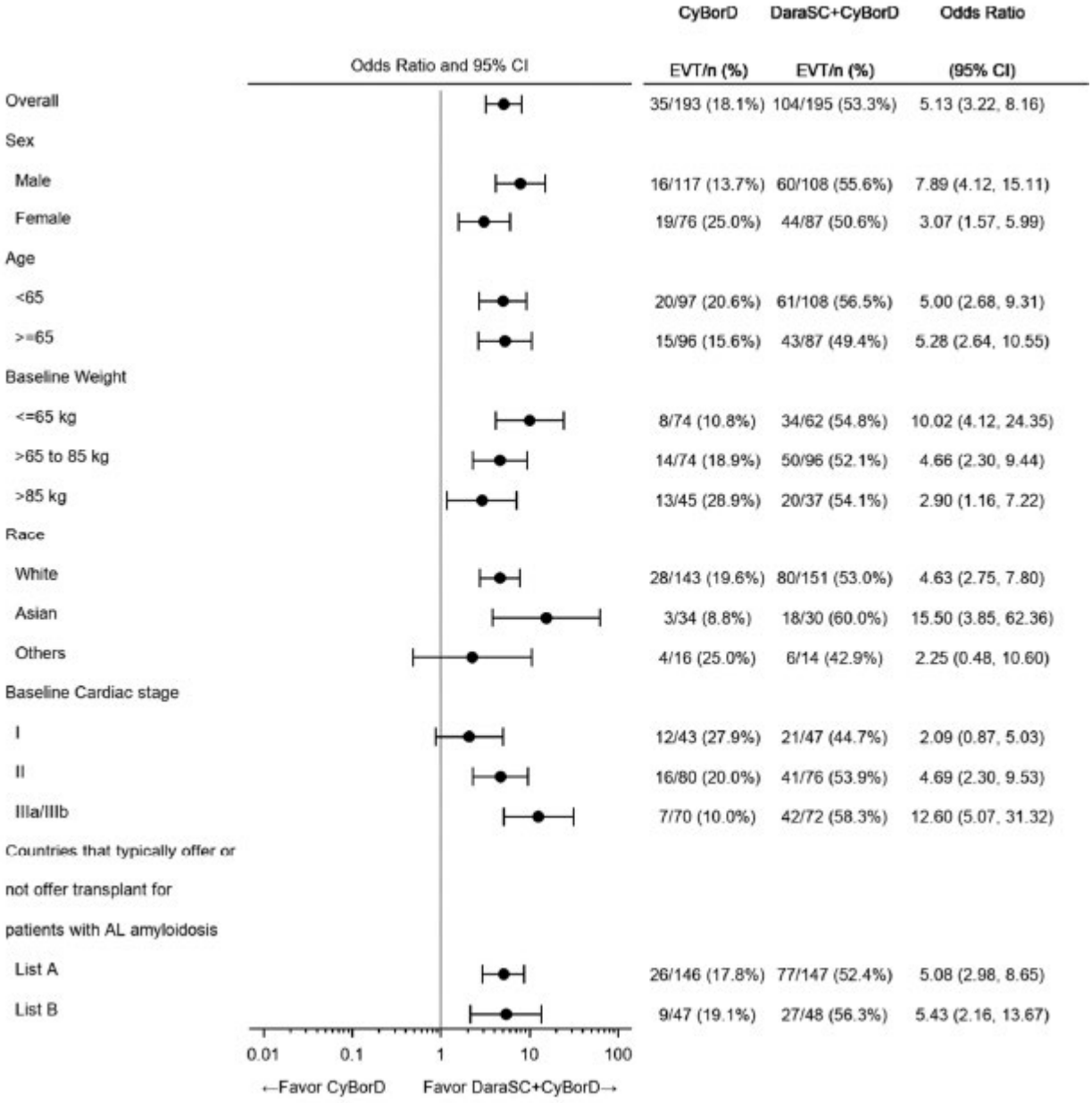
In the model depth of hematologic response is applied as a surrogate for OS. This assumption is not only supported by evidence, but also in line with the treatment goal of AL amyloidosis. See Appendix H for further details.

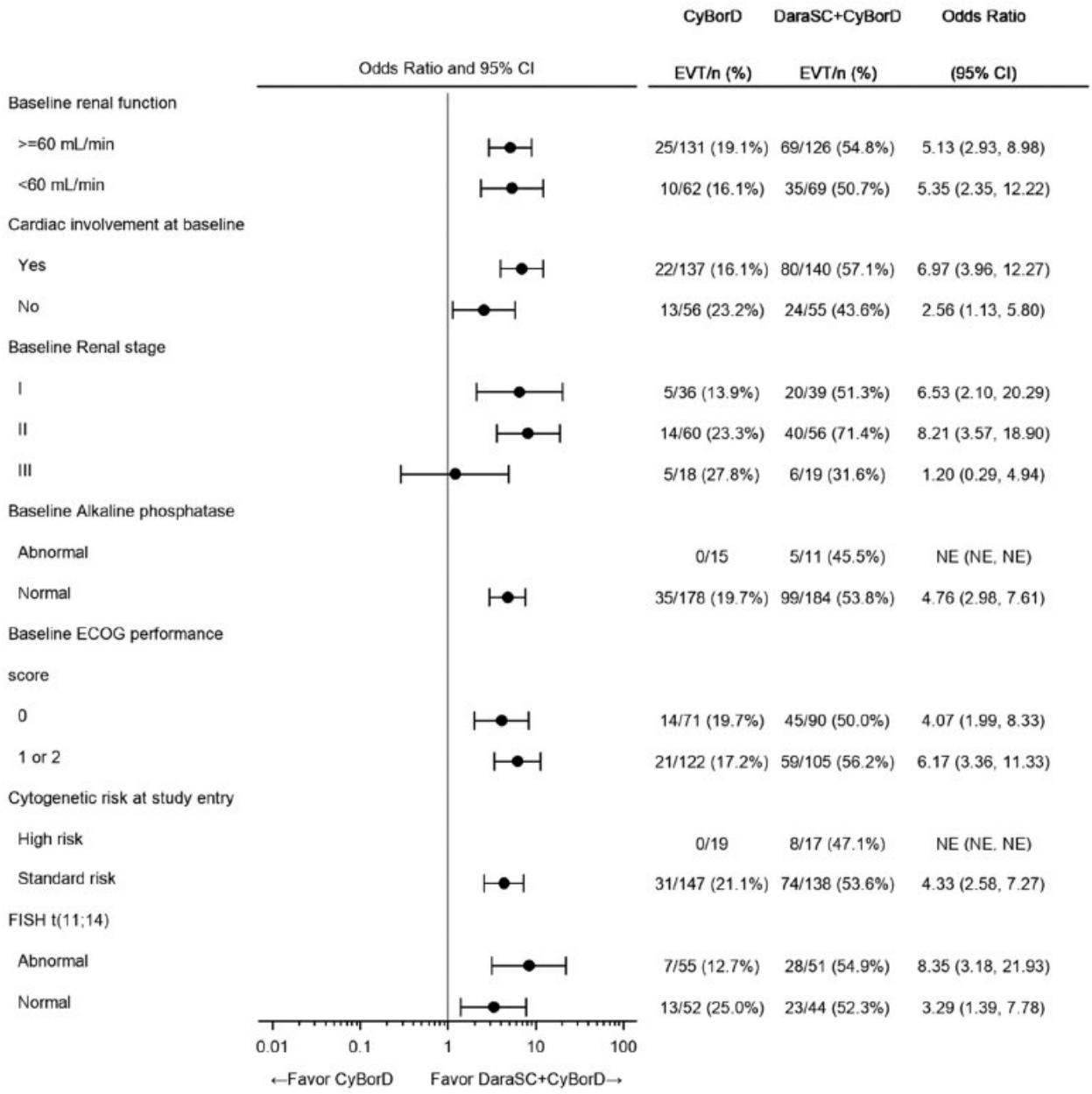
Figure 8: Forest plot of subgroup analyses of CR, as per confirmed IRC assessment; ITT analysis set, ANDROMEDA (panel 1 of 2)



Abbreviations: AL = amyloid light chain; CI = confidence interval; CR = complete hematologic response; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); DaraSC+CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); EVT = event; IRC = independent review committee; ITT = intent-to-treat.

Source: Janssen (2020b).

Figure 9 Forest plot of subgroup analyses of CR, as per confirmed IRC assessment; ITT analysis set, ANDROMEDA (panel 2 of 2)



Abbreviations: CI = confidence interval; CR = complete hematologic response; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); DaraSC+CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); ECOG = Eastern Cooperative Oncology Group; EVT = event; FISH = florescence in situ hybridization; IRC = independent review committee; ITT = intent-to-treat.

Source: Janssen (2020b).

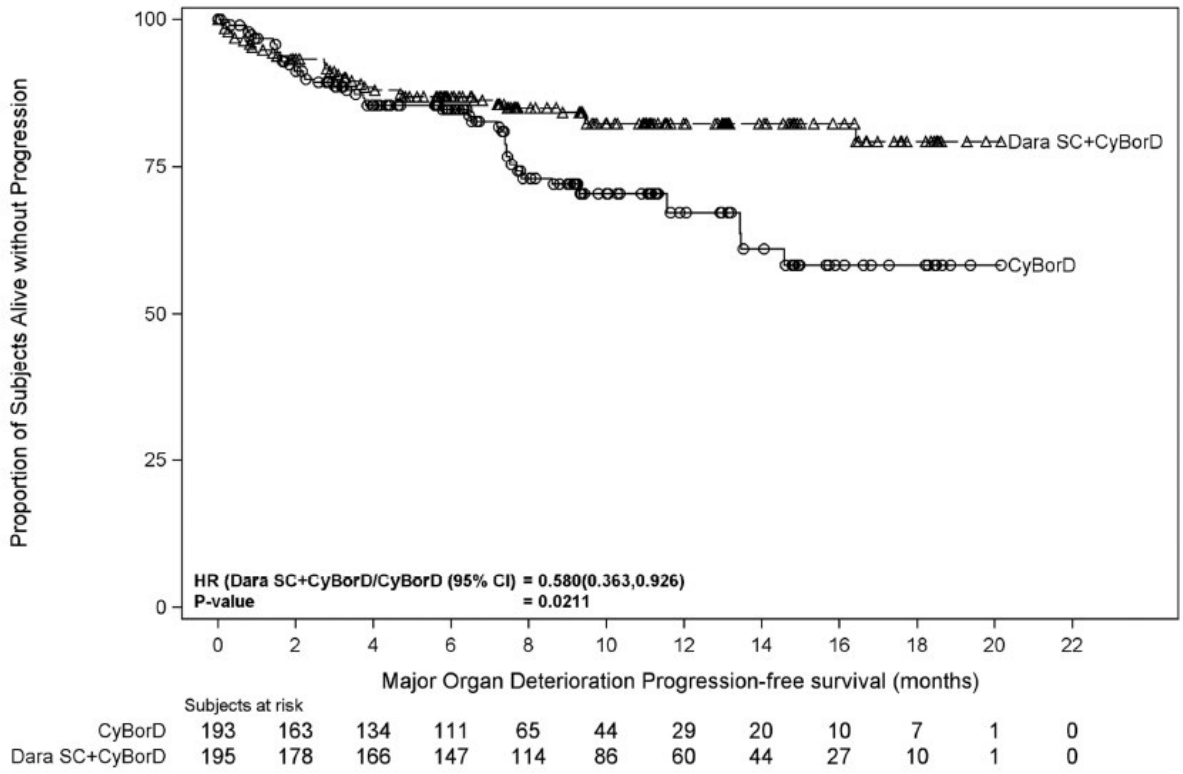
7.1.2.1.2 MOD-PFS (major secondary efficacy endpoint)

Analysis of major organ deterioration – progression-free survival (MOD-PFS) is based on the ITT population. The Kaplan-Meier method was used to estimate the distribution of overall MOD-PFS for each treatment group. The primary treatment comparison of the distribution of overall MOD-PFS is based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated

based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis, and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min).

At a median follow-up duration of 11.4 months, a substantial improvement in major organ deterioration progression-free survival (MOD-PFS)[6] was observed in the D-VCd group compared to VCd alone (Figure 10). The nominal P value for this interim analysis was 0.0211, above the prespecified alpha level (i.e. significance threshold) of 0.00136. However, the substantial treatment difference is demonstrated by the clear separation of the two Kaplan–Meier curves in Figure 10. The median MOD-PFS was not yet reached in either treatment group, with an estimated 18-month MOD-PFS rate of 79.3% in the D-VCd group and 59.8% in the VCd group.

Figure 10: Weighted Kaplan–Meier plot of MOD-PFS, as per IRC assessment; ITT analysis set, ANDROMEDA



Abbreviations: CI = confidence interval; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); Dara SC + CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); IRC = independent review committee; ITT = intent to-treat; MOD-PFS = major organ deterioration progression-free survival. Source: Janssen (2020d).

As shown in Figure 10 above, MOD-PFS rates appeared to diverge beginning at Month 6, after patients completed Cycle 6 of VCd therapy. This may be attributed in part to daratumumab monotherapy delaying hematologic progression in the D-VCd group from Month 6 onwards (i.e. relative to no treatment in the VCd group [among those who did not switch to subsequent therapies]). It may also be related to early cardiovascular-related mortality among patients with advanced cardiac involvement in both treatment groups (chapter 155.1.3), as mortality represented the

[6] Defined as the time from randomization to any of the following events, whichever comes first: Death; End-stage cardiac failure (need for heart transplant, LVAD, or IABP); End-stage renal failure (need for hemodialysis or kidney transplant); Hematologic progression.

primary MOD-PFS event during follow-up. Indeed, these deaths are due to irreversible advanced amyloidosis-related cardiomyopathy (nearly all Mayo Cardiac Stage III), which are not impacted early on by either regimen.

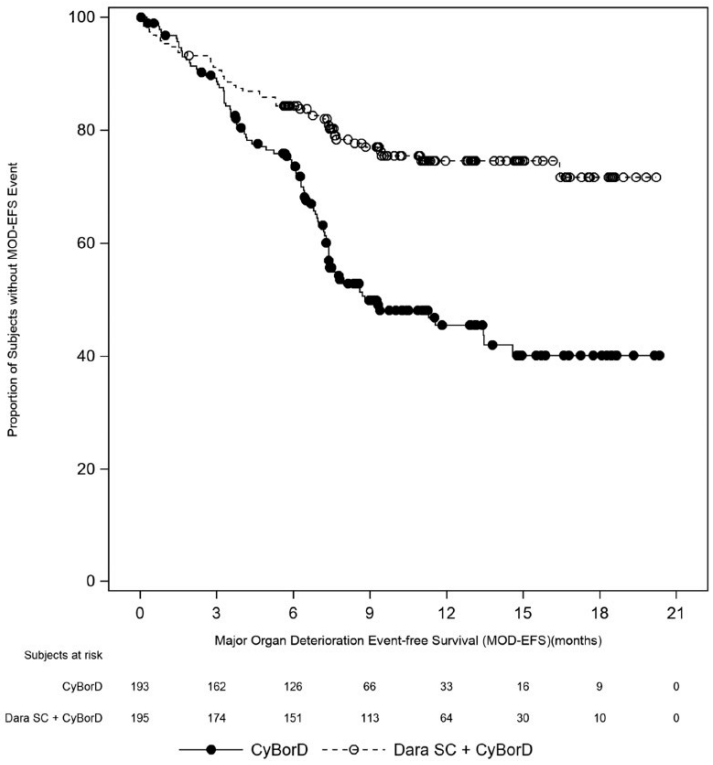
7.1.2.1.3 MOD-EFS

Analysis of major organ deterioration – event-free survival (MOD-EFS) is based on the ITT population. The Kaplan-Meier method was used to estimate the distribution of overall MOD-EFS for each treatment group. The primary treatment comparison of the distribution of overall MOD-EFS is based on a stratified log-rank test. The p-value from a stratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on a stratified Cox's regression model with treatment as the sole explanatory variable. Stratification factors used in the analyses include cardiac stage (Stage I, II, and IIIa), countries that typically offer transplant for patients with AL amyloidosis, and renal function (CrCl ≥60 mL/min or CrCl <60 mL/min).

As per the study design and the current treatment paradigm for AL amyloidosis, patients could switch to subsequent non-cross resistant, anti-plasma cell therapy before hematologic progression or MOD in cases of suboptimal hematologic response or worsening organ function. Therefore, the initiation of subsequent therapy is a key measure of both the speed and depth of hematologic response. As subsequent therapy is not captured by MOD-PFS assessments, major organ deterioration event-free survival (MOD-EFS)[7] was also evaluated (i.e. to assess MOD-PFS events or the initiation of subsequent anti-plasma cell therapy, whichever came first). Preliminary assessment of MOD-EFS showed significantly prolonged survival in the D-VCd group, in comparison with the VCd group. At a median follow-up of 11.4 months, median MOD-EFS was reached at 8.8 months in the VCd group but was not yet reached in the D-VCd group (HR 0.39; 95% CI 0.27-0.56; nominal P < 0.0001) (Figure 11).

[7] Defined as the time from randomization to occurrence of any of the above MOD-PFS events (i.e. death, cardiac or renal failure, hematologic progression), or the initiation of subsequent non-cross resistant anti-plasma cell therapy, whichever comes first.

Figure 11: Weighted Kaplan–Meier plot of MOD-EFS, as per IRC assessment; ITT analysis set, ANDROMEDA



Abbreviations: CI = confidence interval; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); Dara SC + CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); IRC = independent review committee; ITT = intent to-treat; MOD-EFS = major organ deterioration event-free survival.

Source: Janssen (2020d).

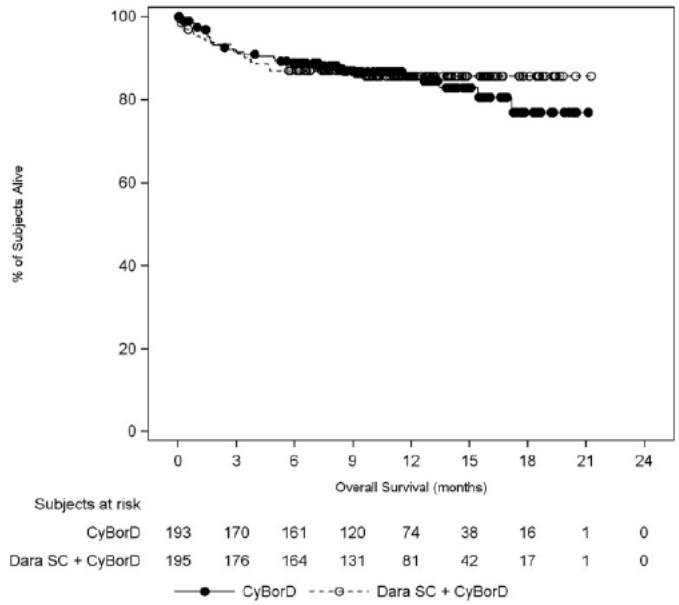
7.1.2.1.4 OS (major secondary efficacy endpoint)

OS is analyzed for the ITT population. The Kaplan-Meier method is used to estimate the distribution of OS for each treatment group. Median OS with 95% CI will be provided. In the primary analysis, the distribution of OS for the 2 treatment groups is compared based on an unstratified log-rank test. A p-value from an unstratified log-rank test will be reported. Hazard ratio and its 95% confidence interval will be estimated based on an unstratified Cox's regression model with treatment as the sole explanatory variable.

12

Figure 12: Weighted Kaplan–Meier plot of OS, ITT analysis set, ANDROMEDA

[8] Note: one patient randomized to the VCd group died prior to receiving study treatment Janssen (2020b). A randomized Phase 3 study to evaluate the efficacy and safety of daratumumab in combination with cyclophosphamide, bortezomib and dexamethasone (CyBorD) compared with CyBorD in newly diagnosed systemic AL amyloidosis (ANDROMEDA; Protocol 54767414AMY3001). Clinical study report. August 18, 2020. Data on file.



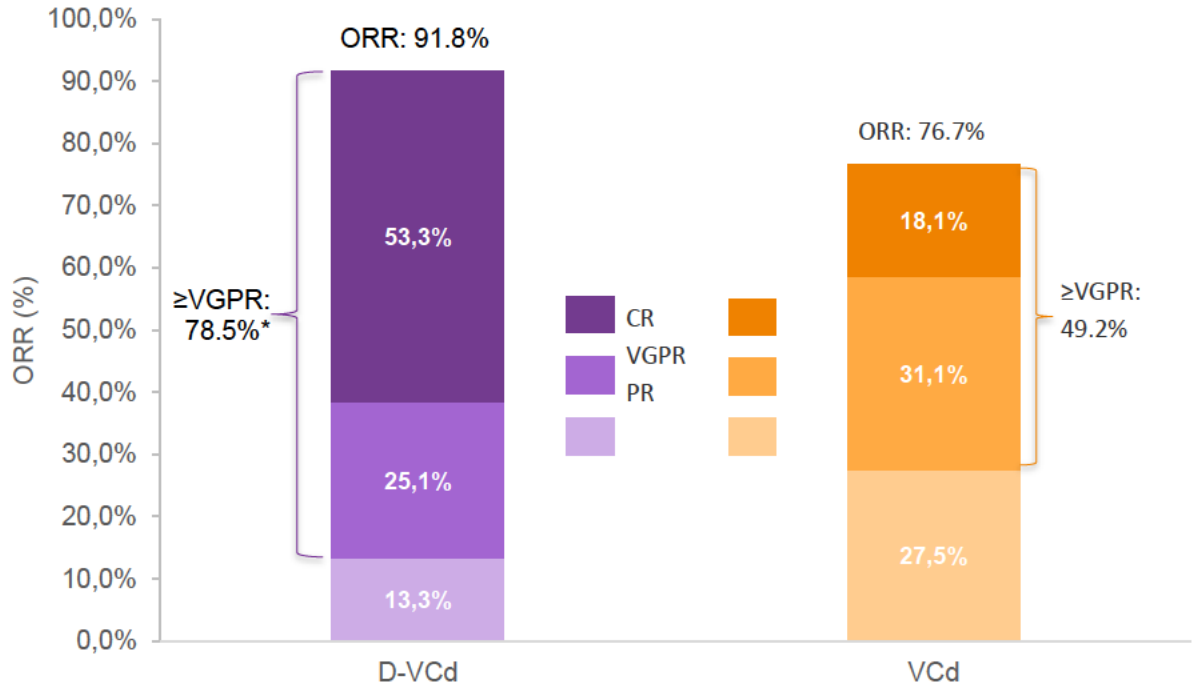
Abbreviations: CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); Dara SC + CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); ITT = intent-to-treat; OS = overall survival.

Source: Janssen (2020b)

7.1.2.1.5 Achievement of ≥VGPR rate

Achievement of hematologic VGPR or better (i.e. VGPR or CR; also referred to as ≥VGPR) was also significantly greater in the D-VCd group than in the VCd group (78.5% vs 49.2%; OR 3.75; 95% CI 2.4-5.9; P < 0.0001) (Figure 13). Accordingly, the overall response rate (i.e. PR, VGPR, and CR combined) was also higher in the D-VCd group (91.8%) than in the VCd group (76.7%).

Figure 13: Achievement of ≥VGPR and ORR, ITT analysis set, ANDROMEDA



*P < 0.0001 for D-VCd vs. VCd.

Abbreviations: CR = complete hematologic response; D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, dexamethasone; ORR = overall response rate; PR = partial response; VCd = VELCADE® (bortezomib), cyclophosphamide, dexamethasone; VGPR = very good partial response.

Source: Janssen (2020b).

7.1.2.1.6 Median time to CR or ≥VGPR

Among patients with CR, the median time to CR was 60 days in the D-VCd group (range: 8-299 days) and 85 days in the VCd group (range: 14-340 days). The time to very good partial response (VGPR) or better was considerably shorter, occurring at a median of 17 days in the D-VCd group (range: 5-336) and at 25 days in the VCd group (range: 8-171). Overall, it was observed that response rates increased with time of exposure in both study arms.

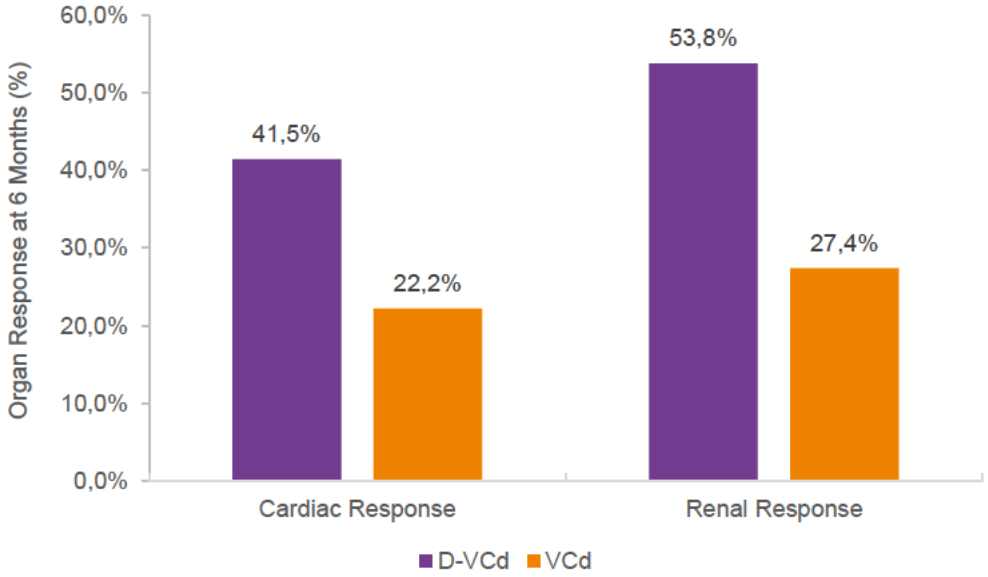
7.1.2.1.7 Duration of hematologic response

At a median follow-up of 11.4 months, the median duration of CR was not yet reached in either the D-VCd group (range: 0.85+ to 17.5+ months) or the VCd group (range: 0.03+ to 18.4+ months). Among the 104 patients who achieved CR in the D-VCd group, 4 (3.8%) died while in CR and none relapsed during follow-up. Among the 35 patients with CR in the VCd group, 2 died while in CR (5.7%) and 2 relapsed (5.7%) during follow-up.

7.1.2.1.8 Cardiac, renal, and liver response rates

Among evaluable patients with cardiac involvement at baseline (D-VCd: n = 118 [61%]; VCd: 117 [61%]), achievement of cardiac response at 6 months was nearly doubled in D-VCd group compared with the VCd group (41.5% and 22.2%; OR 2.44; 95% CI 1.35-4.42; Figure 14) (Janssen, 2020d). Similarly, among evaluable patients with renal involvement at baseline (D-VCd: n = 117 [60%]; VCd: 113 [59%]), achievement of renal response at 6 months was also nearly doubled in D-VCd group compared with the VCd group (53.8% and 27.4%; OR 3.34; 95% CI 1.88-5.94; Figure 14: 6-month cardiac and renal response rates, as per IRC assessment; ITT analysis set, ANDROMEDA (Figure 14). Achievement of hepatic response at 6 months ranged from 40.0% in the D-VCd group to 7.1% in the VCd group, although the number of evaluable patients was too small for any meaningful efficacy comparisons (D-VCd: n = 10; VCd: n = 14).

Figure 14: 6-month cardiac and renal response rates, as per IRC assessment; ITT analysis set, ANDROMEDA



Abbreviations: D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; IRC = independent review committee; ITT = intention-to-treat; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone. Source: Janssen (2020b).

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7.1.2.1.9 Time to cardiac, renal, and liver response

Both cardiac and renal response were reached faster in the D-VCd group than in the VCd group, with or without censoring for subsequent non-cross–resistant anti-plasma cell therapy (Table 10). The median time to cardiac response was 3.02 months in the D-VCd group and 3.84 months in the VCd group, after censoring for subsequent therapy. The median time to renal response was also reached approximately one month faster in the D-VCd group, at 1.22 months compared with 2.20 months in the VCd group. Time to liver response was faster in the D-VCd group if not censoring for subsequent therapy, although the sample size of evaluable patients was too small for meaningful comparisons.

Table 10: Median time to cardiac, renal, and liver response, as per IRC assessment; ANDROMEDA

	D-VCd[a]	VCd[a]
Median time to cardiac response, months (range)		
Censoring for subsequent anti-plasma cell therapy	3.02 months (1.00-10.3)	3.84 months (0.9-2.9)
Not censoring for subsequent anti-plasma cell therapy	2.97 months (1.00-10.3)	3.81 months (0.9-2.9)
Median time to renal response, months (range)		
Censoring for subsequent anti-plasma cell therapy	1.22 months (0.4-9.3)	2.20 months (0.9-14.8)
Not censoring for subsequent anti-plasma cell therapy	1.22 months (0.4-9.3)	1.95 months (0.9-14.8)
Median time to liver response, months (range)		
Censoring for subsequent anti-plasma cell therapy	4.67 months (1.0-9.5)	2.00 months (2.0-2.0)
Not censoring for subsequent anti-plasma cell therapy	4.67 months (1.0-9.5)	5.31 months (2.0-8.6)

[a] Note: the median time to organ response is reported for evaluable responding patients in the D-VCd group (cardiac n = 59; renal n = 83; liver n = 5) and in the VCd group (cardiac n = 41; renal n = 45; liver n = 2).

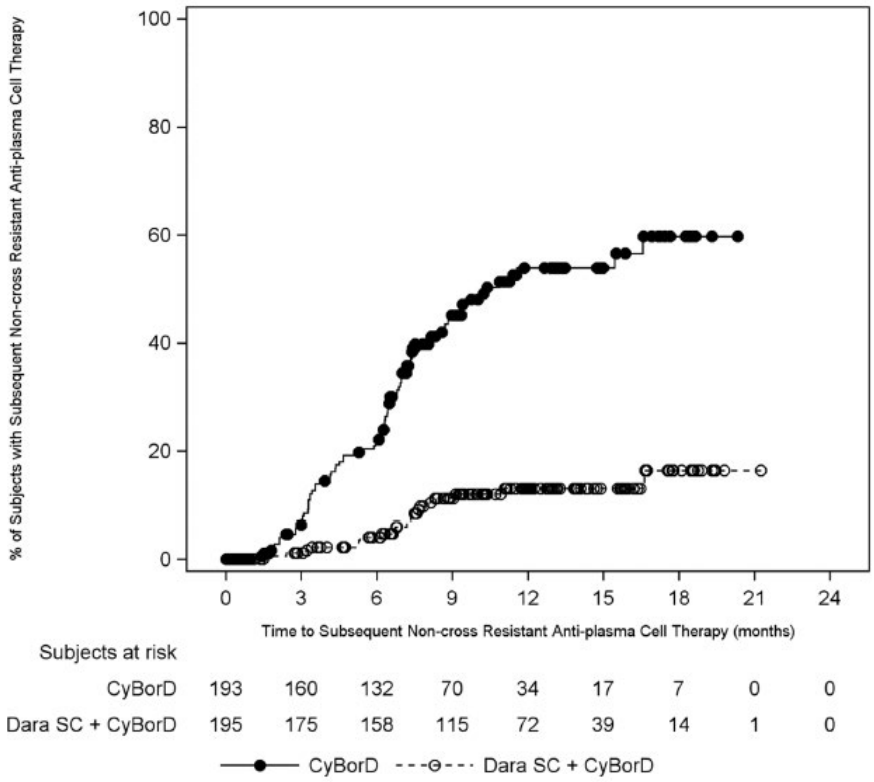
Abbreviations: D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; IRC = independent review committee; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone.

Source: Janssen (2020b).

7.1.2.1.10 Time to initiation of subsequent non-cross resistant anti-plasma cell therapy (secondary endpoint)

Consistent with the higher rates of hematologic response in the D-VCd group, the probability of requiring subsequent non-cross resistant anti-plasma cell therapy was significantly reduced relative to the VCd group (10.8% and 43.0% of patients, respectively; HR 0.20; 95% CI 0.12 0.32; P < 0.0001). Hazard ratio and 95% CI from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with cardiac stage (Stage I, II, and IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis, and renal function (CrCl>=60 mL/min or CrCl <60 mL/min) . The median time to initiation of subsequent non-cross resistant anti-plasma cell therapy was not yet reached in the D-VCd group during follow-up, compared with 10.38 months in the VCd group (HR=0.20, 95% CI: 0.12, 0.32; p<0.0001) (Figure 15) (Janssen, 2020d, c).

Figure 15: Kaplan–Meier plot for time to first subsequent non-cross resistant anti-plasma cell therapy; ITT analysis set, ANDROMEDA



Abbreviations: CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); Dara SC + CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); ITT = intent-to-treat.

Source: Janssen (2020b).

Importantly, among evaluable patients in the VCd safety set (n = 188), 48 patients (25.5%) switched to subsequent daratumumab IV[9] therapy, either alone or in combination with other regimens (Janssen 2020b). This switch to second line daratumumab is consistent with key guideline recommendations, real-world treatment patterns, and the high response rates achieved with daratumumab monotherapy in relapsed or refractory patients.

7.1.2.1.11 EORTC QLQ-C30 fatigue and global health status

During Cycles 1-6, EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0) Fatigue and Global Health Status scores worsened in the VCd group, whereas they generally remained stable in the D-VCd group (Figure 16 and Figure 17). Notably, at Week 16 there was a significant relative reduction in both Fatigue and Global Health Status scores in the VCd group compared with the D-VCd group. The least squares (LS) mean Fatigue score increased (i.e. worsened) by 9.99 points (95% CI 6.21 13.78) from baseline in the VCd group at Week 16, compared with just 1.32 points in the D VCd group (95% CI -2.44 to 5.08; unadjusted P = 0.0007).

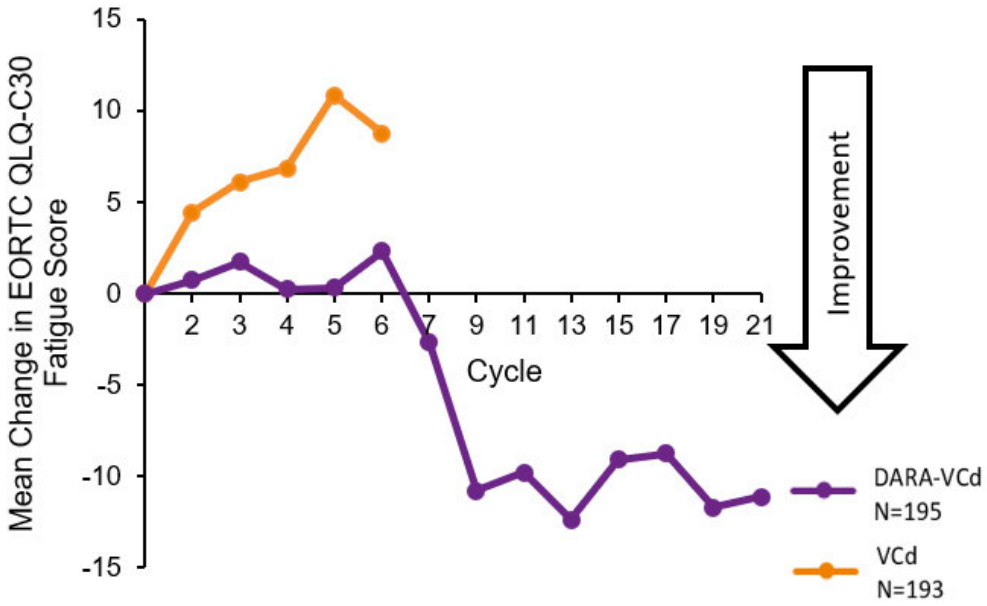
In post-hoc analysis, LS mean were derived based on the Mixed-effects Model for Repeated Measures (MMRM) with baseline PRO score, period, treatment and treatment-by-period interaction as fixed effects and individual subject as

[9] Note: As of the data cut-off on February 14, 2020, subcutaneous daratumumab was not yet approved for the treatment of AL amyloidosis, and would not have been commercially available for patients to switch to.

random effect. The p value does indeed refer to the difference between the LS mean values. The difference and CI between the arms is -8.672[-13.7,-3.68]. For GHS the difference [CI], p-value is 4.681 [0.522,8.840], 0.0274.

Similarly, the LS mean Global Health Status score decreased (i.e. worsened) by 7.24 points (95% CI -10.38 to -4.11) from baseline in the VCd group at Week 16, compared with 2.56 points in the D VCd group (95% CI -5.68 to 0.55; unadjusted P = 0.0274). After completing Cycles 1-6, mean Fatigue and Global Health Status scores both continually improved in the D-VCd group during the daratumumab monotherapy portion of the Treatment Phase (Figure 16 and Figure 17).

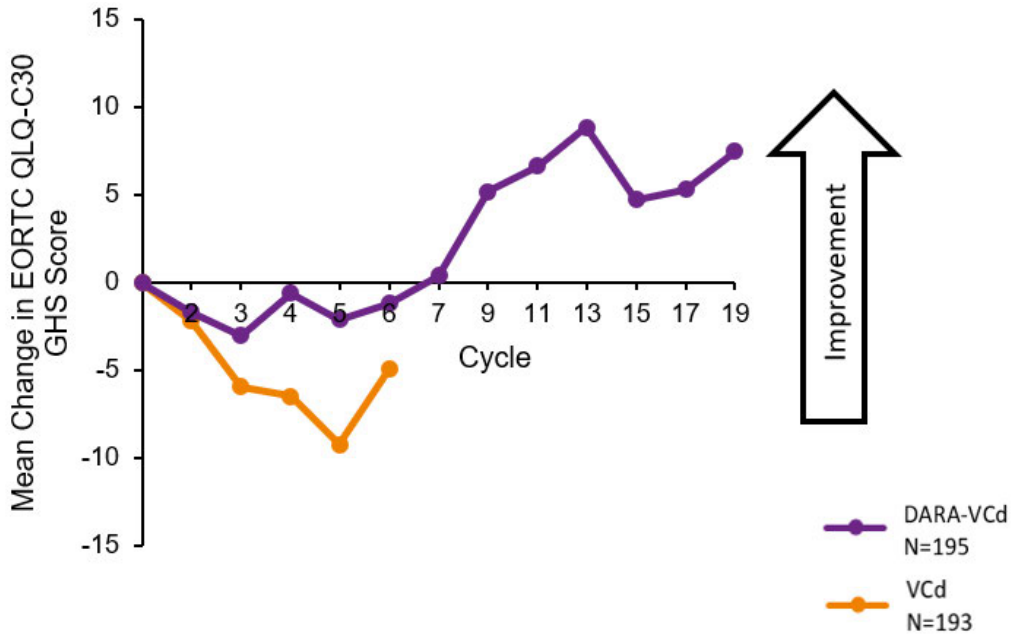
Figure 16: Mean EORTC QLQ-C30 Fatigue scores over time, ITT analysis set, ANDROMEDA



Abbreviations: DARA = daratumumab; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; ITT = intention to treat; VCd = VELCADE® [bortezomib], cyclophosphamide, and dexamethasone.

Sources: Janssen (2020b), Sanchorawala (2020a).

Figure 17: Mean EORTC QLQ-C30 Global Health Status scores over time, ITT analysis set, ANDROMEDA



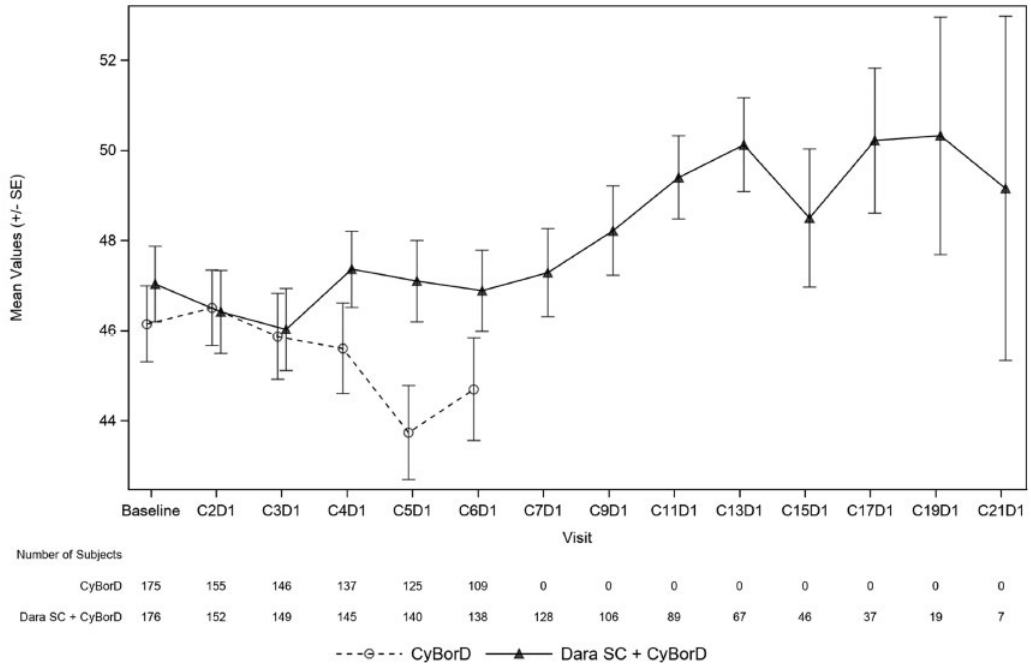
Abbreviations: DARA = daratumumab; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Version 3.0; ITT = intention to treat; VCd = VELCADE® [bortezomib], cyclophosphamide, and dexamethasone.

Sources: Janssen (2020b), Sanchorawala (2020a).

7.1.2.1.12 SF-36 MCS scores

As with EORTC QLQ-C30 scores, Short-Form 36 Version 2 (SF-36v2) mental component summary (MCS) scores remained stable in the D-VCd group during Cycles 1-6, whereas they significantly worsened in the VCd group. At Week 16, LS mean SF-36v2 MCS scores decreased by 2.95 points in the VCd group (95% CI -4.59 to -1.31), compared with just 0.11 points in D-VCd group (95% CI -1.73 to 1.52; unadjusted P = 0.0101) (Figure 5.20). After completing Cycles 1-6, mean MCS scores continually improved in the D-VCd group during the daratumumab monotherapy portion of the Treatment Phase (Figure 18).

Figure 18: Mean SF-36v2 MCS scores over time, ITT analysis set, ANDROMEDA

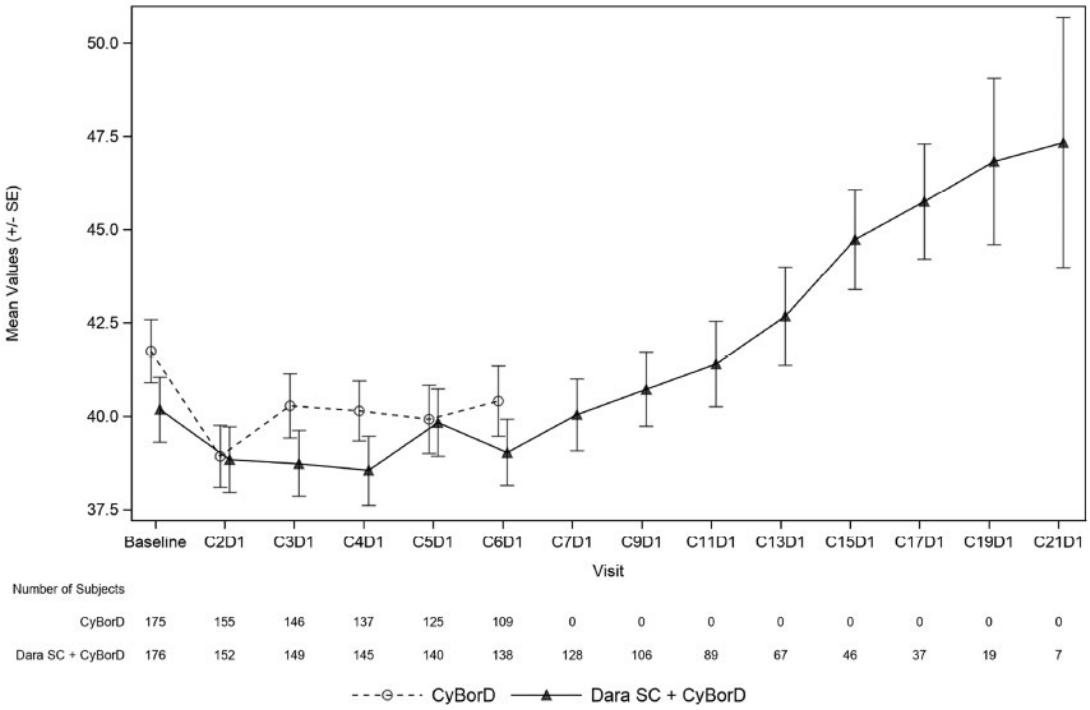


Abbreviations: C = cycle; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); D = day; Dara SC+CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); MCS = mental component summary; SE = standard error; SF-36v2 = Short Form 36 Version 2.

Source: Janssen (2020b).

A similar pattern was also observed for SF-36v2 physical component scores (PCS; exploratory efficacy endpoint). That is, mean PCS scores remained relatively stable during Cycles 1-6 in the D-VCd group, and then continually improved during subsequent daratumumab monotherapy (Figure 19).

Figure 19: Mean SF-36v2 PCS scores over time, ITT analysis set, ANDROMEDA



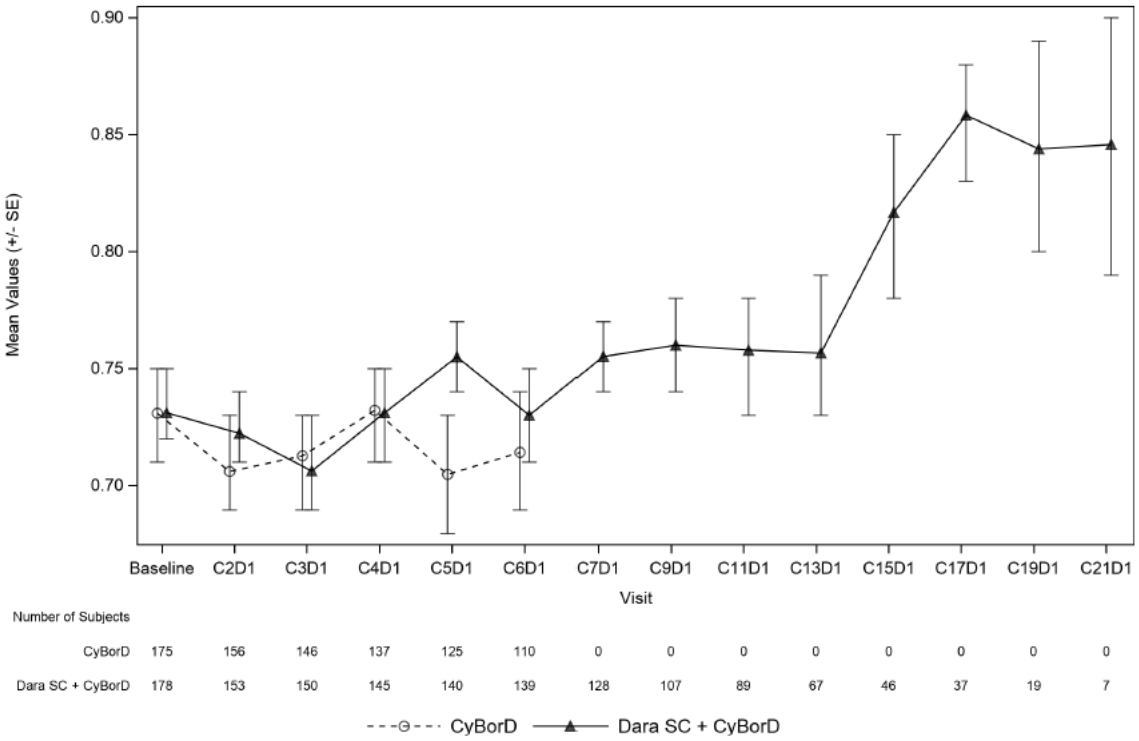
Abbreviations: C = cycle; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); D = day; Dara SC+CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); PCS = physical component summary; SE = standard error; SF-36v2 = Short Form 36 Version 2.

Source: Janssen (2020b).

7.1.2.1.13 EQ-5D-5L scores (Exploratory Efficacy Endpoint)

EuroQoL 5-Dimensions 5 Levels (EQ-5D-5L) scores worsened in the VCd group during Cycles 1-6, whereas they remained relatively stable in the D-VCd group (Figure 5.22). At week 16, there was no change in LS mean EQ-5D-5L utility scores in the D-VCd group (0.00 points; 95% CI 0.032 to 0.033), whereas scores decreased (i.e. worsened) significantly in the VCd group (-0.056 points; 95% CI -0.089 to -0.023; unadjusted P = 0.0104 vs. D-VCd). After completing Cycles 1-6, mean EQ-5D-5L utility scores continually improved in the D-VCd group throughout subsequent daratumumab monotherapy (Figure 20).

Figure 20: Mean EQ-5D-5L utility scores over time, ITT analysis set, ANDROMEDA



Abbreviations: C = cycle; CyBorD = VCd (VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); D = day; Dara SC+CyBorD = D-VCd (daratumumab, VELCADE® [bortezomib], cyclophosphamide, and dexamethasone); EQ-5D-5L = EuroQoL 5-Dimensions 5 Levels; SE = standard error.

Source: Janssen (2020b).

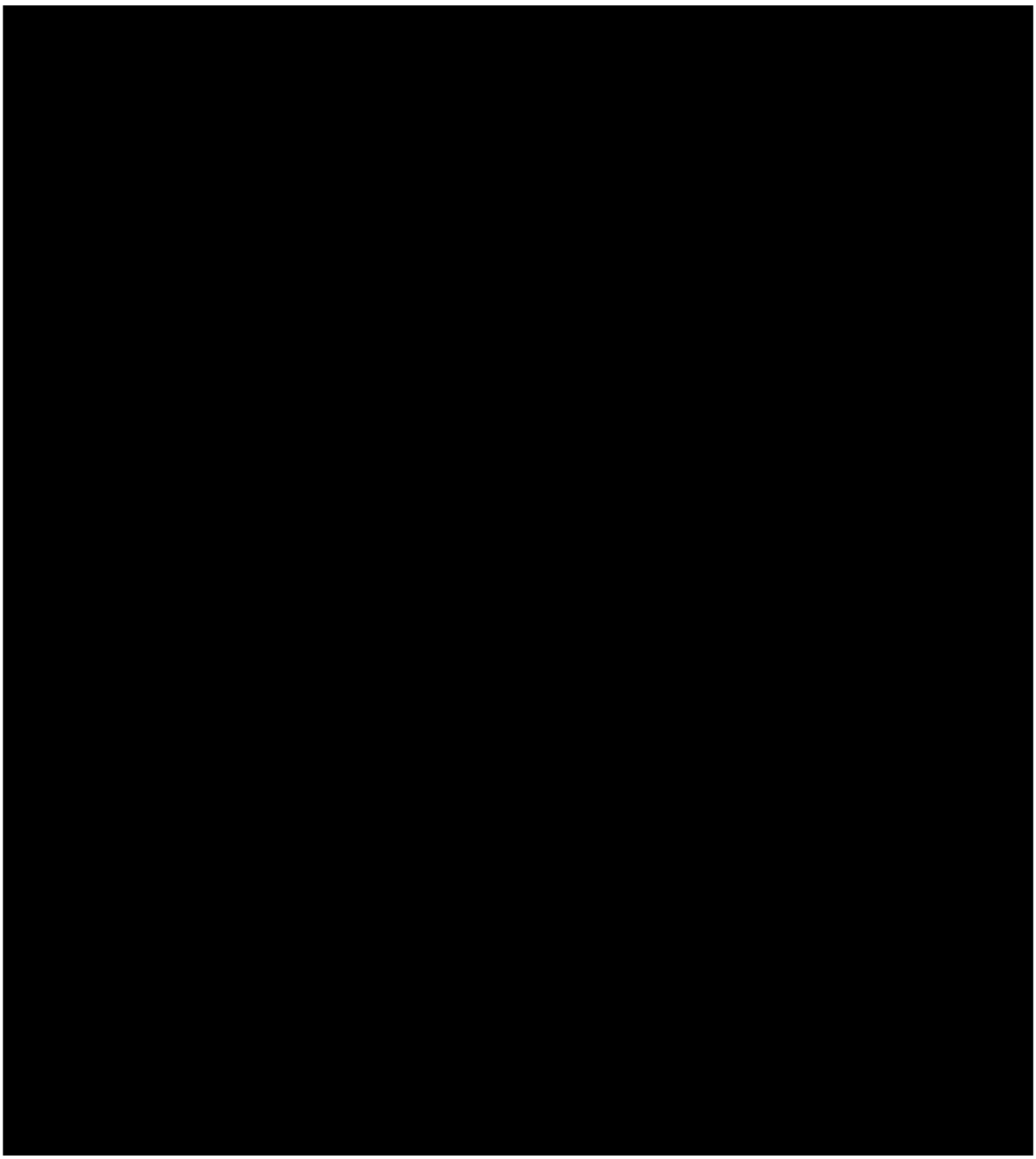
7.1.2.2 18-month landmark results (25.8 months follow-up)

[redacted]

7.1.2.2.1 CR rate (primary endpoint)

[redacted]

Figure 21: Forest Plot of Subgroup Analysis of Confirmed Complete Hematologic Response Rate Based on IRC Assessment; Intent-to-treat Analysis Set Plot 1 of 2



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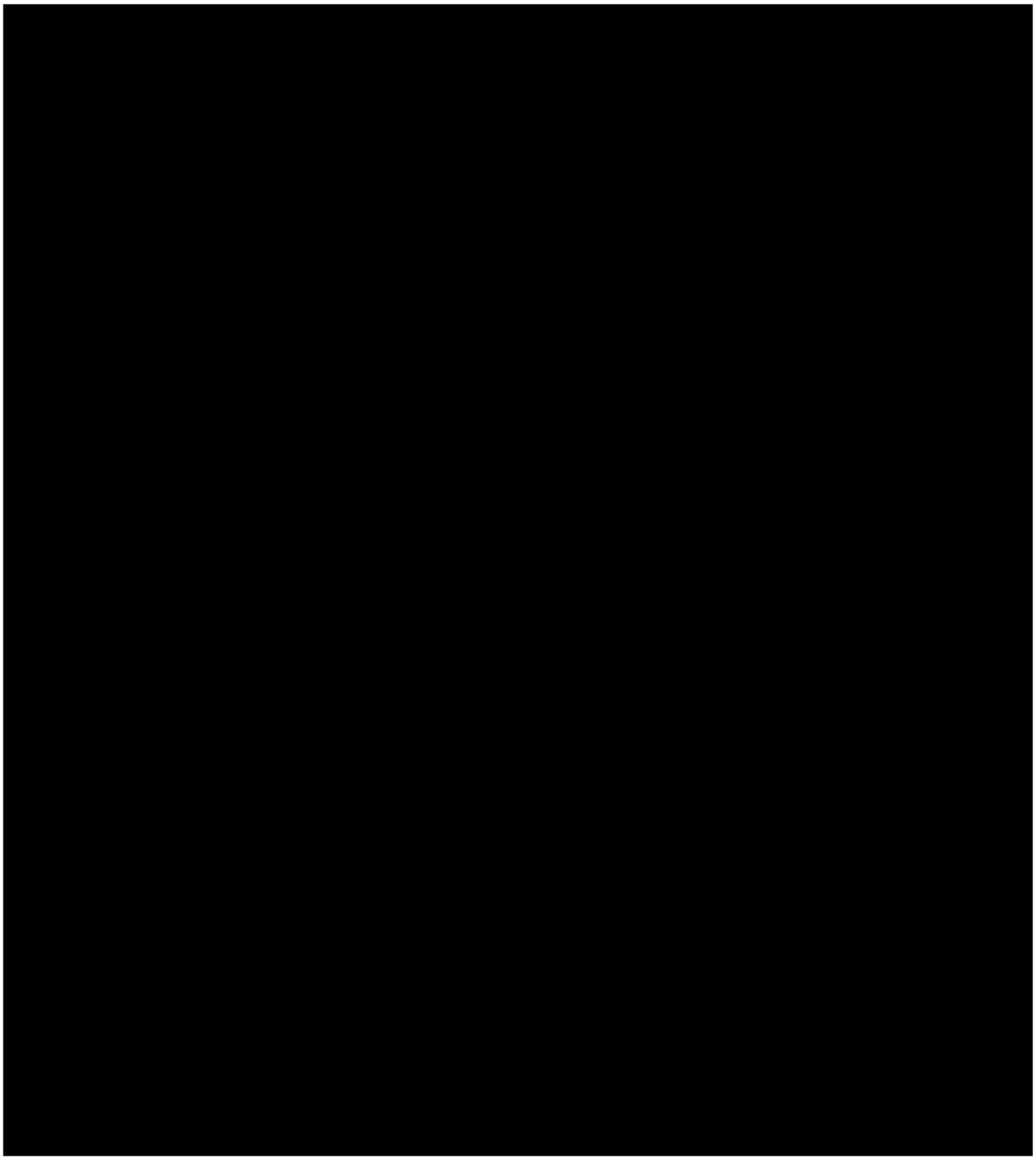
[redacted]

Figure 22: Forest Plot of Subgroup Analysis of Confirmed Complete Hematologic Response Rate Based on IRC Assessment; Intent-to-treat Analysis Set Plot 2 of 2



[redacted]

[redacted]

[redacted]

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[redacted]

[redacted]

7.1.2.2.2 Achievement of ≥VGPR Rate

[redacted]

[redacted]

[10] Note: the interpretation of certain subgroup analyses may be limited by small sample sizes.

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Figure 23: Achievement of ≥VGPR and ORR, ITT analysis set, ANDROMEDA (18-month update)

[redacted]

[redacted]

[redacted]

7.1.2.2.3 Median time to CR or ≥VGPR

[redacted]

7.1.2.2.4 Cardiac and renal response rates

[redacted]

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Figure 24: 6-, 12-, and 18-month cardiac response rates, as per IRC assessment; ITT analysis set, ANDROMEDA (18-month update)

Figure 25: 6-, 12-, and 18-month renal response rates, as per IRC assessment; ITT analysis set, ANDROMEDA (18-month update)

7.1.2.2.5 Time to initiation of subsequent non-cross resistant anti-plasma cell therapy

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[redacted]

7.1.2.2.6 Adverse events

Overall, both the D-VCd and VCd therapies were well tolerated by patients in ANDROMEDA, with no new safety concerns identified for the addition of daratumumab to VCd both in the preliminary and the 18-month landmark analysis (Janssen 2021b). [redacted]

[redacted] More detailed safety data is presented in Appendix F.

7.1.3 Comparative analyses of efficacy and safety

No meta-analysis, narrative synthesis, or indirect comparison was performed as a part of this application.

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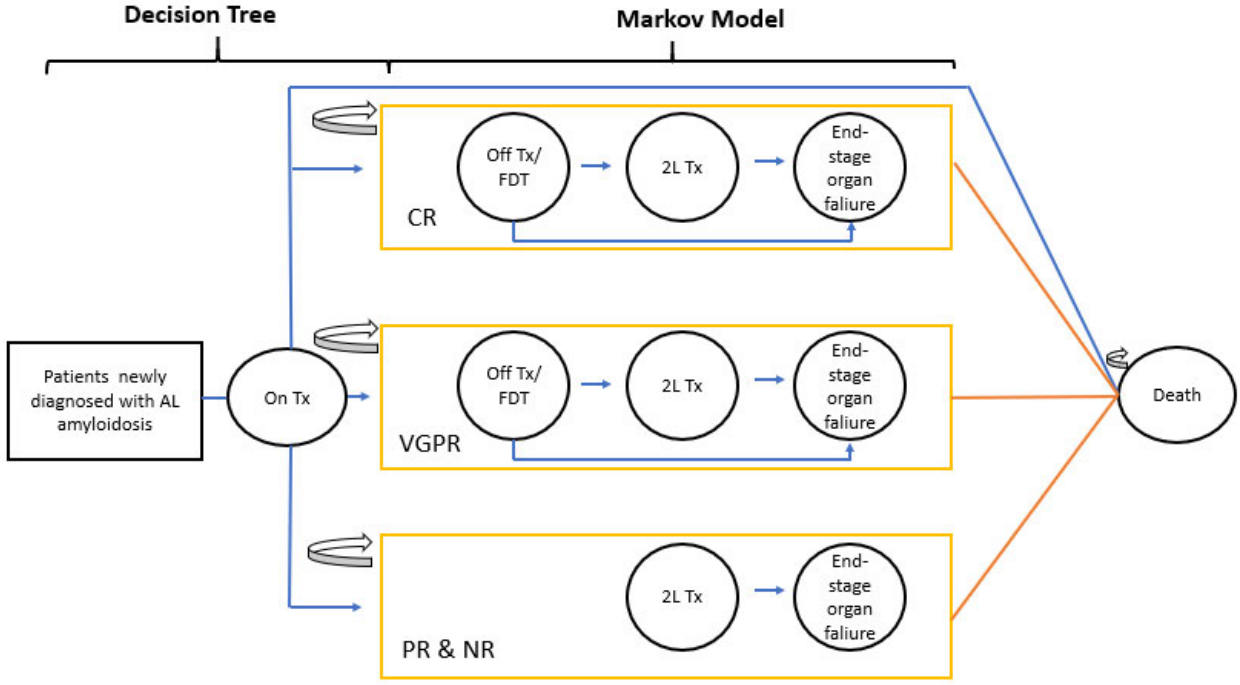
8. Health economic analysis

8.1 Model

The objective of this economic evaluation was to determine the cost effectiveness of daratumumab (DARZALEX®) in combination with bortezomib, cyclophosphamide, and dexamethasone (D-VCd) for the first-line treatment of patients with systemic amyloid light-chain (AL) amyloidosis.

No existing publication of an economic model for AL amyloidosis was identified in the systematic review of the published literature. Therefore, to conduct a CUA for D-VCd an economic model was designed and developed to appropriately reflect the clinical trial evidence and patient pathway. A Microsoft Excel-based decision tree paired with a Markov model was developed to capture all costs and outcomes associated with D-VCd and VCd. The model includes a total of 12 health states, as shown in Figure 26. The specific model design was selected to appropriately reflect clinical practice and the disease course for patients newly diagnosed with AL amyloidosis.

Figure 26: Overview of the model structure



Abbreviations: 1L = first-line; 2L = second-line; AL = amyloid light-chain; FDT = fixed daratumumab treatment; Tx = treatment.

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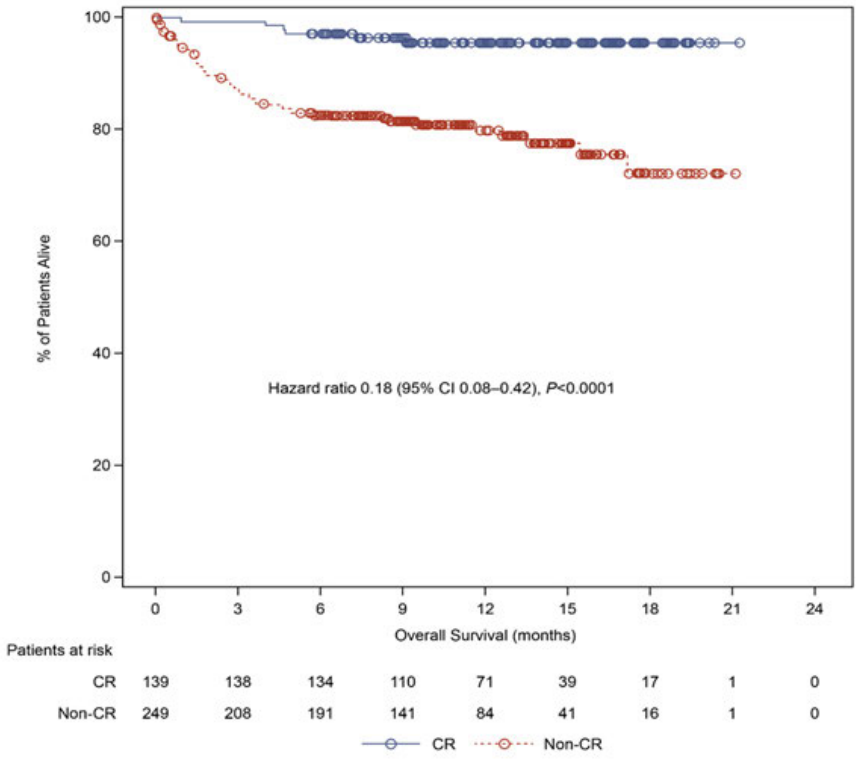
Figure 27: OS in patients from pooled treatment groups stratified by hematologic CR in ANDROMEDA



Abbreviations: CI = confidence interval; CR = complete response; OS = overall survival.

Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months).

The decision tree allows for patient stratification by hematologic response to reflect the goals of first-line therapy of identifying early responders or non-responders at 6 cycles, as well as to demonstrate the value of D-VCd as an effective therapy for achieving early and deep responses, as shown in the ANDROMEDA trial.

The Markov model captures a patient's disease course after being assessed for their initial response to treatment. For initial responders, after they complete their first-line treatment regimen or transition to receive daratumumab monotherapy, patients are monitored (i.e., "watch and wait" approach) and may eventually experience disease relapse necessitating second-line treatment. Initial non-responders are immediately switched to second-line treatment without completing the first-line treatment. According to feedback from clinical experts in the UK and US, it is very uncommon for patients to receive multiple lines of therapy due to the toxicity of drugs used in later lines that outweighs their potential benefits, and as seen in the ANDROMEDA trial data, the majority of patients receive only one line of subsequent therapy (Janssen 2020b). Ultimately patients experience disease progression, which is captured with the 'End-stage Organ Failure' health state.

Given the pre-progression heterogeneity of AL amyloidosis patients based on their treatment status and hematologic response, a three-state model (as has been submitted for previous daratumumab MM indications) would have been inadequate to reflect the complexity of this disease. It was recommended that, for the purpose of economic modelling, multiple health states should be included to appropriately reflect the different depths of response and that the depth of hematologic response should be linked to changes in survival, health-related quality of life (HRQoL), and costs (Papaioannou 2010).

8.1.1 Decision tree

Within the decision tree, all patients are either alive on first-line treatment and are stratified based on their hematologic response (i.e., CR, VGPR, or PR/NR), or dead. End-stage organ failure was not considered in the decision tree, as very few organ deterioration events were reported in the ANDROMEDA trial during the first six months of treatment initiation, suggesting that organ failure is a consequence of disease progression that would occur in the long-term rather than during the first six cycles of the model. The 6-month exit in the decision tree model is in line with the 6 cycles of treatment for VCd in the ANDROMEDA trial and allows for informing hematologic response in the model based on a mature landmark point where patient's best hematologic response is expected to be fully established (Janssen Research and Development 2020a, Wechalekar 2020).

8.1.2 Markov model

Upon exit from the decision tree, patients are stratified into one of three Markov models based on their hematologic response achieved (i.e., CR, VGPR, or PR/NR) as outlined in Figure 26. Patients flow through the individual health states in a linear manner; that is, they can remain in their current state or transition to a progressive state but they cannot transition back to a health state they previously transitioned from. Because the health states for patients achieving CR or VGPR differ from patients achieving PR or NR, patient flow through their respective Markov models will be described based on hematologic response below. For information pertaining to health state transition probabilities, please refer to Appendix L.

8.1.2.1 Patients achieving CR or VGPR

As outlined in Figure 26, the Markov models for CR and VGPR have four identical health states: (1) Off First-line Treatment/fixed daratumumab treatment (Off Tx/FDT), (2) Second-line Treatment (2L Tx), (3) End-stage Organ Failure, (4) Death (described in Table 11 below).

Table 11: Description of model health states

Model health state	Description of patients included in the health state
Off Tx/FDT	D-VCd arm: • Patients who received daratumumab monotherapy for a fixed treatment duration (up to a maximum of 24 cycles) • Patients who have discontinued treatment but have not transitioned to '2L Tx' VCd arm: • Patients who stop any treatment and are observed (i.e., have completed their course of chemotherapy)
2L Tx	Patients go back onto treatment (due to hematologic or organ progression, or at the physician's discretion) and will receive chemotherapy second-line treatment.
End-stage Organ Failure	Encompasses patients that require hemodialysis.
Death	Patients who die in any cycle will move into this health state.

Abbreviations: 1L = first-line; 2L = second-line; AL = amyloid light-chain; FDT = fixed daratumumab treatment; Tx = treatment.

Patients who remain in the 'Off Tx/FDT' health state beyond a maximum of 24 cycles of daratumumab will not receive drug therapy and associated costs (similar to VCd patients). Regardless of their treatment arm, patients in the 'Off Tx/FDT' health state can remain in their current health state or transition to '2L Tx' or 'End-stage Organ Failure' as per ANDROMEDA transition probabilities.

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In the '2L Tx' health state, patients can either remain in this health state or transition to 'End-stage Organ Failure'.
In the 'End-stage Organ Failure' health state patients can remain alive within this health state or die.
At any cycle, patients can die and move from any health state to the absorbing "Death' health state.

8.1.2.2 Patients achieving partial response or no response

As outlined in Figure 26 and Table 12, the Markov model for patients achieving PR or NR has three health states: (1) 2L Tx, (2) End-stage Organ Failure, (3) Death. The primary difference between the Markov models for PR/NR and for CR or VGPR is the absence of the 'Off Tx/FDT' health state. According to published literature and clinical feedback, patients that do not achieve a satisfactory response (i.e., PR or NR) early in their treatment course should immediately switch to a different treatment regimen (Palladini 2016, Merlini 2018, Milani 2018, Fotiou 2020). Thus, those with PR or NR hematologic responses will directly enter the '2L Tx' health state.

In the '2L Tx' health state, patients go back onto treatment (due to hematologic or organ progression, or at the physician's discretion) and will receive treatment for refractory disease. Patients can either remain in this health state or transition to 'End-stage Organ Failure'.

The 'End-stage Organ Failure' health state encompasses patients receiving hemodialysis. Patients can remain alive within this health state (until the end of the time horizon) or die.

At any cycle, patients can die and move from any health state to the absorbing "Death' health state.
Additional details pertaining to the various health states included in the model are provided in Table 12.

Table 12: Overview of decision tree and health states

Decision Tree	Description and Patient Flow	Associated Costs and/or Utilities
CR **VGPR** **PR and NR**	Patients newly diagnosed with AL amyloidosis commence treatment with either D-VCd or VCd Patients remain within the decision tree for six cycles While in the decision tree, patients are either alive and stratified by their hematologic response or dead	First-line drug therapy costs First-line drug administration costs First-line co-medication costs First-line disease monitoring costs First-line AE management costs (one-time cost) Healthcare resource use costs Indirect costs AE utility decrements (one-time decrement) CR, VGPR, PR/NR utilities
Death	Absorbing state Patients can die within the decision tree or from any health state	End of life costs (one-time cost)
By CR, VGPR, and PR/NR		
Off Tx/FDT (CR or VGPR only)	Represents patients in the VCd arm that have completed their treatment course (six cycles) and are being observed	Daratumumab monotherapy drug costs (only for patients in D-VCd arm)

Decision Tree	Description and Patient Flow	Associated Costs and/or Utilities
	Represents patients in the D-VCd arm receiving daratumumab monotherapy up to a maximum of 24 cycles, or being observed Patients can enter this state either directly from the decision Patients can remain in this health state or may transition to '2L Tx', 'End-stage Organ Failure', or 'Death'	Daratumumab monotherapy drug administration costs (only for patients in D-VCd arm) Daratumumab co-medication costs (only for patients in D-VCd arm) First-line disease monitoring costs Healthcare resource use costs Indirect costs CR, VGPR, PR/NR utilities
2L Tx	Represents patients receiving second-line therapy due to relapsed (for CR or VGPR) or refractory (for PR/NR) disease Patients can enter this health state only from the 'Off Tx/FDT' state (for CR or VGPR) or directly from the decision tree (for PR/NR) Patients can remain in this health state or transition to 'End-stage Organ Failure' or 'Death' states	Second-line drug therapy and administration costs (one-time cost) Healthcare resource use costs Indirect costs CR, VGPR, PR/NR utilities 2L Tx utility decrement
End-stage Organ Failure	Represents patients requiring treatment for major organ deterioration including solid organ transplant, implantation of a cardiac assist device, or haemodialysis Patients can enter this health state from the 'Off Tx/FDT' (for CR or VGPR), or '2L Tx' health states (for CR, VGPR, or PR/NR) Patients can remain in this health state until the end of the simulation or transition to 'Death'	One-time organ failure-associated costs (heart or kidney transplant, implantation of cardiac assist device) Recurring organ failure costs (haemodialysis, immunosuppressant therapy) Healthcare resource use costs Indirect costs CR, VGPR, PR/NR utilities End-stage organ failure health state utility decrement Haemodialysis utility decrement Solid organ transplant utility decrement (one-time decrement)

Abbreviations: 2L = second-line; AE = adverse event; AL = amyloid light-chain; C = cyclophosphamide; CR = complete response; D = daratumumab; d = dexamethasone; FDT = fixed daratumumab treatment; NR = no response; PR = partial response; Tx = treatment; V = VELCADE® (bortezomib); VGPR = very good partial response.

* All costs and decrements are recurring (i.e., per-cycle) unless specifically stated otherwise.

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8.1.3 Cycle length

The cycle length selected for the model was 28 days to align with the duration of chemotherapy cycles and observation timepoints in the ANDROMEDA trial (Janssen Research and Development 2018). In general, costs that are applied on a per-cycle basis were calculated based on a 28-day cycle. In some instances where ANDROMEDA IPD were used to inform inputs (e.g., distribution of patients in the decision tree) and were only reported/calculated on a monthly basis, a simplifying assumption was made where one month was equivalent to one model cycle.

8.1.4 Perspective

As recommended in the guidelines *Medicinrådets metodevejledning for vurdering af nye lægemidler* (Medicinrådet 2021) from DMC a restricted societal perspective is applied where relevant transport costs and time spent in connection with treatment for both patients and relatives are included. Productivity losses due to the disease and any impact that treatment are omitted from the analysis, in line with DMC guidelines .

8.1.5 Discounting

A discount rate of 3.5% is applied for both costs and health outcomes within the base case analysis (Medicinrådet 2021)The user can specify which discount rates should apply independently for costs and QALYs. A scenario analysis is included where no discounting is applied.

8.1.6 Time horizon

The time horizon in the model is chosen to be 35 years to reflect a lifetime horizon. As patients enter the model at age 63.1, potential long-term survivors are followed until the age 98.1.

8.1.7 Wastage and dose intensity

Relative dose intensities (RDIs) and drug wastage were also considered in the cost calculations. Drug wastage was assumed to occur for all oral, subcutaneous (SC), and intravenous (IV) therapies and was applied in drug cost calculations by incorporating the cost of an entire package or vial of drug even if its constituents were not completely depleted. If drug wastage is excluded from the analysis, drug costing is based on the cost per drug unit (e.g., per milligram). Where relevant, RDIs were applied in calculating total per cycle drug costs. The mean RDIs for each drug regimen, as reported in the ANDROMEDA clinical study report, are presented in Table 13.

Table 13: Mean relative dose intensities

Drug Regimen	RDI
D-VCd	D: 0.969 V: 0.929 C: 0.847 d: 0.944
VCd	V: 0.951 C: 0.854 d: 0.960

Source: ANDROMEDA CSR (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a).

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8.1.8 Validation

The model underwent internal validation for model calculations and logic testing by the model programmer, as well as a thorough review of all calculations and data inputs for accuracy and logic by a reviewer not involved with the initial model programming. In addition, an external vendor (Costello Medical) conducted an independent quality and sanity check of the model.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Input data used in the cost-effectiveness model are presented in Table 14.

Table 14: Input data used in the model

Name of inputs	Source	Value used in the model	How is the value used in the model/Comments
Complete response	(Palladini 2012)	Exponential parametric distribution	Extrapolation of overall survival for complete responders in Markov model
Very good partial response		Exponential parametric distribution	Extrapolation of overall survival for very good partial responders in Markov model
Partial response / No response		Weibull parametric model	Extrapolation of overall survival for partial responder and no responders in Markov model
State occupancy (cycle 6)			
Complete response	ANDROMEDA 18-month landmark analysis (Janssen 2021a)	[redacted]	Distributing patients based on response category in decision tree to enter long-term Markov models
Very good partial response		[redacted]	
Partial response / No response		[redacted]	The death rates are calculated based on the KM estimated survival rates in the ANDROMEDA trial. At 6 months the survival rate for DVCD and VCD were estimated at 0.87 and 0.888, respectively. Hence, death rate for DVCD is calculated as 1 – 0.87 and 1 – 0.888 for VCD.
Dead		[redacted]	
Adverse events occurrence			
Lymphopenia	ANDROMEDA 12-month landmark analysis (Janssen 2021b)	13.0	Used to inform adverse event disutility and costs
Neutropenia		5.2	
Pneumonia		8.3	

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Name of inputs	Source	Value used in the model	How is the value used in the model/Comments
Diarrhoea		5.7	Used to inform adverse event disutility and costs
Edema		3.1	
Hypokalemia		2.1	
Syncope		6.2	
Cardiac failure		6.2	
Adverse events disutilities			
Lymphopenia	Assumed same as neutropenia	0.09	
Neutropenia	(Nafees 2008)	0.09	
Pneumonia	(Beusterien 2010)	0.2	
Diarrhoea	(Stein 2018)	0.176	Adverse event disutilities are included in the model.
Edema	(Brown 2001)	0.06	
Hypokalemia		0.02	
Syncope	(Sullivan 2011)	0.0039	
Cardiac failure		0.1034	
Adverse events costs			
Lymphopenia	Interactive DRG: 08MA98 (BXXB0) Tværfaglig udredning og behandling for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	Used to inform adverse event costs
Neutropenia	Interactive DRG: 08MA98 (DD709) Neutropeni UNS for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	
Pneumonia	Interactive DRG: 08MA98 (DJ189) Pneumoni UNS for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	

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Name of inputs	Source	Value used in the model	How is the value used in the model/Comments
Diarrhoea	Interactive DRG: 08MA98 (DK529B) Ikke-infektiøs diaré UNS for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	
Edema	Interactive DRG: 08MA98 (BMFF0) Ødembehandling og ødemprofylakse for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	
Hypokalemia	Interactive DRG: 08MA98 (DE876) Hypokaliæmi for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	
Syncope	Interactive DRG: 08MA98 (BXXB0) Tværfaglig udredning og behandling for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1645 DKK	
Cardiac failure	Interactive DRG: 08MA12 (DI509) Hjertesvigt UNS for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	43 621 DKK	
Health state utility values			
Complete response	(Janssen 2021e)	0.790	The utility values are applied to the health states
Very good partial response		0.799	
Partial response and Non response		0.799	
Disease management			
Hematologist visit			
Resource per cycle 1L Tx health state	[redacted]	1.00	Disease management costs are included in model. These values inform the frequency of resource consumption.
Resource use per cycle FDT health state	[redacted]	0.54	

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Name of inputs	Source	Value used in the model	How is the value used in the model/Comments
Resource use per cycle Off Tx health state	[redacted] Janssen Data on File 2021 (UK Delphi Panel)	0.50	
Unit cost	Kommunernes og Regionernes Løndatakontor 2022, Overlæger, lægelige chefer m.v.. bruttoløn OCT 2021 (96949 DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.	1367.12 DKK	
Drug acquisition costs			
Daratumumab		38 901.18 DKK	
Bortezomib		652.42 DKK	
Cyclophosphamide		906.61 DKK	
Dexamethasone		133.00 - 352.70 DKK	
Lenalidomide	Medicinpriser.dk https://www.medicinpriser.dk	3882.91 DKK	Used to calculate drug cost per cycle based on drug strength and dosing schedule.
Valaciclovir		558.49 DKK	
Benadryl		67.95 DKK	
Montelukast		95.00 DKK	
Methylprednisolone		145.00 DKK	
Paracetamol		22.70 DKK	
Drug administration costs			
SC injection administration	Sundhedsdatastyrelsen (2021). Interactive DRG: 08MA12 (BWAA31) Medicingivning ved subkutan injektion for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1617.00 DKK	

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Name of inputs	Source	Value used in the model	How is the value used in the model/Comments
IV bolus administration	Sundhedsdatastyrelsen (2021). Interactive DRG: 08MA98 (BWAA62) Medicingivning ved intravenøs inj. gennem permanent venekateter for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1617.00 DKK	
IV infusion administration	Sundhedsdatastyrelsen (2021). Interactive DRG: 08MA98 (BWAA62) Medicingivning ved intravenøs infusion for (DE858A) AL amyloidose. Available at: http://interaktivdrg.sundhedsdata.dk/	1617.00 DKK	
Oral drug administration	Assumption.	0 DKK	
Monitoring costs			
Hematologist visit	Kommunernes og Regionernes Løndatakontor 2022, Overlæger, lægelige chefer m.v.. bruttoløn OCT 2021 (96949 DKK). available from: https://krl.dk/ Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.	1367.12 DKK	Frequency of unit cost needed per drug.
Subsequent treatment			
Lenalidomide and dexamethasone (Rd)	Danish KOL interview	6 cycles	
Daratumumab, bortezomib and dexamethasone (D-Vd)		8 cycles	
End of life costs			
End of life care	(Round 2015) Mean estimated cost per patient (9914 GBP). Converted to DKK (2015 exchange rate used). Inflated to 2022 value. Available from: www.dst.dk	88 051.19 DKK	7 days of treatment needed, with 58% of patients requiring the resource (Source: Danish KOL input)
Patient costs			
Patient transport costs	DMC guidelines (Medicinrådet 2020b)	100 DKK	Patient cost
Patient time for drug administration (per hour)	(Statistics Denmark 2022a)	179.00 DKK	Patient cost

* Some of these estimates will be presented in other tables in the document. This table is a summary.

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** Calculations: [If intermediate outcome measures were linked to final outcomes, describe them here (for example, if a change in a surrogate outcome was linked to a final clinical outcome). Explain how the relationship was estimated, what sources of evidence were used, how the sources of evidence were identified (e.g. systematic literature review) and what other evidence exists. Details must be provided in a separate appendix with reference here.]

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

Systemic AL amyloidosis is a relatively rare disease. The incidence in Denmark is not known, but the estimated incidence is 12 per million per year (DMSG 2021). The calculated eligible patient population for D-VCd has been validated by two clinical experts contacted by Janssen (see section 0).

There is a significant overlap between amyloidosis and multiple myeloma (MM) and 5-10% of patients with multiple myeloma also have amyloidosis. However, patients with MM have been excluded in the ANDROMEDA study. Clinical guidelines clearly recommend treatment according to treatment guidelines for MM in cases of both MM and systemic AL amyloidosis. Amyloidosis can also occur in a number of other clonal B-cell diseases such as CLL and Waldenström's macroglobulinemia, but the incidence of amyloidosis in these conditions is less than 1% (Comenzo 2012).

8.2.2.1 Patient population

ANDROMEDA (54767414AMY3001) is an ongoing, randomized, open-label, active-controlled, Phase III trial in adult patients with newly diagnosed systemic AL amyloidosis (Janssen 2020b). Patient demographics and disease characteristics were well balanced across the two treatment groups and were reflective of the general patient population with newly diagnosed AL amyloidosis. At baseline, patients had a mean age of 63.1 years (median: 64.0 years), with a total of 163 females (42.0%) and 225 males (58.0%). Most patients had ≥2 affected organs (D-VCd: 66.2%; VCd: 64.8%), most commonly the heart (71.8% and 71.0%, respectively) and the kidneys (59.0% and 59.1%). Approximately one-third of patients had Stage IIIa disease on the Mayo Clinic Cardiac Staging System (D-VCd: 35.9%; VCd: 33.2%). Patients with Stage IIIb disease were excluded during screening although eight patients with initial Stage IIIa disease progressed to stage IIIb disease between screening and baseline assessments (D-VCd: 1.0%; VCd: 3.2%; combined Stage IIIa/IIIb disease: 37.3% and 35.6%, respectively). Fluorescence in situ hybridization (FISH) testing indicated that t(11;14) translocations were present in approximately half of evaluable patients (D-VCd: 53.7% [n evaluable = 95]; VCd: 51.4% [n evaluable = 107]). Among randomized patients (n = 388), a total of 381 (98.2%) received study treatment.

Table 15: Patient population used in the model

Patient population Important baseline characteristics	Clinical documentation / source	Used in the model (number/value)
Mean age (years)	ANDROMEDA (Kastritis 2021b)	63.1
Mean body surface area	ANDROMEDA (Kastritis 2021b)	1.84 m^2
Mean weight	ANDROMEDA (Kastritis 2021b)	73.4 kg
Proportion of females	ANDROMEDA (Kastritis 2021b)	42 %

Abbreviations: kg = kilogram; m^2 = meter squared;

8.2.2.2 Intervention

There are currently no approved medicines for the treatment of systemic AL-amyloidosis. Recent clinical guidelines from the Danish Multidisciplinary Cancer Groups (DMCG) recommend VCd as a first-line regimen for patients with AL

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amyloidosis, and daratumumab-containing regimens for second-line (DMSG 2021). Daratumumab has demonstrated safety and efficacy in numerous clinical studies (Lokhorst 2015, Dimopoulos 2016, Palumbo 2016, Chari 2017, Mateos 2018, Spencer 2018, Facon 2019) and is approved by the EMA and FDA as a monotherapy or in combination regimens for the treatment of patients with MM (U.S. Food and Drug Administration 2018, Darzalex EPAR 2020). An overview of D-VCd is shown in Table 16.

Table 16: Description of intervention used in the model (D-VCd)

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology			
Daratumumab	Weekly for cycles 1-2 (Days 1, 8, 15, 22) Every 2 weeks for cycles 3-6 (Days 1, 15) Every 4 weeks for cycle 7+ (Day 1) For a maximum of 24 cycles	Dose: 1800 mg Administrations: Cycles 1-2: 4 Cycles 3-6: 2 Cycles 7+: 1	
Bortezomib	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 1.3 mg/m^2 Administrations per cycle: 4	
Cyclophosphamide	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 300 mg/m^2 Administrations per cycle: 4	
Dexamethasone	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 40 mg Administrations per cycle: 4	

8.2.2.3 Comparators

In Danish clinical practice, VCd is recommended as a first-line regimen for patients with AL amyloidosis (DMSG 2021). Thus, VCd is considered as the most suitable comparator regimen (Table 17).

Table 17 : Description of comparator used in the model (VCd)

Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
Posology			
Bortezomib	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 1.3 mg/m^2 Administrations per cycle:	

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Intervention	Clinical documentation (including source)	Used in the model (number/value including source)	Expected Danish clinical practice (including source if known)
		4	
Cyclophosphamide	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 300 mg/m² Administrations per cycle: 4	
Dexamethasone	Weekly (Days 1, 8, 15, 22) For a maximum of 6 cycles	Dose: 40 mg Administrations per cycle: 4	

8.2.2.4 Relative efficacy outcomes

Primary goals for treatment of systemic AL amyloidosis are fast and deep hematologic response and involved organ(s) response. In Danish clinical practice, response is an important measure for evaluating treatment efficacy, and adjusting treatment plan (DMSG 2021).

The ambition is that a response of at least Very Good Partial Response (VGRP) is achieved early, to prevent further organ damage, achieve organ response and to improve survival probability. Patients with lower response than VGPR but stable organ function may continue treatment beyond 2-3 cycles to await how hematologic response develops. The closer patients are to VGPR after 2 to 3 cycles, and the better organ function is at baseline, and/or the organs function is stable, the more likely it is considered to wait before subsequent treatment is started in practice. This is also due to limited treatment alternatives in 2nd line.

Hematologic response is measured by negative serum and urine immunofixation, and normalization of FLC levels and FLC ratio, or dFLC alone. Organ response is measured by NT-ProBNP decrease (cardiac response) or decrease in proteinuria (renal response), according to consensus guidelines (Comenzo 2012) (DMSG 2021). Relative efficacy outcomes are presented in Table 18. Further details can be found in Table A3a (Appendix E).

Table 18: Results of ANDROMEDA (NCT03201965)

Clinical efficacy outcome	Clinical documentation	Response rate used in the model (%)
Complete response	ANDROMEDA Trial IPD	[redacted]
Very good partial response		[redacted]
Partial response / No response		[redacted]
Dead		[redacted]

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Source: (Janssen 2021c)

8.2.2.5 Adverse reaction outcomes

Adverse events were captured in the ANDROMEDA trial. Overall, both the D-VCd and VCd therapies were well tolerated by patients in the study. The criteria for identifying an AE were defined as grade ≥3 AE occurring in ≥5% of patients in either treatment arm of the ANDROMEDA trial. Cost for management of AEs are described further in section 8.6. Disutilities associated with treatment-related AEs in AL amyloidosis were taken into consideration. Literature related to oncology has been used to inform AE disutilities. See Appendix F for further details.

Table 19: Adverse event outcomes

Adverse event	Clinical documentation	AE rate used in model (%)	
		D-VCd	VCd
Lymphopenia	ANDROMEDA 12-month landmark analysis (Janssen 2021b)	13.0	10.1
Neutropenia		5.2	2.7
Pneumonia		8.3	4.3
Diarrhea		5.7	3.7
Edema		3.1	5.9
Hypokalemia		2.1	5.3
Syncope		6.2	6.4
Cardiac failure		6.2	2.7

Source: (Janssen 2021b)

8.3 Extrapolation of relative efficacy

Not applicable. Relative efficacy is not extrapolated.

8.3.1 Time to event data – summarized:

Upon exit from the decision tree, patients are stratified into one of three Markov models based on their hematologic response achieved (i.e., CR, VGPR, or PR/NR), as outlined in Figure 26. The extrapolation of overall survival in these three Markov models are presented in Appendix H.

8.4 Documentation of health-related quality of life (HRQoL)

Consistent with the preferred measure of HRQoL by NICE (ie, EQ-5D), (National Institute for Health and Care Excellence) utility values used in the model were based on the EQ-5D-5L data collected in the ANDROMEDA trial. EQ-5D-5L data were collected on day one of each cycle for the first six cycles in both treatment arms and every eight weeks for patients receiving daratumumab monotherapy in cycle 7+. For patients in both treatment arms, EQ-5D-5L data were also collected in the post-treatment (at end of treatment, at start of subsequent therapy, and every six months until MOD-PFS) and long-term follow-up phases (16- and 32-weeks post MOD-PFS) (Janssen Research and Development 2018). The proportion of patients reporting their HRQoL per cycle is reported in Table 20. The five

dimensions of the EQ-5D (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each have five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ-5D-5L values used in the reference case analysis were derived from a utility analysis performed to apply Danish tariffs for EQ-5D-5L in line with the DMC guidelines (Danish Medicines Council 2021, Janssen 2021e) Table 21.

Table 20 EQ-5D assessments counts after accounting for missing values

Visit	Number of expected EQ-5D assessments	Number of EQ-5D responses	Missing EQ-5D assessments	Missing rate
Cycle 1	370	353	17	5%
Cycle 2	365	326	39	11%
Cycle 3	339	307	32	9%
Cycle 4	314	288	26	8%
Cycle 5	297	272	25	8%
Cycle 6	283	262	21	7%
Cycle 7	147	132	15	10%
Cycle 8	130	8	122	94%
Cycle 9	128	111	17	13%
Cycle 10	126	6	120	95%
Cycle 11	125	89	36	29%
Cycle 12	123	2	121	98%
Cycle 13	120	71	49	41%
Cycle 14	119	1	118	99%
Cycle 15	118	51	67	57%
Cycle 17	118	39	79	67%
Cycle 19	117	22	95	81%
Cycle 21	116	7	109	94%
Cycle 23	114	2	112	98%
End of treatment	370	162	208	56%

Note: the missing values are calculated by subtracting the actual responses from the expected responses (after NAs were defined as previously descr bed)

8.4.1 Overview of health state utility values (HSUV)

The EQ-5D utilities from the trial (pooled treatment data) were analyzed by hematologic response state. Because the mean utility value for VGPR (0.709) did not meet initial face validity (i.e., was lower than the derived estimate for PR/NR), a more clinically plausible VGPR utility value was calculated as the mean of CR and PR utility values for use in the model. The mean hematologic response-specific utility values used in the model are presented in Table 21. An alternative assumption where the utility for VGPR was the same as that for CR (Carter 2017), such that the model health state utilities would describe adequate responder versus inadequate responder, was explored in a scenario analysis. A scenario analysis using the mean utility value for VGPR as reported from the trial was also included.

Table 21: Utility values by hematologic response applied in the reference case

Hematologic Response	Instrument	Utility Value, Mean (95% CI)	
CR	EQ-5D-5L	[redacted]	ANDROMEDA IPD (Danish EQ-5D-5L tariff) (Janssen 2021e)
VGPR	EQ-5D-5L	[redacted]	
PR/NR	EQ-5D-5L	[redacted]	

Abbreviations: CR = complete response; NR = no response; PR = partial response; VGPR = very good partial response.
*VGPR utility value was calculated as the mean of CR and PR.
Source: ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a)

8.4.1.1 Utility decrements for adverse events

Health state utility values in the model were the same regardless of treatment, but disutilities associated with AEs were included to distinguish between patients receiving D-VCd and VCd. Utility decrements associated with all grade ≥3 AEs that occurred in at least 5% of patients in either treatment arm were included in the reference case analysis. Disutilities associated with treatment-related AEs in AL amyloidosis were not identified in the SLR for HRQoL. As such, an additional, more generic literature search was conducted to identify AE disutility values related to oncology and/or chemotherapy. This search was successful in identifying published literature sources to inform each AE utility decrement.

The AE disutility value and the length of its application were used to calculate the average QALY lost per event. It was assumed that the duration of grade ≥3 AEs would not last an entire cycle. As described in section 8.6 costs for grade ≥3 AEs were based on AEs associated with hospital admission for a minimum of 21 days. Therefore, it was assumed that the utility decrements for grade ≥3 AEs would also apply for 21 days.

The average QALY lost per event and the proportion of patients experiencing the respective AEs was used to calculate the average QALY lost per patient (Table 22). The total QALYs lost per treatment arm was calculated as a sum of the average QALYs lost per patient and was applied in cycle one to all patients in the appropriate treatment arm (aligns with how AE costs were also applied). The impact of this one-time decrement is assumed to be minimal, given that treatment is a fixed course of therapy with limited duration.

Table 22: Adverse event utility decrements and durations

AE	One-time Utility Decrement	Duration of Adverse Event (Days)	Average QALY Lost per Event	Average QALY Lost per Patient		Data Source/Notes
				D-VCd	VCd	
Cardiac failure	0.1034	21	0.006	0.0004	0.0002	Decrement: (Sullivan 2011) Duration: Assumption*
Diarrhoea	0.176	21	0.010	0.0006	0.0004	Decrement: (Stein 2018) Duration: Assumption*

AE	One-time Utility Decrement	Duration of Adverse Event (Days)	Average QALY Lost per Event	Average QALY Lost per Patient		Data Source/Notes
				D-VCd	VCd	
Edema	0.06	21	0.003	0.0001	0.0002	Decrement: (Brown 2001) Duration: Assumption*
Hypokalemia	0.02	21	0.001	0.00002	0.0001	Decrement: (Sullivan 2011) Duration: Assumption*
Lymphopenia	0.09	21	0.005	0.0007	0.0005	Decrement: Assumed same decrement as neutropenia(Nafees 2008) Duration: Assumption*
Neutropenia	0.09	21	0.005	0.0003	0.0001	Decrement: (Nafees 2008) Duration: Assumption*
Pneumonia	0.2	21	0.011	0.0010	0.0005	Decrement: (Beusterien 2010) Duration: Assumption*
Syncope	0.0039	21	0.00022	0.00001	0.00001	Decrement: (Sullivan 2011) Duration: Assumption*

Abbreviations: AE = adverse event; C = cyclophosphamide; D = daratumumab; d = dexamethasone; NEL = non-elective long stay; QALY = quality adjusted life-year; V = VELCADE® (bortezomib).
*Assumed 21 day duration for utility decrement in alignment with the definition of a "NEL" AE.(Spencer 2018)

Table 23: Total adverse event disutilities by treatment arm

Drug Regimen	Mean Total AE Disutility per Patient
D-VCd	0.002986548
VCd	0.001970545

Abbreviations: AE = adverse event; C = cyclophosphamide; D = daratumumab; d = dexamethasone; V = VELCADE® (bortezomib).

8.4.1.2 Utility decrements for progressed health states

Utility decrements for '2L Tx' and 'End-stage Organ Failure' were applied on a recurring per-cycle basis for as long as the patient remains within the respective health state. The '2L Tx' utility decrement was calculated as the difference between the mean baseline utility score and the mean utility value associated with 'progressive disease' from ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a).

Both structured and systematic literature reviews failed to identify data to inform a utility decrement for patients with end-stage organ failure due to AL amyloidosis. Therefore, a UK-based study on HRQoL for patients with advanced chronic heart failure was used to calculate this utility value (Emin 2016). In this study, a utility value of 0.5 was reported for patients with chronic heart failure that had been assessed for heart transplant (Emin 2016). According to

IPD, the mean baseline utility value for patients in the ANDROMEDA trial was [redacted] The difference between the baseline ANDROMEDA utility value and the utility value reported by Emin *et al.*, (2016) was utilized in the model to inform the utility decrement for patients in the 'End-stage Organ Failure' health state (ie, 0.231). A summary of progression-related health state utility values used in the model is presented in Table 24.

Table 24: Summary of progression-related health-state utility values

Health State	Recurring Utility Decrement	Source
2L Tx	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months)(Janssen Research and Development 2020a)
End-stage Organ Failure	0.231	(Emin 2016)

Abbreviations: 2L = second-line; IPD = individual participant data; Tx = treatment.

8.4.2 Utility decrements for end-stage organ failure events

Utility decrements specific to end-stage organ failure interventions are applied in the model according to their occurrence. Since hemodialysis is a recurring treatment, its associated utility decrement is applied on a per-cycle basis to the proportion of patients requiring the intervention. Conversely, solid organ transplant is a one-time occurrence and thus, the utility decrement is only applied as a one-time decrement specifically to patients who receive a transplant.

The decrement associated with hemodialysis (0.1) was sourced from a systematic literature review of utility-based HRQoL in chronic kidney disease treatments. According to this study, the utility value for patients on hemodialysis was 0.69, which represented a decrement of 0.1 compared to those with chronic kidney disease pre-treatment (Wyld 2012).

If applicable, the utility decrement for solid organ transplant is applied as a one-time decrement in the model only to patients that receive solid organ transplant. There was no data source identified to inform this utility decrement, but a publication was available that provided the change in UK EQ-5D scores for pre- and post-liver transplantation (as a proxy for solid organ transplant) among 455 respondents (Ratcliffe 2002). The mean utility score at 3-months post-transplantation (after adjusting for informative dropout) was similar to the baseline utility score, suggesting that the transplantation event has a transient impact on quality of life (supporting the use of a one-time utility decrement in the model) and that utilities are not significantly different following transplant. Due to the absence of data to parameterize this input and the brief HRQoL impact that would be expected over the duration of a model cycle, a decrement of zero was therefore assumed for the solid organ transplant event. This assumption has no impact on the reference case analysis because solid organ transplant was excluded. However, these inputs can be modified by the user to reflect local practices.

A summary of end-stage organ failure utility decrements applied in the model is presented in Table 25.

Table 25: Summary of end-stage organ failure utility decrements

Intervention	Utility Decrement	Source

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Hemodialysis (recurring)	0.1	(Wyld 2012)
Organ Transplant (one-time)	0	Assumption

8.4.3 Health state utility values used in the health economic model

The CE-model health-state utilities are presented in Table 26. Health state utility values in the model were the same regardless of treatment, but disutilities associated with AEs were included to distinguish between patients receiving D-VCd and VCd. Utility decrements associated with all grade ≥3 AEs that occurred in at least 5% of patients in either treatment arm were included in the reference case analysis. Disutilities associated with treatment-related AEs in AL amyloidosis were not identified in the SLR for HRQoL. As such, an additional, more generic literature search was conducted to identify AE disutility values related to oncology and/or chemotherapy. This search was successful in identifying published literature sources to inform each AE utility decrement.

Table 26: Utility values used in the health economic model

Response-based utilities	HSUV	Source
CR	[redacted]	ANDROMEDA IPD (Danish EQ-5D-5L tariff) (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a) (Janssen 2021e)
VGPR	[redacted]	ANDROMEDA IPD (Danish EQ-5D-5L tariff) (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a) (Janssen 2021e)
PR/NR	[redacted]	ANDROMEDA IPD (Danish EQ-5D-5L tariff) (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a) (Janssen 2021e)
Health state utility decrement		
2L Tx	[redacted]	ANDROMEDA IPD (primary analysis; February 2020; median follow-up: 11.4 months) (Janssen Research and Development 2020a)
End-stage Organ Failure	0.236	(Emin 2016)
Intervention utility decrement		
Hemodialysis	0.1	(Wyld 2012)
Adverse events		
Cardiac failure	0.1034	(Sullivan 2011)
Diarrhoea	0.176	(Stein 2018)

Medicinrådet Dampfærgevej 27-29, 3. th. DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Response-based utilities	HSUV	Source
Oedema	0.06	(Brown 2001)
Hypokalemia	0.02	(Sullivan 2011)
Lymphopenia	0.09	Assumed same decrement as neutropenia (Nafees 2008)
Neutropenia	0.09	(Nafees 2008)
Pneumonia	0.2	(Beusterien 2010)
Syncope	0.0039	(Sullivan 2011)

Abbreviations: 2L = second line; CR = complete response; NR = no response; PR = partial response; Tx = ; VGPR = very good partial response.
*VGPR utility value was calculated as the mean of CR and PR.

Danish tariff for the EQ-5D-5L was applied in estimating the health state utility values (Jensen 2021). This approach is in accordance with the Danish Medicines Council (DMC) guidelines, which refer to the use of EQ-5D-5L for patient reported outcomes data as the preferred outcome measure (Medicinrådet 2020a). The utility analysis was based on descriptive statistics where 6-months ITT pooled utility values were used to inform health state utility values. Alternative approaches of using data that was not pooled or using a mixed model approach yielded predictions of utility values not clinically reliable in that utility values for patients not responding to treatment were higher than utility values for patients responding to treatment. It should be noted however that the assumption of normality underpinning the mixed model was not met.

Utility decrements for '2L Tx' and 'End-stage Organ Failure' were applied on a recurring per-cycle basis for as long as the patient remains within the respective health state.

As recommended in the Danish guidelines (Medicinrådet 2020a), an age-adjustment of the utility values was performed to ensure that the relative level of utility values would decline in a rate consistent with the expected decline in HRQoL observed within the general Danish population.

8.5 Age-adjusted utility values

Utility values were age-adjusted using a multiplication factor derived from the values reported in (Wittrup-Jensen 2009) as recommended in the guidelines (Medicinrådet 2020a).

8.6 Resource use and costs

Cost parameters included in the model were first-line drug therapy costs, first-line drug administration costs, first-line co-medication costs, first-line disease monitoring costs, first-line AE management costs, second-line drug therapy costs, end-stage organ failure management costs, health state-specific healthcare resource use costs, and end of life costs.

The drug administration costs for 1L treatment are presented in Table 27.

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Table 27: Drug acquisition costs used in the model

Drug	Drug Units	Unit Strength	Cost per pack (DKK) Pharmacy purchase price (PPP)	Source
First-line drug regimen				
Daratumumab	1	1800 mg	38 901.18	(Medicinpriser 2022)
Bortezomib	1	3.5 mg	652.42	
Cyclophosphamide	100	50 mg	906.61	
Dexamethasone	100	4 mg	352.70	
Second-line drug regimen				
Lenalidomide	21	25 mg	3 882.91	(Medicinpriser 2022)
Dexamethasone	20	1 mg	133.00	
Daratumumab	1	1800 mg	38 901.18	
Bortezomib	1	3.5 mg	652.42	
Co-medication				
Valaciclovir	60	250 mg	558.49	(Medicinpriser 2022)
Benadryl	21	10 mg	67.95	
Dexamethasone PO	20	1 mg	133.00	
Montelukast	28	4 mg	95.00	
Methylprednisolone PO	100	4 mg	145.00	
Paracetamol PO	100	500 mg	22.70	

Source: (Medicinpriser 2022)

Table 28: Administration unit costs

Type of Administration	Unit Cost (DKK)	Source(s)/Notes
SC	1617.00	DRG: 08MA12 (BWAA31) Medicingivning ved subkutan injektion (DE858A) AL amyloidose
IV – bolus	1617.00	DRG: 08MA98

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Type of Administration	Unit Cost (DKK)	Source(s)/Notes
		(BWAA62) Medicingivning ved intravenøs inj. gennem permanent venekateter (DE858A) AL amyloidose.
IV - infusion	1617.00	08MA98 (BWAA62) Medicingivning ved intravenøs infusion for (DE858A) AL amyloidose
PO	0.00	Assumption

Abbreviations: IV = intravenous; PO = oral; SC = subcutaneous.
Sources: (Sundhedsdatastyrelsen 2022)

Monitoring of treated patients included routine haematologist visits that occurred while a patient was in the '1L Tx' or 'Off Tx/FDT' health state. The unit costs are presented in Table 29.

Table 29: Disease monitoring unit costs

Item	Unit Cost (DKK)	Source(s)/Notes
Hematologist Visit	1368.37	Kommunernes og Regionernes Løndatakontor 2021, Overlæger, lægelige chefer m.v.. bruttoløn MAJ 2021 (97038DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

Source: available from: https://krl.dk/

Healthcare resource use costs for disease management in the model included emergency room visits, long- (i.e. ≤24 hours) and short-stay (i.e. >24 hours) inpatient hospitalizations, intensive care unit admissions, and visits to a haematologist, specialist nurse, nephrologist, or cardiologist. A summary of the healthcare resource use costs included in the model is presented in Table 30.

Table 30: Healthcare resource unit costs

Item	Unit Cost (DKK)	Source(s)/Notes
Emergency Room Visit	1645.00	DRG: MDC08 (BWST2A) Multidisciplinaer akutmodtagelse af ikke-traume patient for (DE858A) AL amyloidose
Long Hospital Stay (>24h)	43 621.00	Assumed same as >12 hour stay for procedures in the DRG grouper.
Short Hospital Stay (≤24h)	1645.00	Assumed same as <12 hour stay for procedures in the DRG grouper.

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Item	Unit Cost (DKK)	Source(s)/Notes
Intensive Care Unit	1645.00	Assumed same as short hospital stay unit cost.
Hematologist Visit	1367.12	Overlæger, lægelige chefer m.v.. bruttoløn OCT 2021 (96949 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Specialist Nurse Visit	1368.37	Sykepleier - Spesialsykepleier
Nephrologist Visit	1367.12	Overlæger, lægelige chefer m.v.. bruttoløn OCT 2021 (96949 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.
Cardiologist Visit	1367.12	Overlæger, lægelige chefer m.v.. bruttoløn OCT 2021 (96949 DKK). Calculated: salary/hours per month and multiplied by two according to Medicine council 2020.

The criteria for including an AE in the health economics analaysis were defined as grade ≥3 AE occurring in ≥5% of patients in either treatment arm of the ANDROMEDA trial. A summary of AE management costs is presented Table 31. The cost of AE management was applied in the model as a one-time cost per patient in the first cycle. Given the low AE rate and short duration of treatment as a fixed course of chemotherapy, it was assumed that a one-off cost would have minimal impact on the total cost of treatment. Note that fatigue was reported as a grade ≥3 AE occurring in ≥5% of subjects (3.2% VCd, 5.2% D-VCd). In the 18-month landmark update. Yet, fatigue may be cost may mainly apply to outpatient setting and not require longer inpatient stays and are therefore not included in the model.

Table 31: Adverse event unit costs

Adverse Event (Grade ≥3 or NEL)	Unit Cost (DKK)	Source(s)/Notes
Lymphopenia	1645.00	DRG: 08MA98 (BXXB0) Tværfaglig udredning og behandling (DE858A) AL amyloidose
Neutropenia	1645.00	DRG: 08MA98 (DD709) Neutropeni UNS (DE858A) AL amyloidose
Pneumonia	1645.00	DRG: 08MA98 (DJ189) Pneumoni UNS (DE858A) AL amyloidose
Diarrhoea	1645.00	DRG: 08MA98 (DK529B) Ikke-infektiøs diaré UNS (DE858A) AL amyloidose

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Adverse Event (Grade ≥3 or NEL)	Unit Cost (DKK)	Source(s)/Notes
Edema	1645.00	DRG: 08MA98 (BMFF0) Ødembehandling og ødemprofylakse (DE858A) AL amyloidose
Hypokalaemia	1645.00	DRG: 08MA98 (DE876) Hypokaliæmi (DE858A) AL amyloidose
Syncope	1645.00	DRG: 08MA98 (BXXB0) Tværfaglig udredning og behandling (DE858A) AL amyloidose
Cardiac Failure	43 621.00	DRG: 08MA12 (DI509) Hjertesvigt UNS (DE858A) AL amyloidose

Abbreviations: DRG= diagnosis-related group; DKK = Danish krone

Source: (Sundhedsdatastyrelsen 2022)

8.7 Results

8.7.1 Base case overview

Results for the reference case analysis for D-VCd and VCd are summarized in Table 32. Over a 35-year time horizon, VCd was associated with a lower total cost; however, D-VCd was associated with higher LYs and QALYs. The ICER for the reference case was 363 273 DKK per QALY gained. The Off Tx/FDT health state accounts for about 70% of the incremental QALYs gain whereas first line acquisition costs drive the incremental cost.

8.7.2 Base case results

Results of the analysis are shown in Table 32. The incremental QALYs are 2.53, with the off TX/FDT health state accounting for the most of the QALY gain. The cost categories explaining most of the incremental costs are 1L drug therapy costs and subsequent treatment costs. The incremental costs are estimated to 919 845 DKK. Taken together, this amounts to an incremental cost-effectiveness ratio of 363 273 DKK.

Table 32: Base case results

	D-VCd	VCd	Incremental
Life years			
Total life years gained	8.67	5.38	3.30
Quality adjusted life years			

	D-VCd	VCd	Incremental
1L Tx	0.36	0.37	-0.01
Off Tx/FDT	3.91	1.48	2.43
2L Tx	2.19	1.97	0.22
End-stage Organ Failure	0.05	0.16	-0.10
AE Disutility	0.00	0.00	0.00
Total QALYs	**6.50**	**3.97**	**2.53**
Costs (DKK)			
Total 1L Drug Therapy Costs	1 083 824	18 139	1 065 685
Total 1L Drug Administration Costs	106 138	48 357	57 781
Co-medication Costs	14 878	4 872	10 007
Healthcare Resource Use Costs	235 712	163 594	72 118
Adverse Event Costs	3 422	1 810	1 612
1L Disease Monitoring Costs	7 972	0	7 972
Subsequent Therapy Drug Costs	13 277	325 396	-312 119
Organ Failure Costs	4 689	13 774	-9 085
Indirect Costs	71 985	41 347	30 638
End of Life Costs	100 663	105 427	-4 764
Total costs	**1 642 560**	**722 715**	**919 845**
Incremental cost per QALY (ICER, DKK)			**363 273**

Abbreviations: 1L = first-line; 2L = second-line; AL = amyloid light-chain; DKK = Danish krone; FDT = fixed daratumumab treatment; LYs = Life years; QALYs = Quality adjusted life years; Tx = treatment; VCd = bortezomib, cyclophosphamide and dexamethasone

8.8 Sensitivity analyses

8.8.1 Deterministic sensitivity analyses

Table 33 summarizes the deterministic sensitivity analyses for D-VCd versus VCd. Figure 28 illustrates the magnitude that the ICER per QALY changes when each input is varied. Deterministic sensitivity analysis (DSA) was undertaken by varying key parameters by their standard error, 95% CI or +/- 20% of the expected values (base case) based on data availability. The 10 most influential parameters are displayed. The ICER is found to be most sensitive to changes in the utility value of complete responders, the Daratumumab acquisition cost and the duration of treatment for D-VCd.

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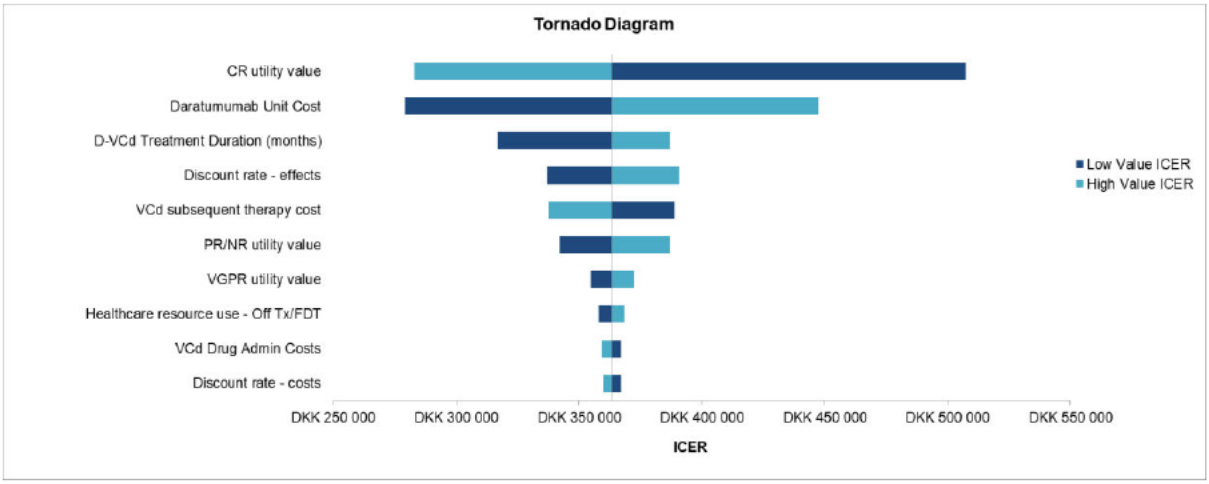
Table 33: Deterministic sensitivity analyses results

	Low Value ICER	High Value ICER	Incremental
CR utility value	484 712	270 231	214 482
Daratumumab Unit Cost	262 859	431 150	168 291
D-VCd Treatment Duration (months)	300 356	370 865	70 509
Discount rate - effects	375 960	318 049	57 911
VCd subsequent therapy cost	321 858	373 066	51 208
PR/NR utility value	326 809	369 859	43 050
VGPR utility value	338 837	355 575	16 737
Healthcare resource use - Off Tx/FDT	341 861	352 147	10 286
VCd Drug Admin Costs	350 824	343 185	7 639
Discount rate - costs	343 509	350 499	6 990

Figure 28: Tornado diagram for DSA



8.8.2 Probabilistic sensitivity analyses

The results of the PSA (for 1000 iterations) are presented in Table 34 which also presents results from the deterministic analysis for comparison. This analysis supports the conclusions from the deterministic analysis but indicate a slightly higher cost per QALY gained than what was found in the deterministic analysis.

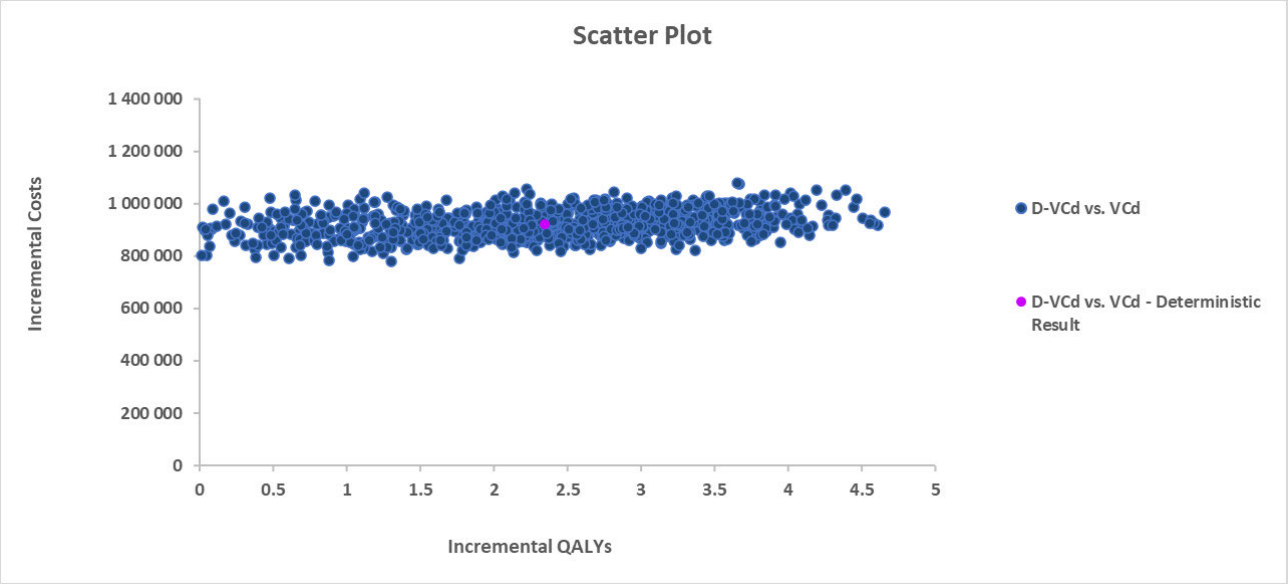
Table 34: Mean discounted costs and QALYs from the PSA

Treatment	Total Costs (DKK)	Total QALYs	Incremental Costs (DKK)	Incremental QALYs	ICER (Cost/QALY) (DKK)

D-VCd	1 619 555	6.18	921 304	2.35	392 546
VCd	698 251	3.83			

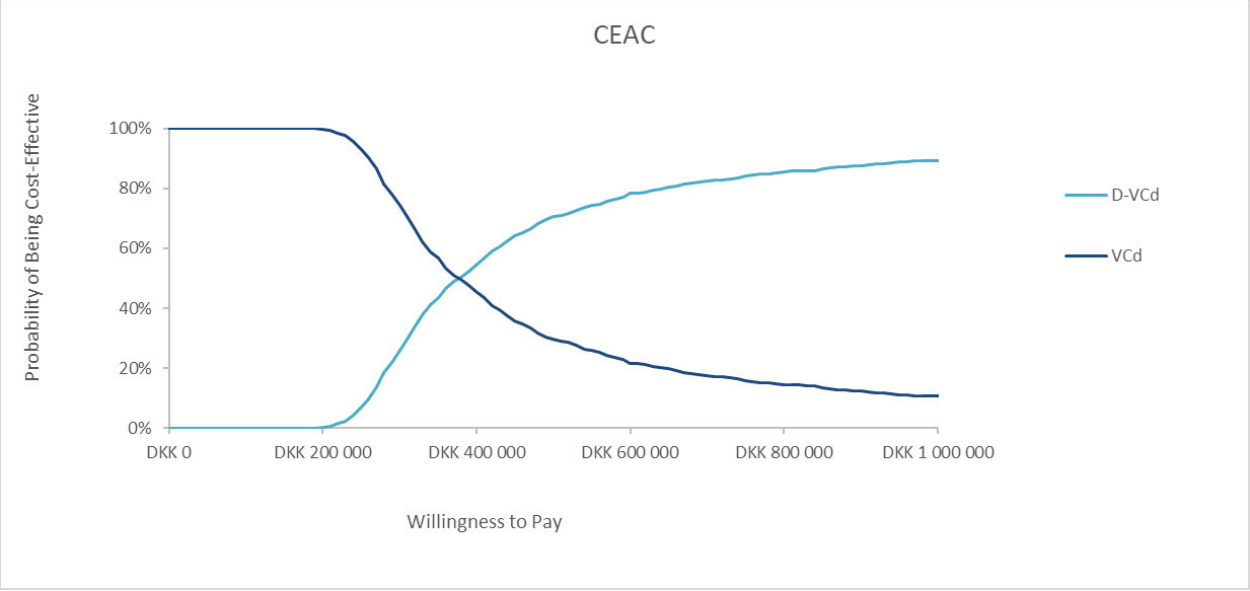
The result of the cost-effectiveness analyses is presented in a cost-effectiveness plane in Figure 29.

Figure 29: Cost-effectiveness plane: D-VCd versus VCd



The cost-effectiveness acceptability curve (CEAC) is shown in Figure 30. As indicated, the probability that D-VCd is a cost-effective intervention exceeds the 50% point at a WTP threshold of 380 000 DKK.

Figure 30: Cost-effectiveness acceptability curve showing the probability of treatments being cost-effective as a function of the willingness-to-pay (DKK)



8.9 Scenario analyses

The results of the scenario analyses are presented in Table 35. The largest increased in the ICER was seen assuming the same subsequent treatment regime for D-VCd and VCd of 100% of patients being treated with lenalidomide and Dexamethasone (Rd) in second line, rendering an ICER of 485 289 DKK. Discounting cost by 4% and effects by 0% yields the lowest ICER of 240 226 DKK.

Table 35: Results of scenario analyses

Scenario	Incremental LYs	Incremental QALYs	Incremental Costs	ICER (Cost/QALY)
Shortened time horizon (20 years)	2.78	2.19	896 043	408 779
Discounting cost 0% and effect 4%	3.12	2.40	983 734	409 244
Discounting cost 4% and effect 0%	5.07	3.80	913 726	240 226
Payer perspective	3.30	2.53	886 565	350 129
Exclude organ failure costs	3.30	2.53	928 930	367 155
VCd subsequent treatment: Rd 100%	3.30	2.53	1 228 802	485 289
ANDROMEDA ITT mean treatment duration (D-VCd 16.5 months, VCd 4.36 months)	3.30	2.53	826 271	327 170
ANDROMEDA max treatment duration (D-VCd 24 months, VCd 5.52 months)	3.30	2.54	979 114	386 190

Abbreviations: LYs = Life years; QALYs = Quality adjusted life years; VCd = bortezomib, cyclophosphamide and dexamethasone

Scenario analysis results were generated by manually running the model analysis.

9. Budget impact analysis

Based on estimates from clinical experts Janssen has contacted, the majority of patients will receive daratumumab containing regimens (D-VCd) for second line treatment (see Section 5.2). This highlights the current unmet need for treatments in this patient group.

With an estimated incidence of about 55 patients relevant for treatment of D-VCd, it is expected that about 33 patients (60%) will be prescribed the combination already from year 1 in case of reimbursement, and 44 patients (80%) in year 2 (Table 36).

Table 36: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
D-VCd	33	44	44	45	45
VCd	22	11	11	11	11

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of patients	55	55	55	56	56

Table 37: Number of patients expected to be treated over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
D-VCd	0	0	0	0	0
VCd	55	55	56	56	56
Total number of patients	**55**	**55**	**56**	**56**	**56**

Per-patient cost estimates are presented in Table 38 in case D-VCd is recommended and in Table 39 in case D-VCd is not recommended.

Table 38: Costs per patient per year - if the pharmaceutical is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Costs per patient	425,082	711,513	695,249	699,803	692,423

Table 39: Costs per patient per year - if the pharmaceutical is NOT recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Costs per patient	390 530	445 354	488 769	533 631	563 549

Budget consequences in case of reimbursement of D-VCd are expected to be 177 million DKK after five years 5 (Table 40), taking the sum of the annual incremental costs.

Table 40: Expected budget impact of recommending the pharmaceutical for the current indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	**44 858 691**	**63 627 670**	**65 120 962**	**67 838 829**	**69 078 481**
Total 1L Drug Therapy Costs	30,070,905	48,213,708	48,213,708	49,304,939	49,304,939
Total 1L Drug Administration Costs	4,241,326	5,219,380	5,219,380	5,325,913	5,325,913
Co-medication Costs	458,338	715,720	715,720	730,768	730,768
Healthcare Resource Use Costs	1,452,049	2,404,578	3,311,824	4,245,076	5,077,004
Adverse Event Mgmt Costs	152,740	170,477	170,477	173,899	173,899

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	Year 1	Year 2	Year 3	Year 4	Year 5
1L Disease Monitoring Costs	145,841	357,032	357,032	365,146	365,146
Subsequent Therapy Drug Costs	5,287,334	3,101,976	3,361,292	3,569,791	3,727,404
End-stage Organ Failure Costs	9,866	27,436	59,655	100,886	144,532
End of Life Costs	3,040,292	3,417,364	3,711,874	4,022,411	4,228,875
Minus: **The pharmaceutical under consideration is NOT recommended**	**21 479 169**	**24 494 464**	**26 882 277**	**29 349 681**	**30 995 213**
Total 1L Drug Therapy Costs	997,640	997,640	997,640	1,015,779	1,015,779
Total 1L Drug Administration Costs	2,659,614	2,659,614	2,659,614	2,707,971	2,707,971
Co-medication Costs	267,943	267,943	267,943	272,814	272,814
Healthcare Resource Use Costs	1,530,164	2,572,217	3,456,528	4,302,900	4,993,611
Adverse Event Mgmt Costs	99,530	99,530	99,530	101,339	101,339
1L Disease Monitoring Costs	-	-	-	-	-
Subsequent Therapy Drug Costs	12,844,550	14,152,801	15,146,757	16,186,949	16,776,658
End-stage Organ Failure Costs	15,837	56,272	124,095	212,641	306,128
End of Life Costs	3,063,891	3,688,448	4,130,171	4,549,288	4,820,912
Budget impact of the recommendation	**23 379 522**	**39 133 206**	**38 238 685**	**38 489 149**	**38 083 268**

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10. Discussion on the submitted documentation

Patients with AL amyloidosis face a large unmet medical need and significantly reduced survival and HRQoL. Despite this, no new or approved treatment options have been made available to these patients. Off-label usage of VCd represents the standard of care in most countries, but many patients with AL amyloidosis still have insufficient hematologic responses and progressive organ damage. Therefore, a strong need exists for an effective and approved first-line therapy for this patient population. The decision problem in this economic evaluation was '*What is the ICER for D-VCd compared with VCd in the first-line treatment of patients with systemic AL amyloidosis in Denmark?'.*

No existing economic models for AL-amyloidosis were identified in a SLR of the published literature to serve as a precedent in development of the current analysis. Although this *de novo* global model represents the first economic model in AL amyloidosis, economic models with a similar structure have been used to model other diseases and was accepted in their respective HTA submissions. This is also the first economic evaluation to consider the cost effectiveness of D-VCd in the treatment of patients newly diagnosed with AL amyloidosis in Denmark. Based on RCT data from ANDROMEDA, treatment with D-VCd is anticipated to delay progression to subsequent therapy, delay hematologic/organ progression, provide better quality of life, and extend survival. The analysis accordingly showed that, compared with VCd, D-VCd was more costly (DKK 919 845) and more effective (3.3 LYs and 2.53 QALYs), with an ICER of DKK 363 273 per QALY gained. The deterministic reference case results were well-supported by PSA results and several scenario analyses. Results are driven largely by survival, drug costs (first-line and subsequent therapy), and end-stage organ failure costs, as D-VCd patients live longer and accrue more health benefits and costs.

OS data from ANDROMEDA is immature and as such, the primary OS data informing the reference case was taken from an external publication (Palladini 2012). This publication was extrapolated in order to model a lifetime horizon for patients in CR, VGPR, PR, and NR in the reference case. Methodological best practices were followed for extrapolation and for choosing the most clinically valid distributions. This is based on the proportion of patients achieving a hematological response which is a recognized surrogate for OS (Kastritis 2021a). In ANDROMEDA, the OS data is too immature and the median follow up is only 11.4 months, therefore we cannot see this difference compared to the lifetime horizon in the model. Patients enter the OS curve at their level of hematological response based on ANDROMEDA data at the time of decision tree exit, and the OS is projected based on this. Since this projection was based on natural history data where DVCd was not available, this can be expected this to be a conservative estimate.

A further limitation was the need for some assumptions to populate the model, owing to immature data or the paucity of costing/resource use and utility data for AL amyloidosis in the literature. However, conservative assumptions were used, or assumptions were rationalized. For example, total costs in the model assume one subsequent line of therapy for patients undergoing treatment for AL amyloidosis. Although patients may require more than one subsequent line of therapy, clinical feedback indicated that most patients with AL amyloidosis only receive one subsequent line of therapy. Furthermore, data currently available from the ANDROMEDA trial indicated that most patients only received one subsequent line of therapy. Relatedly, the subsequent therapy costs for patients in the VCd arm were calculated assuming the maximum eight cycles of D-Vd as reported by Palumbo *et al*. (Palumbo 2016) but this is unlikely to be an overestimate because the publication found a total of 79.8% of the patients in the D-Vd group received the maximum of eight cycles. Other input assumptions in the model, such as applying upfront costs and decrements for AEs, are expected to have minimal impact.

Despite these limitations, a number of strengths of the model and analysis should be recognized. A strength of the current analysis is that it reflects the AL amyloidosis natural disease course and treatment pathway. Drug therapy, co-medication, adverse event management, healthcare resource use, and disease monitoring costs were populated to

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reflect recent Danish-specific values, having been sourced from Danish clinical guidelines (DMSG 2021), the Danish DRG database and procedure cost lists (Sundhedsdatastyrelsen 2022), the Danish drugs costs database (Medicinpriser) or published literature reporting Danish-specific values.

Another strength of this analysis was the use of clinical evidence for an AL amyloidosis population from the phase 3 ANDROMEDA clinical trial as the best available source in D-VCd-treated patients with AL amyloidosis. The model was informed with as much trial data as possible in order to have consistency with the trial findings. Notably, patient stratification by hematologic response in the decision tree and mortality distributions and transition probabilities in the Markov model were informed by ANDROMEDA IPD.

Taken together, this economic analysis predicted that compared to the current standard of care (VCd), D-VCd would be more costly and more effective in the treatment of patients newly diagnosed with AL amyloidosis. Given the dire need for an effective, approved therapy to treat this debilitating disease, D-VCd should become the new standard of care for patients with newly diagnosed AL amyloidosis in Denmark.

11. List of experts

Not applicable.

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14. Appendix A – Literature search for efficacy and safety of intervention and comparator

A systematic literature review was not performed since the ANDROMEDA study contains a direct comparison between D-VCd and the relevant comparator VCd.

15. Appendix B – ongoing studies

Clinicaltrials.gov search

Terms and Synonyms Searched:

Terms	Search Results*	Entire Database**
Synonyms		
bortezomib, Dexamethasone, Cyclophosphamide	--	0 studies
Cyclophosphamide	6 studies	4,501 studies
Carloxan	1 studies	239 studies
Ciclofosfamida	1 studies	242 studies
Ciclofosfamide	1 studies	246 studies
Cicloxal	1 studies	239 studies
Clafen	1 studies	239 studies
Claphene	1 studies	240 studies
CP monohydrate	1 studies	236 studies
CYCLO-cell	1 studies	233 studies
Cycloblastin	1 studies	254 studies
Cycloblastine	1 studies	238 studies
Cyclophospham	1 studies	240 studies
Cyclophosphamidum	1 studies	238 studies
Cyclophosphan	1 studies	238 studies
Cyclophosphane	1 studies	234 studies
Cyclophosphanum	1 studies	233 studies
Cyclostin	1 studies	237 studies
Cyclostine	1 studies	235 studies

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Terms	Search Results*	Entire Database**
Synonyms		
Cytophosphane	1 studies	281 studies
Fosfaseron	1 studies	234 studies
Genoxal	1 studies	235 studies
Genuxal	1 studies	234 studies
Ledoxina	1 studies	234 studies
Mitoxan	1 studies	237 studies
Neosar	1 studies	445 studies
Syklofosfamid	1 studies	235 studies
WR- 138719	1 studies	235 studies
and cytoxan	--	32 studies
cyclophos	--	4 studies
Cytoxan Lyophilized	--	3 studies
Endoxan	--	300 studies
NSC 26271	--	12 studies
Procytox	--	61 studies
Sendoxan	--	10 studies
Dexamethasone	6 studies	3,820 studies
Alin	1 studies	145 studies
Baycuten	1 studies	128 studies
Decadron	1 studies	563 studies
Aacidexam	1 studies	128 studies
Adexone	1 studies	127 studies
Aknichthol Dexa	1 studies	126 studies
Alba-Dex	1 studies	127 studies
Amplidermis	1 studies	125 studies
Anemul mono	1 studies	125 studies

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Terms	Search Results*	Entire Database**
Synonyms		
auricularum	1 studies	126 studies
Auxiloson	1 studies	126 studies
Baycadron	1 studies	98 studies
BB 1101	1 studies	602 studies
Cortidexason	1 studies	127 studies
Cortisumman	1 studies	126 studies
Decacort	1 studies	127 studies
Decadrol	1 studies	127 studies
Decalix	1 studies	126 studies
Decameth	1 studies	126 studies
Decasone R.p.	1 studies	126 studies
Dectancyl	1 studies	127 studies
Dekacort	1 studies	126 studies
Deltafluorene	1 studies	126 studies
Deronil	1 studies	129 studies
Desamethasone	1 studies	130 studies
Desameton	1 studies	127 studies
Dexa-Mamallet	1 studies	126 studies
Dexa-Rhinosan	1 studies	125 studies
Dexa-Scheroson	1 studies	125 studies
Dexa-sine	1 studies	125 studies
Dexacortal	1 studies	128 studies
Dexacortin	1 studies	125 studies
Dexafarma	1 studies	125 studies
Dexafluorene	1 studies	126 studies
Dexalocal	1 studies	126 studies

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Terms	Search Results*	Entire Database**
Synonyms		
Dexamecortin	1 studies	126 studies
Dexameth	1 studies	141 studies
Dexamethasonum	1 studies	126 studies
Dexamonozon	1 studies	126 studies
Dexapos	1 studies	126 studies
Dexinoral	1 studies	126 studies
Dexone	1 studies	137 studies
Dinormon	1 studies	125 studies
Fluorodelta	1 studies	126 studies
Fortecortin	1 studies	144 studies
Gammacorten	1 studies	128 studies
Hexadecadrol	1 studies	131 studies
Hexadrol	1 studies	164 studies
Lokalison-F	1 studies	126 studies
Loverine	1 studies	127 studies
Methylfluorprednisolone	1 studies	126 studies
Millicorten	1 studies	127 studies
Mymethasone	1 studies	126 studies
Orgadrone	1 studies	127 studies
Spersadex	1 studies	130 studies
Visumetazone	1 studies	128 studies
Aeroseb-Dex	--	43 studies
Cebedex	--	1 studies
Corson	--	3 studies
Dalalone	--	1 studies
Deca	--	24 studies

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Terms	Search Results*	Entire Database**
Synonyms		
Decaject	--	1 studies
Decaspray	--	8 studies
Dekasol LA	--	1 studies
Dexacen	--	1 studies
Dexametasona	--	5 studies
Dexasone	--	34 studies
Dexpak	--	26 studies
Dextenza	--	49 studies
Dexycu	--	8 studies
Dezone	--	2 studies
disaimisong	--	1 studies
Maxidex	--	49 studies
Oradexon	--	6 studies
Ozurdex	--	119 studies
Soludecadron	--	2 studies
Solurex	--	4 studies
Trabit	--	1 studies
voren	--	1 studies
bortezomib	6 studies	1,029 studies
velcade	1 studies	676 studies
ps 341	1 studies	210 studies
LDP 341	1 studies	139 studies
MLN341	1 studies	141 studies
Amyloidosis	6 studies	767 studies
Amyloid	4 studies	445 studies

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--	No studies found
*	Number of studies in the search results containing the term or synonym
**	Number of studies in the entire database containing the term or synonym

Applied Filters: ☑ **Recruiting** ☑ **Not yet recruiting** ☑ **Active not recruiting** ☑ **Enrolling by invitation**

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Study List:

Study 1:
Title: A Study to Evaluate the Efficacy and Safety of Daratumumab in Combination With Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared to CyBorD Alone in Newly Diagnosed Systemic Amyloid Light-chain (AL) Amyloidosis
Status: Active, not recruiting
Study Results: Has Results
Conditions: Amyloidosis
Interventions: Drug: Cyclophosphamide|Drug: Bortezomib|Drug: Dexamethasone, 40 mg|Drug: Daratumumab
URL: https://ClinicalTrials.gov/show/NCT03201965

Study 2:
Title: A Study of Daratumumab-Based Therapies in Participants With Amyloid Light Chain (AL) Amyloidosis
Status: Recruiting
Study Results: No Results Available
Conditions: Amyloidosis
Interventions: Drug: Daratumumab|Drug: Cyclophosphamide|Drug: Bortezomib|Drug: Dexamethasone

URL: https://ClinicalTrials.gov/show/NCT05250973

Study 3:
Title: Comparison of BTD and BCD Based Regimens in the Treatment of AL Amyloidosis
Status: Recruiting
Study Results: No Results Available
Conditions: Immunoglobulin Light-Chain Amyloidosis
Interventions: Drug: Thalidomide|Drug: Cyclophosphamide

URL: https://ClinicalTrials.gov/show/NCT04612582

Study 4:
Title: A Study to Evaluate the Safety and Tolerability of CAEL-101 in Patients With AL Amyloidosis
Status: Active, not recruiting
Study Results: No Results Available
Conditions: AL Amyloidosis
Interventions: Drug: CAEL-101|Drug: SoC: cyclophosphamide, bortezomib, and Dexamethasone (CyBorD)|Drug: Daratumumab
URL: https://ClinicalTrials.gov/show/NCT04304144

Study 5:
Title: Isatuximab as Upfront Therapy for the Treatment of High Risk AL Amyloidosis
Status: Recruiting
Study Results: No Results Available
Conditions: AL Amyloidosis

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Interventions: Drug: Bortezomib|Drug: Cyclophosphamide|Drug: Dexamethasone|Biological: Isatuximab

URL: https://ClinicalTrials.gov/show/NCT04754945

Study 6:
Title: A Study to Evaluate the Efficacy and Safety of CAEL-101 in Patients With Mayo Stage IIIa AL Amyloidosis
Status: Recruiting
Study Results: No Results Available
Conditions: AL Amyloidosis
Interventions: Drug: CAEL-101|Other: Placebo|Drug: cyclophosphamide, bortezomib, and dexamethasone (CyBorD) regimen
URL: https://ClinicalTrials.gov/show/NCT04512235

Clinicaltrialsregister.eu search

EudraCT Number: 2016-001737-27
Sponsor Protocol Number: 54767414AMY3001
Sponsor Name: Janssen-Cilag International N.V.
Full Title: A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared With CyBorD Alone in Newly Diagnos...
Start Date: 2018-04-16
Medical condition: AL Amyloidosis (Newly Diagnosed Systemic AL Amyloidosis)
Disease: Version: 20.0, SOC Term: 10021428 - Immune system disorders, Classification Code: 10002022, Term: Amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DE(Ongoing) BE(Ongoing) SE(Ongoing) ES(Ongoing) HU(Ongoing) NL(Ongoing) GB(GB - no longer in EU/EEA) GR(Ongoing) DK(Ongoing) PL(Ongoing) IT(Ongoing) RO(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-001737-27

EudraCT Number: 2018-004333-33
Sponsor Protocol Number: EMN22/54767414AMY2005
Sponsor Name: European Myeloma Network
Full Title: Phase 2 study of daratumumab monotherapy in previously untreated patients with stage 3B light chain (AL) amyloidosis
Start Date: 2019-07-08
Medical condition: Patients with newly diagnosed stage 3B AL amyloidosis

Disease: Version: 20.0, SOC Term: 10021428 - Immune system disorders, Classification Code: 10002022, Term: Amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: GR(Ongoing) NL(Ongoing) FR(Ongoing) IT(Ongoing)

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Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-004333-33

EudraCT Number: 2021-002639-48
Sponsor Protocol Number: 54767414AMY2009
Sponsor Name: Janssen-Cilag International N.V.
Full Title: A Phase 2, Multicohort Study of Daratumumab-Based Therapies in Participants with Amyloid Light Chain (AL) Amyloidosis
Start Date: 2022-07-25
Medical condition: Amyloid Light Chain Amyloidosis
Disease: Version: 23.0, SOC Term: 100000004870, Classification Code: 10083938, Term: Amyloid light-chain amyloidosis, Level: LLT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DE(Ongoing) ES(Ongoing) IT(Ongoing) NL(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-002639-48

EudraCT Number: 2019-001962-13
Sponsor Protocol Number: AC-016-IT
Sponsor Name: FONDAZIONE I.R.C.C.S. POLICLINICO SAN MATTEO
Full Title: A multi-center open label phase II study of daratumumab and pomalidomide in previously treated patients with AL amyloidosis
Start Date: 2021-01-13
Medical condition: AL amyloidosis
Disease: Version: 20.0, SOC Term: 10021428 - Immune system disorders, Classification Code: 10002022, Term: Amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-001962-13

EudraCT Number: 2011-001787-22
Sponsor Protocol Number: AC-007-IT
Sponsor Name: OSPEDALE POLICLINICO S. MATTEO
Full Title: An open-label, phase II study of Pomalidomide and Dexamethasone (PDex) for previously treated patients with AL amyloidosis
Start Date: 2012-05-02
Medical condition: Previously treated AL amyloidosis
Disease: Version: 14.1, SOC Term: 10021428 - Immune system disorders, Classification Code: 10002022, Term: Amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2011-001787-22

EudraCT Number: 2018-002089-37
Sponsor Protocol Number: EMN18

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Sponsor Name: EUROPEAN MYELOMA NETWORK
Full Title: A MULTICENTER, OPEN LABEL, RANDOMIZED PHASE II STUDY COMPARING DARATUMUMAB combined with BORTEZOMIB-CYCLOPHOSPHAMIDE-DEXAMETHASONE (Dara-VCd) VERSUS THE ASSOCIATION OF BORTEZOMIB-THALIDOMIDE-DEXAME...
Start Date: 2019-03-04
Medical condition: YOUNG PATIENTS AFFECTED BY MULTIPLE MYELOMA (MM) TO THE DIAGNOSIS ELIGIBLE TO THE AUTOLOGOUS TRANSMISSION OF STEM CELLS
Disease: Version: 20.0, SOC Term: 100000004864, Classification Code: 10028228, Term: Multiple myeloma, Level: LLT
Population Age: Adults
Gender: Male, Female
Trial protocol: IT(Ongoing) GR(Ongoing) CZ(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002089-37

EudraCT Number: 2021-000037-14
Sponsor Protocol Number: NEOD001-301
Sponsor Name: Prothena Biosciences Limited
Full Title: A Phase 3, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Birtamimab Plus Standard of Care vs. Placebo Plus Standard of Care in Mayo Stage IV Subjects with ...
Start Date: 2021-09-01
Medical condition: AL amyloidosis involves a hematologic disorder caused by clonal plasma cells that produce misfolded immunoglobulin light chains. Overproduction of misfolded light chains results in both soluble, a...
Disease: Version: 20.0, SOC Term: 10021428 - Immune system disorders, Classification Code: 10036673, Term: Primary amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DK(Ongoing) HU(Ongoing) DE(Ongoing) PT(Ongoing) PL(Ongoing) ES(Ongoing) GR(Ongoing) NL(Ongoing) IT(Ongoing) IE(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-000037-14

EudraCT Number: 2020-000713-32
Sponsor Protocol Number: CAEL101-302
Sponsor Name: Alexion Pharmaceuticals, Inc.
Full Title: A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dysc...
Start Date: 2020-12-23
Medical condition: stage IIIa cardiac AL amyloidosis
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DE(Ongoing) GB(GB - no longer in EU/EEA) GR(Ongoing) PL(Ongoing) BE(Ongoing) AT(Ongoing) NL(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-000713-32

EudraCT Number: 2019-004254-28

Sponsor Protocol Number: CAEL101-301
Sponsor Name: Caelum Biosciences, Inc.
Full Title: A Phase 3, Double-Blind, Multicenter Study to Evaluate the Efficacy and Safety of CAEL-101 and Plasma Cell Dyscrasia Treatment Versus Placebo and Plasma Cell Dyscrasia Treatment in Plasma Cell Dysc...
Start Date: 2021-01-07
Medical condition: stage IIIb cardiac AL amyloidosis
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: FR(Ongoing) DE(Ongoing) GB(GB - no longer in EU/EEA) GR(Ongoing) PL(Ongoing) BE(Ongoing) AT(Ongoing) NL(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-004254-28

EudraCT Number: 2017-002210-31
Sponsor Protocol Number: AC-012-EU
Sponsor Name: Amyloid Center - Biotechnology Research Laboratories Policlinico San Matteo
Full Title: A randomized phase II/III trial of doxycycline vs. standard supportive therapy in newly-diagnosed cardiac AL amyloidosis patients undergoing bortezomib-based therapy
Start Date: 2019-05-31
Medical condition: Light chain (AL) amyloidosis is a protein conformational disease, caused by a small bone marrow plasma cell clone producing light chains (LCs) that undergo conformational changes, aggregate and d...
Disease:
Population Age: Adults
Gender: Male, Female
Trial protocol: DE(Prematurely Ended) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-002210-31

EudraCT Number: 2013-000432-10
Sponsor Protocol Number: 26866138MMY2084
Sponsor Name: DUTCH BELGIAN COOPERATIVE GROUP FOR HEMATOLOGY ONCOLOGY - HOVON
Full Title: A PHASE II MULTI-CENTRE, RANDOMIZED, OPEN LABEL STUDY OF PROLONGED THERAPY WITH SUBCUTANEOUS BORTEZOMIB TWICE MONTHLY ASSOCIATED WITH DEXAMETHASONE, IN RELAPSED AND REFRACTORY MULTIPLE MYELOMA PAT...
Start Date: 2013-05-23
Medical condition: Patients with Multiple Myeloma
Disease:
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2013-000432-10

EudraCT Number: 2021-003008-42
Sponsor Protocol Number: ZN-d5-003
Sponsor Name: K-Group Alpha, Inc

Full Title: A Single-Arm, Open-Label, Phase 1/2 Study of ZN-d5 for the Treatment of Relapsed or Refractory Light Chain (AL) Amyloidosis
Start Date: 2021-12-22
Medical condition: Relapsed or Refractory Light-Chain Amyloidosis
Disease: Version: 23.0, SOC Term: 100000004870, Classification Code: 10083938, Term: Amyloid light-chain amyloidosis, Level: LLT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: GR(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2021-003008-42

EudraCT Number: 2018-002098-23
Sponsor Protocol Number: ALN-TTRSC02-002
Sponsor Name: Alnylam Pharmaceuticals, Inc.
Full Title: HELIOS-A: A Phase 3 Global, Randomized, Open-label Study to Evaluate the Efficacy and Safety of ALN-TTRSC02 in Patients with Hereditary Transthyretin Amyloidosis (hATTR Amyloidosis)
Start Date: 2019-05-09
Medical condition: Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis)
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Disease: Version: 20.0, SOC Term: 10010331 - Congenital, familial and genetic disorders, Classification Code: 10019889, Term: Hereditary neuropathic amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DE(Ongoing) PT(Ongoing) GB(GB - no longer in EU/EEA) BG(Ongoing) ES(Ongoing) BE(Ongoing) GR(Ongoing) NL(Ongoing) CY(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2018-002098-23

EudraCT Number: 2020-004627-16
Sponsor Protocol Number: 70233
Sponsor Name: Helsinki University Hospital
Full Title: Clinical Validation of Quantitative Flutemetamol PET/CT in Cardiac Amyloidosis
Start Date: 2020-11-25
Medical condition: Cardiac amyloidosis
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: FI(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2020-004627-16

EudraCT Number: 2019-003153-28
Sponsor Protocol Number: ALN-TTRSC02-003
Sponsor Name: Alnylam Pharmaceuticals, Inc.
Full Title: HELIOS-B: A Phase 3 Global, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Clinical Outcomes, Efficacy and Safety of Vutrisiran in Patients with Transthyretin Amyloidosis with C...

Start Date: 2019-12-23
Medical condition: Transthyretin Amyloidosis with Cardiomyopathy (ATTR Amyloidosis with Cardiomyopathy)
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: LV(Ongoing) PT(Ongoing) HU(Ongoing) SI(Ongoing) NO(Ongoing) LT(Ongoing) ES(Ongoing) AT(Ongoing) DK(Ongoing) DE(Ongoing) GB(GB - no longer in EU/EEA) PL(Ongoing) NL(Ongoing) HR(Ongoing) CZ(Ongoing) IT(Prematurely Ended)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-003153-28

EudraCT Number: 2017-001621-41
Sponsor Protocol Number: AC-011-IT
Sponsor Name: FONDAZIONE I.R.C.C.S. POLICLINICO SAN MATTEO
Full Title: A phase III randomized study of doxycycline and tauroursodeoxycholic acid (Doxy/TUDCA) plus standard supportive therapy versus standard supportive therapy alone in cardiac amyloidosis caused by tra...
Start Date: 2017-11-30
Medical condition: Cardiac amyloidosis caused by transthyretin
Disease: Version: 20.0, SOC Term: 10007541 - Cardiac disorders, Classification Code: 10007509, Term: Cardiac amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2017-001621-41

EudraCT Number: 2016-000489-50
Sponsor Protocol Number: AC-009-IT
Sponsor Name: FONDAZIONE I.R.C.C.S. POLICLINICO SAN MATTEO
Full Title: A Phase II, Single Arm, Open Label, Efficacy and Safety Study of NEOD001 in Subjects with Light Chain (AL) Amyloidosis with Hepatic Involvement
Start Date: 2017-10-03
Medical condition: AL amyloidosis with hepatic involvement
Disease: Version: 20.0, SOC Term: 10019805 - Hepatobiliary disorders, Classification Code: 10075251, Term: Hepatic amyloidosis, Level: PT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-000489-50

EudraCT Number: 2010-022395-31
Sponsor Protocol Number: AC-004-EU
Sponsor Name: E.M.N. - EUROPEAN MYELOMA NETWORK
Full Title: A randomized open-label multicenter phase III trial of Melphalan and Dexamethasone (MDex) versus Bortezomib, Melphalan and Dexamethasone (BMDex) for untreated patients with systemic light-chain (AL...
Start Date: 2010-10-07
Medical condition: AL amyloidosis

Disease: Version: 9.1, SOC Term: , Classification Code: 10035227, Term: , Level: HLGT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: IT(Completed) SE(Ongoing) DK(Completed) GB(GB - no longer in EU/EEA) GR(Ongoing) ES(Ongoing) DE(Completed) CZ(Completed)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-022395-31

EudraCT Number: 2006-003563-31
Sponsor Protocol Number: 26866138CAN 2021
Sponsor Name: European Myeloma Network
Full Title: Phase II Study of Combination Bortezomib (VELCADE, PS-341), Dexamethasone, and Rituximab (MabThera) (BDR) in Patients with previously untreated Waldenstrom's Macroglobulinemia (WM).
Start Date: 2007-03-09
Medical condition: Newly diagnosed Waldenstrom's macroglobulinemia (WM)
Disease: Version: 8.1, SOC Term: , Classification Code: 10054695, Term: Waldenstrom's macroglobulinemia, Level: LLT
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: DK(Ongoing) NL(Ongoing) ES(Ongoing) FR(Ongoing) IT(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-003563-31

EudraCT Number: 2019-002873-80
Sponsor Protocol Number: AMILCA-DIFLU
Sponsor Name: FUNDACION JIMENEZ DIAZ HEALTH RESEARCH INSTITUTE
Full Title: Unicentre, open, uncontrolled clinical trial to assess the morphological, biochemical and functional effects of Diflunisal treatment in patients with transthyretin cardiac amyloidosis
Start Date: 2020-01-14
Medical condition: transthyretin cardiac amyloidosis
Disease:
Population Age: Adults, Elderly
Gender: Male, Female
Trial protocol: ES(Ongoing)
Link: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2019-002873-80

16. Appendix C - Main characteristics of included studies

Table 41: Key characteristics of the ANDROMEDA study

Trial name: ANDROMEDA	NCT number: NCT03201965
Objective	To evaluate the efficacy and safety of daratumumab plus VCd as compared to VCd alone in adult patients with newly diagnosed systemic AL amyloidosis.

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Trial name: ANDROMEDA	NCT number: NCT03201965
Publications – title, author, journal, year	(Kastritis 2020d) (Palladini 2020a) (Wechalekar 2020) (Suzuki 2020) (Sanchorawala 2020b) (Minnema 2020) (Comenzo 2020)
Study type and design	A randomized, open-label, active-controlled, phase III study. Patients were randomly assigned in a 1:1 ratio to receive either subcutaneous daratumumab plus VCd (D-VCd) or VCd alone, after balancing for cardiac stage (ie, Stage I, II, and IIIA), renal function (ie, creatine clearance [CrCl] ≥60 or <60 mL/min), and the availability of ASCT.
Sample size (n)	388
Main inclusion and exclusion criteria	Patients were included if they were: • at least 18 years of age with a histopathologic diagnosis of systemic AL amyloidosis (affecting one or more organs and, • measurable hematologic disease. Patients were excluded if they had: • received previous therapy for AL amyloidosis, • had symptomatic multiple myeloma according to International Myeloma Working Group criteria had an Eastern Cooperative Oncology Group performance-status score of more than 2 (on a 5-point scale in which higher numbers indicate greater disability), • had an estimated glomerular filtration rate of less than 20 ml per minute per 1.73 m^2 of body surface area, or • had evidence of a severe cardiovascular condition including an N-terminal pro–B-type natriuretic peptide level of more than 8500 ng per litre, a systolic blood pressure of less than 90 mm Hg, or a New York Heart Association classification of stage IIIB or IV at screening.
Intervention	<u>D-VCd</u> Patients received 1800 mg of daratumumab per 15 ml administered subcutaneously, coformulated with recombinant human hyaluronidase PH20, weekly in cycles 1 and 2, every 2 weeks in cycles 3 through 6, and every 4 weeks thereafter until disease progression, the start of subsequent therapy, or for a maximum of 24 cycles from the start of the trial, whichever occurred first. All the patients received subcutaneous bortezomib at a dose of 1.3 mg per m^2 of body-surface area, cyclophosphamide at a dose of 300 mg per m^2 orally or intravenously (500 mg maximum weekly dose), and dexamethasone at a dose of 40 mg orally or intravenously once weekly for six cycles of 28 days each.

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Trial name: ANDROMEDA	NCT number: NCT03201965
Comparator	**VCd** All the patients received subcutaneous bortezomib at a dose of 1.3 mg per m^2 of body-surface area, cyclophosphamide at a dose of 300 mg per m^2 orally or intravenously (500 mg maximum weekly dose), and dexamethasone at a dose of 40 mg orally or intravenously once weekly for six cycles of 28 days each.
Follow-up time	Median follow-up of 11.4 months (range, 0.03 to 21.3)
Is the study used in the health economic model?	Yes

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Primary, secondary and exploratory endpoints	**Endpoints included in this application:**

Complete response (CR)

- Per consensus guidelines (Comenzo, Reece et al. 2012), negative serum and urine immunofixation and normalization of FLC levels and FLC ratios
- Per clarifications during the trial based on recent evidence (Muchtar, Gertz et al. 2017, Manwani, Cohen et al. 2019, Sidana, Dispenzieri et al. 2020) (recommended by the Steering Committee and agreed upon by the Independent Review Committee), if iFLC level is lower than ULN, normalization of uninvolved FLC and FLC ratio is not required when determining CR

MOD-PFS

- Defined as the time from randomization to any of the following events, whichever comes first:
- Death
- End-stage cardiac failure (need for heart transplant, LVAD, or IABP)
- End-stage renal failure (need for hemodialysis or kidney transplant)
- Hematologic progression:
- From CR: abnormal FLC ratio (light chain ratio must double) or
- From CR/VGPR/PR: 50% increase in serum M protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present) or
- FLC increase of 50% to >100 mg/L

Overall Survival (OS)

Time from the date of randomization to the date of the patients' death. Patients who are lost to follow-up will be censored at the time of lost to follow-up. Patients who are still alive at the clinical cut-off date for the analysis will be censored at the last known alive date.

Major organ deterioration event free survival (MOD-EFS)

Defined as the time from randomization to occurrence of any of the above MOD-PFS events (ie, death, cardiac or renal failure, hematologic progression), or the initiation of subsequent non-cross resistant anti-plasma cell therapy, whichever comes first.

Achievement of organ response (in the heart, kidneys, and/or liver) at 6 months

Proportion of cardiac/renal/liver response-evaluable patients who achieved an organ response at 6 months

- Cardiac response: NT-proBNP response (>30% and >300 ng/l decrease in patients with baseline NT-proBNP level ≥650 ng/l) or NYHA class response (≥2 class decrease in patients with baseline NYHA class 3 or 4)
- Renal response: ≥30% decrease in proteinuria or a drop of proteinuria below 0.5 g/24 hours in the absence of renal progression (see below)
- Liver response: ≥50% decrease in abnormal alkaline phosphatase level; decrease in liver size radiographically by ≥2 cm

Mean change in EORTC QLQ C30 Fatigue and Global Health Status scores

Mean change in SF-36v2 MCS scores

Time to initiation of subsequent non-cross resistant anti-plasma cell therapy

- The time from randomization to initiation of a subsequent non-cross resistant, anti-plasma cell therapy

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- Death prior to subsequent non-cross resistant anti-plasma cell therapy is considered as an event

Achievement of a very good partial response (VGPR) or better

- Achievement of either CR (see definition above) or VGPR, defined as:
- Baselinea dFLC ≥50 mg/L: reduction in dFLC to <40 mg/L
- Baselinea dFLC <50 mg/L: ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours

Time to CR (or VGPR or better)

- The time from randomization to the first efficacy evaluation at which the patient meets all criteria for CR (or VGPR or better; see definitions above)

Duration of hematologic response

Includes duration of CR, duration of VGPR or better response, and duration of PR or better response.

- Duration of CR: the time from the date of initial documentation of CR to the date of first documented evidence of hematologic PD. For patients who have not progressed, data will be censored at the last disease assessment.
- Duration of hematologic VGPR or better: the time from the date of initial documentation of hematologic VGPR or better to the date of first documented evidence of hematologic PD. For patients who have not progressed, data will be censored at the last disease assessment.
- Duration of hematologic PR or better response: the time from the date of initial documentation of hematologic PR or VGPR or CR to the date of first documented evidence of hematologic PD. For patients who have not progressed, data will be censored at the last disease assessment.

Time to cardiac, renal, and liver response

The time from randomization to the first efficacy evaluation at which the patient meets heart, kidney, or liver response criteria (evaluated separately; see above)

Time to cardiac, renal, and liver progression

- Cardiac progression: NT-proBNP progression (>30% and >300 ng/l increase)b or cTn progression (≥33% increase) or ejection fraction progression (≥10% decrease)
- Renal progression: ≥25% decrease in eGFR
- Liver progression: ≥50% increase in alkaline phosphatase above the lowest value

Other endpoints:

Hematologic PFS (HemPFS)

Time from the date of randomization to the date of first documented hematologic disease progression (see definition above) or death from any cause.

Achievement of minimal residual disease (MRD) in patients with CR

- The presence of residual malignant plasma cell DNA was evaluated in bone marrow samples from patients who achieved CR, using clonoSEQ v2.0 (Adaptive, Seattle) next generation sequencing:
- MRD negativity thresholds included 10-4 10-5, and 10-6

SF-36v2, EORTC QLQ-C30, and EQ-5D-5L scores

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Trial name: ANDROMEDA	NCT number: NCT03201965
	Assessment of physical functioning, symptom improvement, functional improvement, and health utility as measured by the SF-36v2, EORTC QLQ-C30 with supplemental symptom items, and the EQ-5D-5L Diastolic heart dysfunction
Method of analysis	All efficacy analyses were intention-to-treat analyses. Time-to-event variables were evaluated using the Kaplan–Meier method.
Subgroup analyses	
Other relevant information	

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17. Appendix D - Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

17.1 Comparability of patients across studies

No comparative analysis was performed for this application. Therefore only the baseline characteristics of the head-to-head ANDROMEDA trial are presented

Table 42: Summary of patient disposition, demographics, and disease characteristics, ITT analysis set, ANDROMEDA

	D-VCd (n = 193)	VCd (n = 195)	Total (n = 388)
Patient Disposition			
Analysis set: intent-to-treat	193	195	388
Patients randomized but not treated	5 (2.6%)	2 (1.0%)	7 (1.8%)
Patients treated	188 (97.4%)	193 (99.0%)	381 (98.2%)
Patient Demographics			
Age, years			
Mean (SD)	62.2 (10.16)	64.0 (9.66)	63.1 (9.94)
Median (range)	62.0 (34-87)	64.0 (35-86)	64.0 (34-87)
Sex, n (%)			
Female	87 (44.6%)	76 (39.4%)	163 (42.0%)
Male	108 (55.4%)	117 (60.6%)	225 (58.0%)
Race, n (%)			
American Indian or Alaska Native	1 (0.5%)	2 (1.0%)	3 (0.8%)
Asian	30 (15.4%)	34 (17.6%)	64 (16.5%)
Black or African American	6 (3.1%)	7 (3.6%)	13 (3.4%)
Native Hawaiian or Other Pacific Islander	0	1 (0.5%)	1 (0.3%)
White	151 (77.4%)	143 (74.1%)	294 (75.8%)
Multiple	0	1 (0.5%)	1 (0.3%)
Unknown	7 (3.6%)	5 (2.6%)	12 (3.1%)
Ethnicity, n (%)			
Hispanic or Latino	9 (4.6%)	13 (6.7%)	22 (5.7%)
Not Hispanic or Latino	179 (91.8%)	176 (91.2%)4 (2.1%)	355 (91.5%)

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	D-VCd (n = 193)	VCd (n = 195)	Total (n = 388)
Unknown	7 (3.6%)		11 (2.8%)
Weight, kg			
Mean (SD)	73.38 (15.896)	73.41 (17.345)	73.40 (16.611)
Median (range)	73.0 (41.5-141.5)	70.0 (38.0; 134.6)	72.0 (38.0-141.5)
Height, cm			
Mean (SD)	167.32 (10.449)	168.13 (10.231)	167.72 (10.336)
Median (range)	167.20 (140.0-190.5)	168.10 (139.1-193.0)	168.00 (139.1-193.0)
Body surface area, m^2			
Mean (SD)	1.84 (0.237)	1.84 (0.255)	1.84 (0.246)
Median (range)	1.83 (1.3-2.5)	1.81 (1.2-2.7)	1.81 (1.2-2.7)
Baseline ECOG PS score, n (%)			
0	90 (46.2%)	71 (36.8%)	161 (41.5%)
1	86 (44.1%)	106 (54.9%)	192 (49.5%)
2	19 (9.7%)	16 (8.3%)	35 (9.0%)
Disease Characteristics			
Time since initial AL amyloidosis, days	101.5 (220.22)	62.4 (90.70)	82.1 (169.63)
Mean (SD)	48.0 (8-1,611)	43.0 (5-1,102)	43.0 (5-1,611)
Median (range)			
Type of measurable disease, n (%)	21 (10.8%)	8 (4.2%)	29 (7.6%)
Serum M-protein only	110 (56.7%)	122 (64.2%)	232 (60.4%)
Serum FLC only	63 (32.5%)	60 (31.6%)	123 (32.0%)
Serum M-protein + FLC			
Light chain isotype, n (%)			
Lambda	158 (81.0%)	149 (77.2%)	307 (79.1%)
Kappa	37 (19.0%)	44 (22.8%)	81 (20.9%)
Organ involvement, n (%)			
Heart	140 (71.8%)	137 (71.0%)	277 (71.4%)
Kidney	115 (59.0%)	114 (59.1%)	229 (59.0%)
Liver	15 (7.7%)	16 (8.3%)	31 (8.0%)
Gastrointestinal system	30 (15.4%)	16 (8.3%)	59 (15.2%)
Lung	3 (1.5%)	5 (2.6%)	8 (2.1%)
Nerve	42 (21.5%)	33 (17.1%)	75 (19.3%)
PNS	32 (16.4%)	24 (12.4%)	56 (14.4%)

	D-VCd (n = 193)	VCd (n = 195)	Total (n = 388)
ANS	11 (5.6%)	11 (5.7%)	22 (5.7%)
Soft tissue	51 (26.2%)	55 (28.5%)	106 (27.3%)
Number of organs involved			
Mean (SD)	2.0 (0.97)	2.0 (1.03)	2.0 (1.00)
Median (range)	2.0 (1-5)	2.0 (1-6)	2.0 (1-6)
Organ involvement category, n (%)			
1 organ	66 (33.8%)	68 (35.2%)	134 (34.5%)
2 organs	76 (39.0%)	77 (39.9%)	153 (39.4%)
≥3 organs	53 (27.2%)	48 (24.9%)	101 (26.0%)
Mayo Clinic Cardiac Stage[a], (%)			
I	47 (24.1%)	43 (22.3%)	90 (23.2%)
II	76 (39.0%)	80 (41.5%)	156 (40.2%)
IIIa	70 (35.9%)	64 (33.2%)	134 (34.5%)
IIIb	2 (1.0%)	6 (3.1%)	8 (2.1%)
NYHA class, n (%)			
I	101 (51.8%)	94 (48.7%)	195 (50.3%)
II	77 (39.5%)	89 (46.1%)	166 (42.8%)
IIIA	17 (8.7%)	10 (5.2%)	27 (7.0%)
Renal function (creatinine clearance), n (%)			
<60 mL/min	69 (35.4%	62 (32.1%)	131 (33.8%)
≥60 mL/min	126 (64.6%)	131 (67.9%)	257 (66.2%)
Chronic kidney disease stage[b], n (%)			
I	60 (30.8%)	55 (28.5%)	115 (29.6%)
II	69 (35.4%)	76 (39.4%)	145 (37.4%)
III	51 (26.2%)	41 (21.2%)	92 (23.7%)
IV	15 (7.7%)	21 (10.9%)	36 (9.3%)
V (end-stage renal disease)	0	0	0
Renal stage[b], n (%)			
I	107 (55.4%)	101 (52.3%)	208 (53.9%)
II	67 (34.7%)	74 (38.3%)	141 (36.5%)
III	19 (9.8%)	18 (9.3%)	37 (9.6%)
Cytogenetic risk at study entry[d], n (%)	17 (11.0%)	19 (11.4%)	36 (11.2%)

	D-VCd (n = 193)	VCd (n = 195)	Total (n = 388)
High risk	138 (89.0%)	147 (88.6%)	285 (88.8%)
Standard risk			
t(11;14) translocation (FISH), n (%)	51/95 (53.7%)	55/107 (51.4%)	106/202 (52.5%)

a Cardiac stage is based on both NT-proBNP and hs-cTnT levels.

b Chronic kidney disease stage is based on eGFR.

c Renal stage is based on eGFR and proteinuria testing.

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

Abbreviations: ANS = autonomic nervous system; D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; dFLC = difference in involved and uninvolved free light chains; ECOG PS = Eastern Cooperative Oncology Group Performance Status; eGFR = estimated glomerular filtration rate; FISH = florescence in situ hybridization; FLC = free light chain; iFLC = involved free light chain; hs-cTnT high sensitivity cardiac troponin T; ITT = intent-to-treat; NT-proNBP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; PNS = peripheral nervous system; SD = standard deviation; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone.

Source: Janssen (2020b)

17.2 Comparability of the study populations with Danish patients eligible for treatment

Based on feedback from Danish clinical expert opinion, the ANDROMEDA trial population can be considered representative for the Danish population.

18. Appendix E - Efficacy and safety results per study

18.1 Definition, validity and clinical relevance of included outcome measures

Table 43: Outcome measures included in the ANDROMEDA trial

Outcome measure	Definition	Validity	Clinical relevance
Primary outcome measures			
Hematologic complete response	An involved free light-chain level less than the upper limit of the normal range with negative serum and urine immunofixation; normalization of the uninvolved free light-chain level or free light-chain ratio was not required to determine a complete response.	The response had to be confirmed by a subsequent assessment during or after the trial treatment, as assessed by the independent review committee, whose members were unaware of the trialgroup assignments (Manwani 2019, Muchtar 2019a, Sidana 2020).	In-line with consensus guidelines for AL amyloidosis (Comenzo 2012).
Secondary outcome measures			
Major organ deterioration–progression-free survival	Composite endpoint of clinically observable endpoints and was defined from randomization to any one of the following events, whichever comes first: • Death • Clinical manifestation of cardiac failure ○ Defined as need for cardiac transplant, left ventricular assist device (LVAD), or intra-aortic balloon pump (IABP) • Clinical manifestation of renal failure		In-line with consensus guidelines for AL amyloidosis (Comenzo 2012).

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Outcome measure	Definition	Validity	Clinical relevance
	○ Defined as the development of end-stage renal disease (need for hemodialysis or renal transplant) • Development of hematologic progressive disease as per consensus guidelines ○ From hematologic complete response, abnormal free light chain ratio (light chain ratio must double), or from any response, a 50% increase in serum M-protein to >0.5 g/dL or 50% increase in urine M-protein to >200 mg/day (a visible peak must be present) • Free light chain increase of 50% to >100 mg/L		
Organ response rate	For kidney, heart, liver was defined as the proportion of baseline organ involved patients who achieved organ response in each corresponding organ.		
Overall survival	The time from the date of randomization to the date of the patient's death. If the patient was alive or the vital status was unknown, then the patient's data were censored at the date the patient was last known to be alive.		
Rate of hematologic complete response at 6 months	The proportion of patients who achieve a hematologic complete response at 6 months, according to the consensus guidelines for AL amyloidosis during or after the study treatment.		
Improvement in health-related quality of life	The change from baseline in the EORTC QLQC30 Global Health Status scale score.		

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Outcome measure	Definition	Validity	Clinical relevance
Rate of hematologic very good partial response or better	The proportion of patients who achieved hematologic complete response or very good partial response.		
Time to response (hematologic complete response or very good partial response)	The time between the date of randomization and the first efficacy evaluation at which the patient had met all criteria for hematologic response (hematologic complete response or very good partial response).		
Duration of response (hematologic complete response or very good partial response)	The time between the date of initial documentation of response to the date of first documented evidence of hematologic progressive disease. For patients who have not progressed, data were censored at the last disease assessment.		
Time to organ response	The time between the date of randomization and the first efficacy evaluation at which the patient had each corresponding organ response.		
Time to organ progression	The time from the date of randomization to the date of each corresponding organ progression per consensus guidelines.		

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18.2 Results per study

Table 44: Results of the ANDROMEDA study - 18 month landmark analysis

ANDROMEDA (NCT03201965)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
VGPR or better (CR+VGPR)	VCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]				Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. The stratification factors from IWRS are: cardiac staging (I, II, IIIa), countries that typically offer or not offer transplant for patients with AL amyloidosis (List A, List B), and baseline renal function (CrCl>=60 mL/min or CrCl <60 mL/min). An odds ratio > 1 indicates an advantage for D-VCd. P-value from the Cochran Mantel-Haenszel Chi-Squared test.	(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								

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ANDROMEDA (NCT03201965)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Overall response (CR+VGPR +PR)	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Best response category											
Complete response	VCd	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]					(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Very good partial response	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Partial response	VCd	[redacted]	[redacted]								(Janssen 2021c)

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ANDROMEDA (NCT03201965)				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Not response	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Progressive disease	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Not evaluable	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Time to response											

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ANDROMEDA (NCT03201965)												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median time to complete hematologic response (months)	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)
Median time to VGPR or better (months)	VCd	[redacted]	[redacted]								(Janssen 2021c)
	D-VCd	[redacted]	[redacted]								(Janssen 2021c)

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19. Appendix F - Safety data for intervention and comparator

[redacted] A summary of the commonly reported Grade 3 or 4 TEAEs (i.e. reported in ≥5% of patients) is presented in Table 45. These adverse events (AEs) are included in the health economic model.

Table 45: Most commonly reported Grade 3/4 TEAEs (in ≥5% of patients) by preferred term; safety analysis set, ANDROMEDA - 18-month landmark analysis

Adverse event	D-VCd (n = 193) Cycles 1-6	VCd (n = 188) Total/ Cycles 1-6[a]
≥1 Grade 3 or 4 TEAE, n (%)	[redacted]	[redacted]
Lymphopenia	[redacted]	[redacted]
Pneumonia	[redacted]	[redacted]
Diarrhea	[redacted]	[redacted]
Cardiac failure	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]
Syncope	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]
Peripheral edema	[redacted]	[redacted]
Hypokalemia	[redacted]	[redacted]

[a] VCd treatment was limited to Cycles 1-6 only.

Abbreviations: D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; TEAE = treatment-emergent adverse event; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone).

Source: (Janssen 2021c)

[redacted]

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Table 46: Summary deaths and cause of deaths; safety analysis set, ANDROMEDA - 18-month landmark analysis

	D-VCd (n = 193)	VCd (n = 188)
Total number of deaths, n (%)		
Total	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Related	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]
Disease progression	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths within 30 days of last study treatment dose, n (%)		
Total	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Related	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Other	[redacted]	[redacted]
Deaths within 60 days of first study dose, n (%)		
Total	[redacted]	[redacted]
Adverse event	[redacted]	[redacted]
Related	[redacted]	[redacted]
Unrelated	[redacted]	[redacted]
Progressive disease	[redacted]	[redacted]
Other	[redacted]	[redacted]

Abbreviations: D-VCd = daratumumab, VELCADE® (bortezomib), cyclophosphamide, and dexamethasone; VCd = VELCADE® (bortezomib), cyclophosphamide, and dexamethasone).

Source: (Janssen 2021c)

20. Appendix G - Comparative analysis of efficacy and safety

No meta-analysis, narrative synthesis, or indirect comparison was performed as a part of this application. For direct comparative analysis please refer to Appendix E.

21. Appendix H – Extrapolation

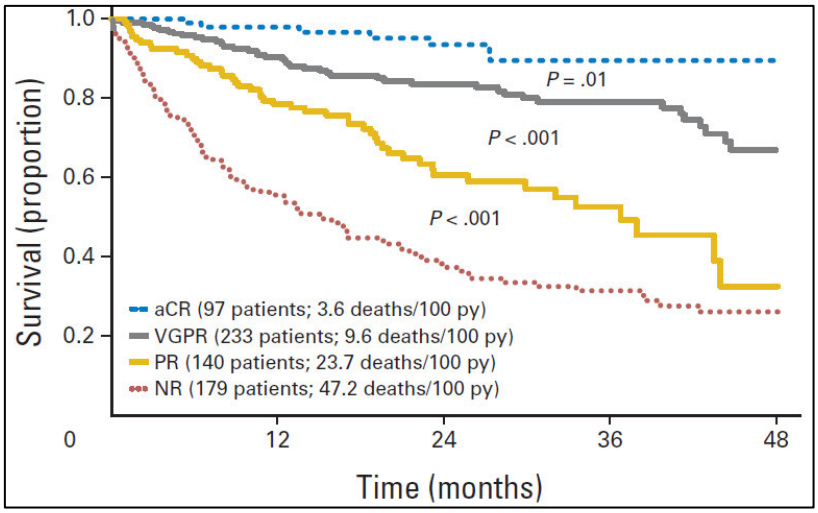
External data sources

The global model structure was developed based on the use of hematologic response as a measure of treatment efficacy in clinical practice, and further supported by the established validity of early hematologic response as a surrogate endpoint and prognostic factor for survival in the literature (Gertz 2007, Wechalekar 2007, Kastritis 2010a, Palladini 2012, Kastritis 2015, Palladini 2015, Manwani 2018a, Nguyen 2018, Wong 2018, Kastritis 2020a). Therefore, to inform the Markov model, OS curves stratified by hematologic response were needed.

As described in chapter 7.1.2.1.4, 86% of patients were still alive in the ANDROMEDA trial at the time of the first clinical cut-off (February 2020; median follow-up: 11.4 months). Statistically robust long-term extrapolation of effectiveness was limited by the ANDROMEDA OS KM data immaturity and, consequently, the use of external/published data for natural history landmark survival was explored.

One data source was identified through a targeted literature search that reported OS curves by hematologic response achieved relevant at landmark timepoints, Palladini et al., (2012). A digitized, overlaid version of the four curves depicting OS by hematologic response at six months is presented in Figure 31.

Figure 31: Palladini et al., (2012) overall survival by hematologic response



Abbreviations: aCR = amyloid complete response; NR = no response; PR = partial response; VGPR = very good partial response.
Source: (Palladini 2012).

In a systematic literature review, Palladini et al. 2012 was identified as the only robust enough evidence source available with 6 month OS based on hematological response. The Palladini et al., (2012) article is widely recognized and cited in AL amyloidosis literature. The study by was a retrospective study aimed to identify and validate criteria for response to first-line treatment in AL amyloidosis (Palladini 2012). The population described in the article by Palladini et al., (2012) was similar to the population included in the ANDROMEDA trial, and survival rates are expected to apply for the model's population of interest as well. For example, patients in the ANDROMEDA trial and in Palladini et al., (2012) were of similar age, had a similar proportion of male subjects,

and the same median number of organs involved. The patient populations had similar NT-proBNP and cardiac troponin levels, comparable levels of involved free light chains, and similar dFLC measurements. The Palladini et al., (2012) study had a slightly lower proportion of patients (25.4% vs. 36.6%) classified as Mayo stage III (Palladini 2012, Janssen Research and Development 2020b). See Table 47 for features of the study.

The most notable difference between patients in the ANDROMEDA trial and Palladini et al., (2012) study is the type of first-line treatment received, as the published OS curves reflect the use of Md in the majority of cases. Indeed, 44.6% and 3.2% of patients in the Palladini et al., (2012) article received Md and bortezomib-based therapies. However, despite the changes in the standard of care since 2012, a visual comparison of the overlaid OS curves suggests that trends in OS based on patient hematologic response remain unchanged. Therefore, irrespective of which first-line regimen is used, the goal of treatment is to achieve a rapid, deep hematologic response (while minimizing toxicity) to improve patient outcomes (Fotiou 2020). Taken together, this suggests that survival is driven by depth of hematologic response and mitigates the limitation imposed by using a relatively older OS data source.

Table 47: Features of Palladini et al., (2012)

Characteristics of the study	
Number of patients	816
Patient Population	Newly diagnosed
Publication Year	2012
First-line Regimens Received	Md (44.6%) ASCT (15.9%) Thalidomide (14.6%) Lenalidomide (5.3%) V-based (3.2%) Dexamethasone (2.9%) Mp (2.4%) Other (11.1%)
Second-line Regimens Received	NR
Median Follow-up	33 months
Age (median, years)	63 (IQR: 55-71)
Sex (% male)	59.9%
Organ Involvement (#, median)	2 (IQR: 1-2)
Kidney (%)	68.1%
Heart (%)	64.8%
Liver (%)	16%
PNS/ANS Involvement	18.7%[a]

Mayo Cardiac Stage (%)	
I	30.9%
II	43.7%
III	25.4%
IIIa	NR
IIIb	NR
NT-proBNP (ng/L, median)	1587 (IQR: 351-4,670)
dFLC (mg/L, median)	157 (IQR: 70-460)

Abbreviations: ANS = autonomic nervous system; ASCT = autologous stem cell transplant; IQR = interquartile range; M = melphalan; N/A = not applicable; NR = not reported; NT-pro PNS = peripheral nervous system; V= VELCADE® (bortezomib).
a ANS involvement not reported, only PNS.
Sources: (Palladini 2012)

Modelling effectiveness in the decision tree

The decision tree highlighted the treatment benefit of D-VCd; that is, affording patients deeper hematologic response earlier in the treatment course. The patient distribution within the decision tree is presented in Table 48; see subsequent section for further details on how these patient distributions were calculated).

Table 48: Hematologic response (6-month) distribution with the decision tree

[redacted]

Hematologic response distribution

Patient-level data from the ANDROMEDA 18-month landmark analysis (Nov 2020 data cut-off) was used to inform the decision tree with respect to the proportion of patients in each treatment group achieving CR, VGPR, and PR/NR or who died within each one-month window (assumed to be equal to one-cycle). In accordance with the ANDROMEDA CSR 6-month landmark analysis, a two-month window was used to capture hematologic response data for patients in cycle six, thereby ensuring that all appropriate hematologic response data were captured (e.g. for patients that may have experienced treatment delays). The resulting 6-month CR rates were consistent with the reported ITT landmark analysis. For any instance where an alive patient's hematologic response status was not reported in a particular cycle, they were classified as PR/NR (a simplistic

assumption that was applied equally to both treatment groups in order to avoid overestimating treatment benefit). An alternative assumption for handling non-evaluable/missing response data using last observation carried forward was explored as an alternative scenario.

Overall survival for PR/NR

PR and NR KM curves from Palladini et al., (2012) were digitized, extrapolated, and visually assessed to demonstrate that the extrapolated data appropriately fit the PR and NR KM data. The six-month landmark PR KM curve, NR KM curve and their associated curve extrapolations are presented in Figure 32 and Figure 33, respectively. For the extrapolations at the six-month landmark, OS in the Log-normal (PR and NR), Log-logistic (PR and NR), and Gompertz (NR) extrapolations was noted to plateau above zero or did not reach 0% survival within a reasonable time frame, whereas the tail ends of the other extrapolations were more realistic. The Exponential, Weibull, Gamma, and Generalized Gamma extrapolations appeared clinically plausible and can be considered for informing OS when 6-month exit from the decision tree is selected.

According to ANDROMEDA IPD, patients that achieve NR by 6-months comprise 68% of all patients that are PR or NR at the six-month landmark irrespective of treatment arm. Because patients with NR represented a larger proportion of the weighting applied in generating the blended PR/NR curve in the reference case, AIC and BIC for the NR curve were used to determine which parametric survival function was best-fit. According to AIC and BIC, the Weibull parametric survival function generated the curve best-fit for patients with NR and is therefore the recommended extrapolation function if/when 6-month exit from the decision tree is selected. To align with the NR curve extrapolation, the Weibull parametric survival function should also used to extrapolate the PR curve. Of note, the Weibull survival function was also clinically plausible and a good statistical fit to the PR curve (Table 49).

Table 49: Fit statistics for OS based hematologic response (Palladini et al., (2012))

The Palladini et al., (2012) PR and NR curves (six-month landmark) were used to generate a single, blended OS curve. The proportion of patients in PR and NR at six months, as reported in the ANDROMEDA trial was used to apply weighting to the blended PR/NR OS curve to more adequately reflect the appropriate patient population.(Janssen Research and Development

2020b) The PR and NR KM curves along with their respective blended PR/NR survival curve extrapolations are depicted in Figure 34.

Figure 32: Unadjusted OS curve extrapolations for patients with PR from Palladini et al., (2012)

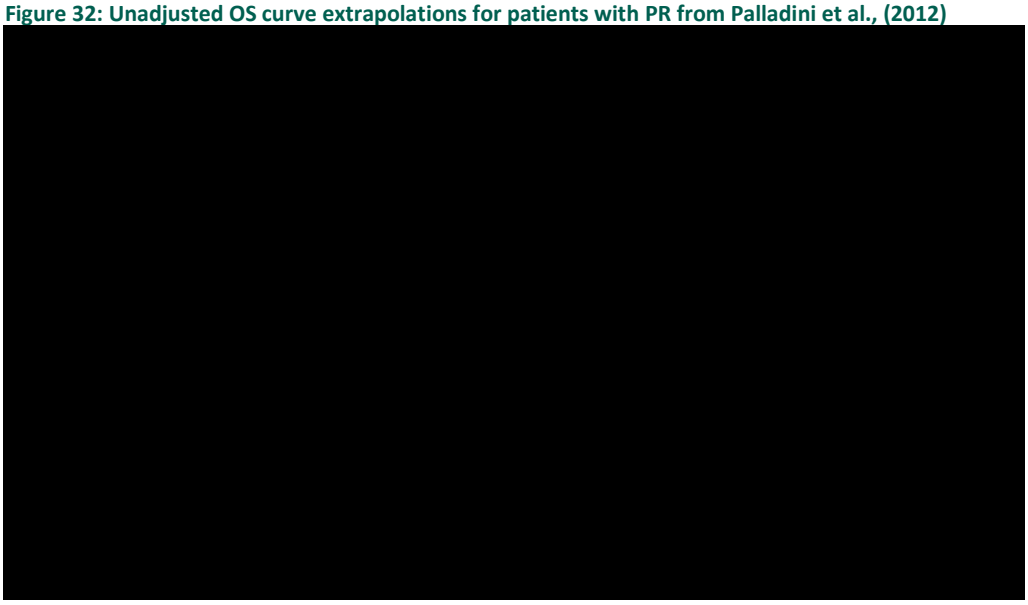


Figure 33: Unadjusted OS curve extrapolations for patients with NR from Palladini et al., (2012)

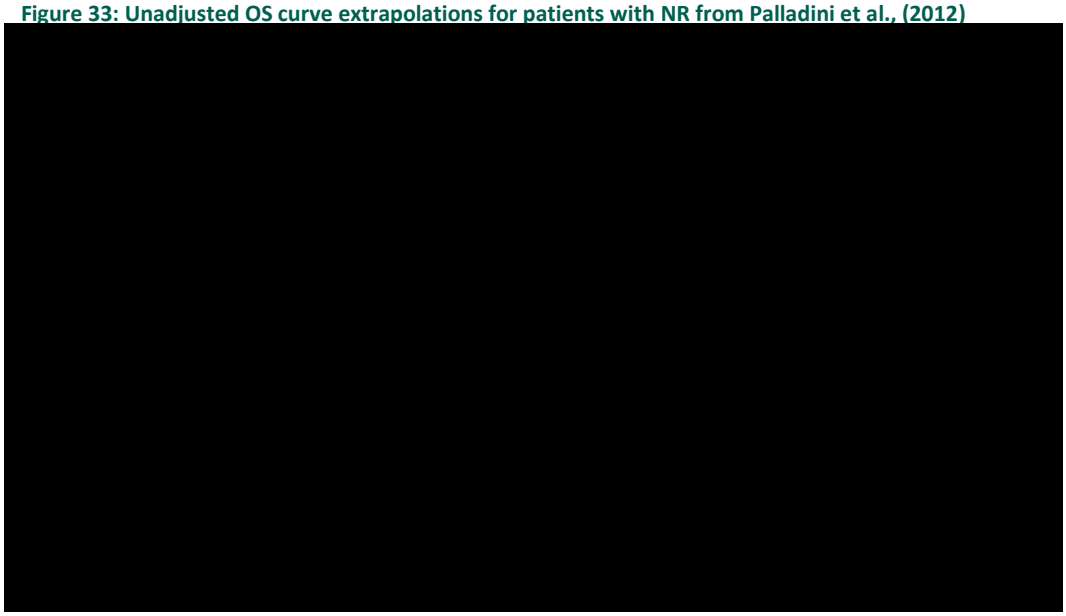


Figure 34: Unadjusted blended PR and NR OS curve extrapolations)

Overall survival for CR and VGPR

Digitized and extrapolated KM data from Palladini et al., (2012) is used to inform OS for CR and VGPR. After digitizing and extrapolating the CR and VGPR curves, the curves were visually assessed and shown to appropriately fit the CR and VGPR KM data. The KM curves with their associated extrapolations using all seven parametric survival functions for patients with CR and VGPR are presented in Figure 35 and Figure 36, respectively.

By visual inspection, all CR extrapolations have a similar and appropriate fit to their respective CR KM data; however, all extrapolations predict a clinically implausible lifespan.

By visual inspection, all VGPR extrapolations have a similar and appropriate fit to their respective KM data (Figure 36). The Log-normal and Log-logistic VGPR extrapolations plateau above zero and predict a clinically implausible lifespan. The Exponential, Weibull, Gompertz, Gamma, and Generalized Gamma functions generate more realistic extrapolations and, according to AIC and BIC, the curve extrapolated using the Exponential parametric survival function has the best fit (Table 49).

Figure 35. Unadjusted OS curve extrapolations for patients with CR from Palladini et al., (2012)

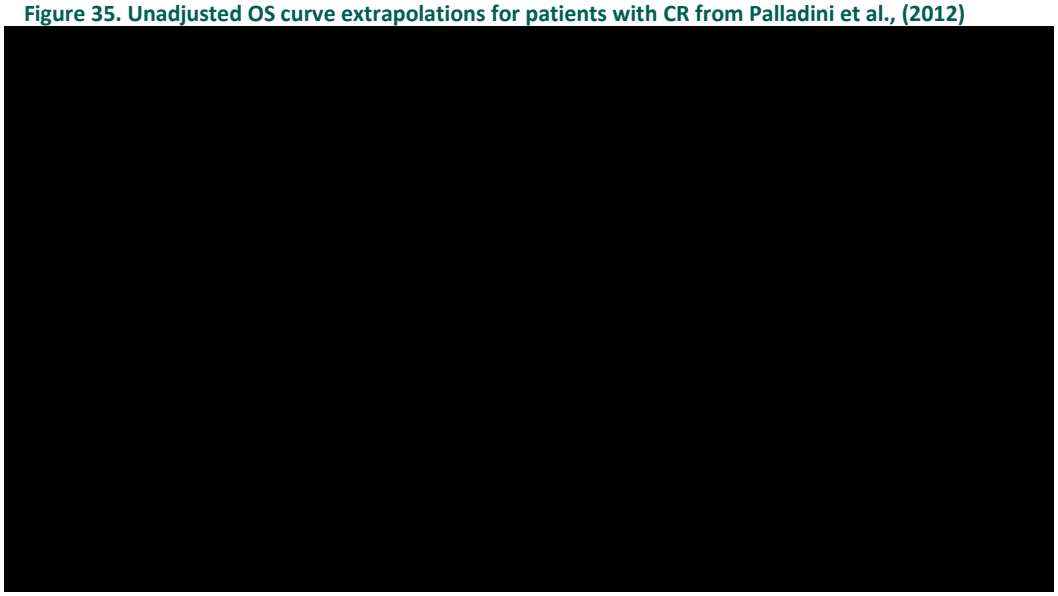
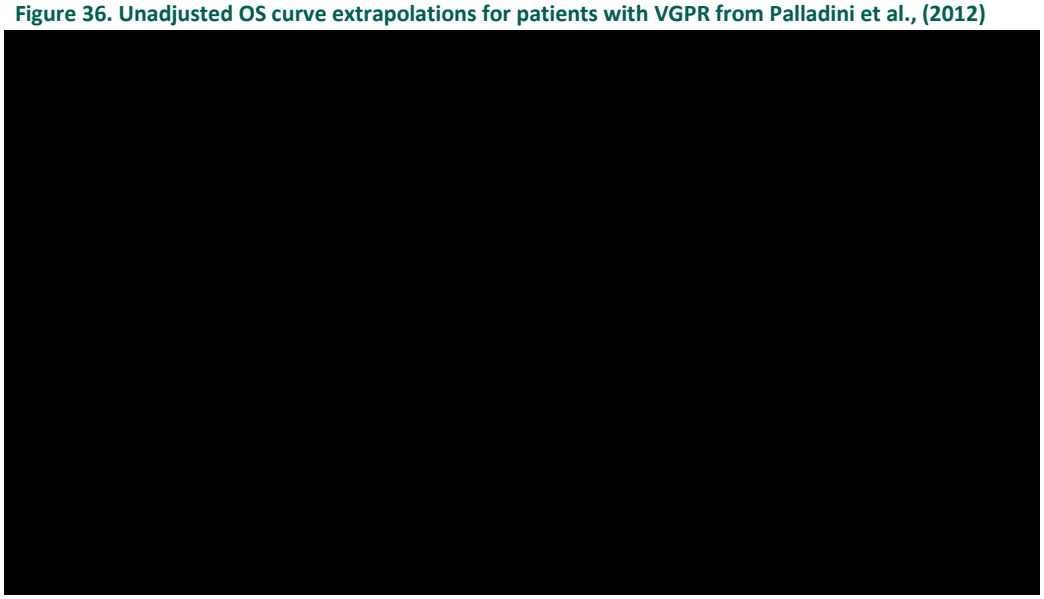


Figure 36. Unadjusted OS curve extrapolations for patients with VGPR from Palladini et al., (2012)



Overall survival by depth of hematologic response

Within the decision tree, the number of deaths in each cycle was dependent on treatment (as reported in the ANDROMEDA trial), rather than on hematologic response. In contrast, OS in the

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Markov model was dictated by depth of hematologic response as a surrogate for OS, according to the KM curves reported by Palladini et al., (2012). That is, OS is dependent on the survival curves stratified by CR, VGPR, and PR/NR regardless of which treatment regimen patients receive.

Therefore, the distribution of hematologic response achieved at the end of the decision tree was assumed to predict treatment-specific OS over time. This assumption is supported by the wealth of evidence supporting the relationship between depth of hematologic response and improved OS, (Gertz 2007, Wechalekar 2007, Kastritis 2010a, Palladini 2012, Kastritis 2015, Palladini 2015, Manwani 2018a, Nguyen 2018, Wong 2018, Kastritis 2020d, Janssen Research and Development 2021) and is aligned with the goal of AL amyloidosis treatment to achieve the best hematologic response possible (Milani 2018).

Patient flow through model health states

Within the Markov model, the extrapolated OS curves were used to determine the transitions to death (i.e. the number of patients who died between cycles *n* and *n+1*). The number of patients who would be alive in each health state per cycle was determined using both mortality distribution and transition probabilities.

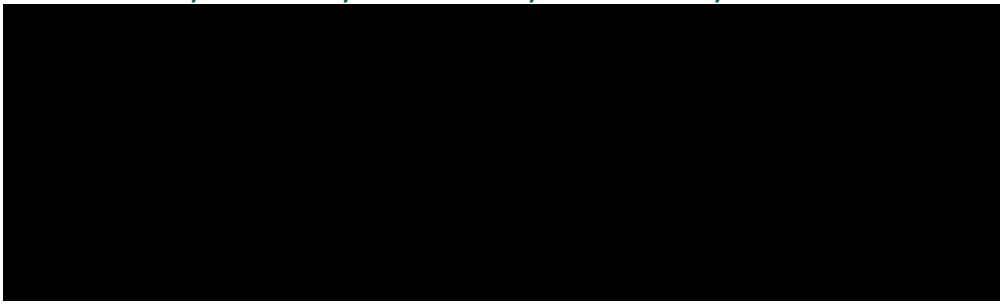
Mortality distribution

The probability of survival (based on OS curves and general population mortality) determined the number of deaths per cycle, but not which health states those deaths came from. Instead of assuming an equal risk of death across health states, the state-specific probabilities of mortality from the trial were used. In addition, because early, sudden deaths (while on treatment) are possible in patients with AL amyloidosis, two different mortality distributions were considered in the model to account for the potential change in early vs. long-term health state-specific probabilities of mortality. All deaths that occurred over the trial period (during the first 6-months and from post-6-months to end of follow-up) were reviewed in the patient-level data to see which health state the patient was in before they died. It was assumed that the mortality distribution was the same regardless of hematologic response and treatment, such that the health state would dictate the risk of death, but the hematologic response would dictate the total number of deaths.

The number of patients that died during each cycle were removed from specific health states according to their respective mortality distribution Table 50**.** Appropriately removing “dead” patients in cycle *n* was necessary to avoid overestimating the number of patients who would be transitioning into cycle *n+1*.

After initial cycles, cycles seven and beyond, ANDROMEDA IPD indicated that the majority of deaths occurred in the ‘End-stage Organ Failure’ health state. It should be noted that due to the short trial follow-up time at the primary analysis (February 2020; median follow-up: 11.4 months), only a small number of events (n=8) were available to calculate the mortality distribution for cycles seven and beyond.

Table 50: Mortality distribution by health state for cycles seven and beyond



[redacted]

For any cycle where the mortality distribution led to more deaths within a particular health state than the number of patients available, all patients were first removed from that health state and then the remainder would be taken out of the health state with the highest number of patients. For example, if there were 5 alive patients in the '2L Tx' health state, but the mortality distribution required 7 deaths, all 5 patients would be removed from '2L Tx', with the remaining 2 patients taken from another health state with the highest number of patients in that cycle. This model functionality might help to alleviate concerns with assuming a constant mortality distribution.

The remaining alive patients in each cycle were distributed amongst the various health states according to their respective transition probabilities.

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22. Appendix I – Literature search for HRQoL data

The HRQoL evidence review was conducted to identify health state utility values or algorithms to derive utility values and addressed the following research question: What HRQoL evidence exists for patients with AL amyloidosis?

All database searches for the HRQoL evidence review were initially conducted in April 2021 and updated in November 2021 (described herein). Searches were not limited by interventions or comparators. The grey literature search of HTA websites for the economic evidence SLR (November 2021) encompassed grey literature sources for HRQoL evidence. As such, a separate search using the CADTH Grey Matters Checklist (Canadian Agency for Drugs and Technologies in Health) was performed for the HRQoL SLR (January 2022).

Table 51: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Embase.com	1974 to 2021	03.11.2021
Medline	Ovid	1946 to 2021	03.11.2021

22.1.1 Search strategy

The pre-specified PICOS inclusion and exclusion criteria in Table 52 were used to identify studies relevant to this review.

Table 52: Summary of inclusion and exclusion criteria for the health-related quality of life evidence literature search

Item	Inclusion Criteria	Exclusion Criteria
Population	Study populations: Humans only; women and men ≥18 years of age AL amyloidosis	Study populations: Non-human <18 years of age Other forms of amyloidosis (eg, senile, familial/hereditary, and secondary), multiple myelomas, or lymphomas as primary diagnosis
Interventions/ Comparators	All interventions	NA
Outcomes	Direct utility values, equations used to derive utility values, or utility increments/decrements Includes EQ-5D (3L or 5L), EORTC QLQ-C30, SF-36v2, SF-6D or HUI values Includes utility values for baseline or specific health states (eg, for responders, non-responders, etc.)	Title and Abstract Screening phase Studies that do not report utility values or health-related quality of life (HRQoL) Full-text Screening Phase

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Item	Inclusion Criteria	Exclusion Criteria
	Utility mapping or equations used to derive utility values based on any other outcomes	Studies that report only HRQoL measures other than EQ-5D, EORTC QLQ-C30, SF-36, SF-6D, or HUI
Study design	Any RCTs or observational studies reporting utility values (EQ-5D [3L or 5L], EORTC QLQ-C30, SF-36v2, SF-6D, or HUI) Any utility elicitation studies (eg, TTO, SG, VAS) Any CUAs reporting utility values used in their analysis Any studies reporting utility mapping or regression equations used to derive utility values Conference abstracts reporting utility values or equations	Full-text Screening Phase Editorials, letters, news articles
Study Language	Articles in English	Non-English articles
Date Restrictions	Conference abstracts and posters from the last two years (Jan 2019 and later)	Conference abstracts and posters before 2019

Abbreviations: AL = amyloid light-chain; CUA = cost-utility analyses; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = European Quality of Life Five Dimensions Questionnaire; HRQoL = health-related quality of life; HUI = health utility index; NA = not applicable; SF-6D = Short Form Six-Dimension Health Survey; SF-36v2 = Short-Form 36-Item Health Survey version 2; SG = standard gamble; TTO = time trade-off; VAS = visual analog scale.

Table 53: Search strategy for the health-related quality of life evidence review

#	Searches	Results
1	"Value of Life"/	148202
2	Quality of Life/	755243
3	quality of life.ti,kf.	255168
4	((instrument or instruments) adj3 quality of life).ab.	8629
5	Quality-Adjusted Life Years/	44111
6	quality adjusted life.ti,ab,kf.	37714
7	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.	61842
8	disability adjusted life.ti,ab,kf.	9087
9	daly*.ti,ab,kf.	8576
10	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.	73499

11	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kf.	5002
12	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.	1478
13	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.	17362
14	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.	99
15	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.	910
16	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.	53390
17	(hye or hyes).ti,ab,kf.	226
18	(health* adj2 year* adj2 equivalent*).ti,ab,kf.	103
19	(pqol or qls).ti,ab,kf.	1097
20	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.	1437
21	nottingham health profile*.ti,ab,kf.	2803
22	sickness impact profile.ti,ab,kf.	2348
23	exp health status indicators/	365072
24	(health adj3 (utilit* or status)).ti,ab,kf.	186715
25	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.	35938
26	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.	28695
27	disutilit*.ti,ab,kf.	1579
28	rosser.ti,ab,kf.	240
29	willingness to pay.ti,ab,kf.	17544
30	standard gamble*.ti,ab,kf.	2054
31	(time trade off or time tradeoff).ti,ab,kf.	3671
32	tto.ti,ab,kf.	3102
33	(hui or hui1 or hui2 or hui3).ti,ab,kf.	4416
34	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.	50235

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35	duke health profile.ti,ab,kf.	204
36	functional status questionnaire.ti,ab,kf.	290
37	dartmouth coop functional health assessment*.ti,ab,kf.	26
38	(WHOQOL or WHOQOL-BREF).ti,ab,kf.	8369
39	(chronic respiratory questionnaire or chronic respiratory disease questionnaire or CRQ).ti,ab,kf.	1711
40	(St* George* Hospital questionnaire or SGRQ).ti,ab,kf.	5703
41	DIsability RElated to COPD Tool.ti,ab,kf.	7
42	london handicap scale.ti,ab,kf.	201
43	((modified medical research council dyspn?ea or MMRC) adj scale).ti,ab,kf.	1091
44	"MRC-D".ti,ab,kf.	3
45	(airways questionnaire or AQ20).ti,ab,kf.	110
46	(breathing problems questionnaire or BPQ or "BPQ-S").ti,ab,kf.	281
47	COPD activity rating scale.ti,ab,kf.	4
48	COPD assessment test.ti,ab,kf.	3289
49	(clinical COPD questionnaire or CCQ).tw,kf.	962
50	(("10" or ten) adj item respiratory illness questionnaire).ti,ab,kf.	3
51	"RIQ-MON10".ti,ab,kf.	2
52	"cost of illness"/	50114
53	(cost? adj3 illness*).ti,ab,kf.	8831
54	exp Disability Evaluation/	224346
55	((disabil* or disabled or impaired or impairment*) adj3 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kf.	112371
56	burden*.ti,ab,kf.	661889
57	(toll or tolls).ti,ab,kf.	116540
58	exp Severity of Illness Index/	291353
59	((disease* or illness* or sickness*) adj3 sever* adj2 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kf.	22231
60	((disease* or illness* or sickness*) adj2 impact?).ti,ab,kf.	26570

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61	Absenteeism/	27793
62	absentee*.ti,ab,kf.	16606
63	Presenteeism/	2203
64	presentee*.ti,ab,kf.	4630
65	productivit*.ti,ab,kf.	151051
66	((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kf.	310328
67	((work* or employ*) adj5 abilit*).ti,ab,kf.	31123
68	(time adj1 away).ti,ab,kf.	1839
69	Sick Leave/	12778
70	((sick or medical) adj leave).ti,ab,kf.	13604
71	or/1-70 [QoL/DISEASE BURDEN]	2992841
72	exp amyloidosis/	77156
73	amyloidos$.ti,ab,kw,kf.	60505
74	or/72-73 [Amyloidosis]	88993
75	71 and 74	4731
76	exp animals/ not humans.sh.	32680367
77	75 not 76	1386
78	77 use ppez	1220
79	socioeconomics/	148832
80	exp quality of life/	780356
81	quality of life.ti,kw.	245612
82	((instrument or instruments) adj3 quality of life).ab.	8629
83	quality-adjusted life year/	44111
84	quality adjusted life.ti,ab,kw.	37181
85	(qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kw.	61337
86	disability-adjusted life year/	2839
87	disability adjusted life.ti,ab,kw.	8947
88	daly*.ti,ab,kw.	8537
89	(sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or	73325

	shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kw.	
90	(sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short form6).ti,ab,kw.	4986
91	(sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kw.	1472
92	(sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kw.	17315
93	(sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kw.	99
94	(sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kw.	908
95	(hql or hqol or h qol or hrqol or hr qol).ti,ab,kw.	53068
96	(hye or hyes).ti,ab,kw.	224
97	(health* adj2 year* adj2 equivalent*).ti,ab,kw.	100
98	(pqol or qls).ti,ab,kw.	1093
99	(quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kw.	1429
100	nottingham health profile*.ti,ab,kw.	2801
101	nottingham health profile/	566
102	sickness impact profile.ti,ab,kw.	2344
103	sickness impact profile/	9631
104	health status indicator/	27209
105	(health adj3 (utilit* or status)).ti,ab,kw.	182591
106	(utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kw.	35788
107	(preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kw.	28566
108	disutilit*.ti,ab,kw.	1575
109	rosser.ti,ab,kw.	237
110	willingness to pay.ti,ab,kw.	17494
111	standard gamble*.ti,ab,kw.	2054

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112	(time trade off or time tradeoff).ti,ab,kw.	3660
113	tto.ti,ab,kw.	3080
114	(hui or hui1 or hui2 or hui3).ti,ab,kw.	4395
115	(eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kw.	50113
116	duke health profile.ti,ab,kw.	204
117	functional status questionnaire.ti,ab,kw.	290
118	dartmouth coop functional health assessment*.ti,ab,kw.	26
119	(WHOQOL or WHOQOL-BREF).ti,ab,kw.	8338
120	(chronic respiratory questionnaire or chronic respiratory disease questionnaire or CRQ).ti,ab,kw.	1710
121	"St. George Respiratory Questionnaire"/	3798
122	(St* George* Hospital questionnaire or SGRQ).ti,ab,kw.	5693
123	DIsability RElated to COPD Tool.ti,ab,kw.	7
124	london handicap scale.ti,ab,kw.	201
125	((modified medical research council dyspn?ea or MMRC) adj scale).ti,ab,kw.	1078
126	"MRC-D".ti,ab,kw.	3
127	(airways questionnaire or AQ20).ti,ab,kw.	109
128	(breathing problems questionnaire or BPQ or "BPQ-S").ti,ab,kw.	281
129	COPD activity rating scale.ti,ab,kw.	4
130	COPD assessment test.ti,ab,kw.	3286
131	(clinical COPD questionnaire or CCQ).ti,ab,kw.	961
132	(("10" or ten) adj item respiratory illness questionnaire).ti,ab,kw.	3
133	"RIQ-MON10".ti,ab,kw.	2
134	"cost of illness"/	50114
135	(cost? adj3 illness*).ti,ab,kw.	7059
136	disability/	116044
137	((disabil* or disabled or impaired or impairment*) adj3 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kw.	110667
138	disease burden/	58614

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139	burden*.ti,ab,kw.	658580
140	(toll or tolls).ti,ab,kw.	112135
141	"severity of illness index"/	281651
142	((disease* or illness* or sickness*) adj3 sever* adj2 (estimat* or evaluat* or instrument or instruments or measur* or scale? or score? or weight? or valu*)).ti,ab,kw.	22138
143	((disease* or illness* or sickness*) adj2 impact?).ti,ab,kw.	26467
144	absenteeism/	27793
145	absentee*.ti,ab,kw.	16519
146	presenteeism/	2203
147	presentee*.ti,ab,kw.	4621
148	productivity/	57791
149	productivit*.ti,ab,kw.	150159
150	((work* or employ*) adj5 (absenc* or absent* or presenc* or present*)).ti,ab,kw.	310347
151	((work* or employ*) adj5 abilit*).ti,ab,kw.	30908
152	(time adj1 away).ti,ab,kw.	1836
153	medical leave/	7506
154	((sick or medical) adj leave).ti,ab,kw.	12813
155	or/79-154 [QoL/DISEASE BURDEN]	2922133
156	exp *amyloidosis/	53881
157	AL amyloidosis/	3839
158	amyloidos$.ti,ab,kw.	60124
159	or/156-158 [Amyloidosis]	74704
160	(exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/) and (human/ or normal human/ or human cell/)	42803438
161	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/	54488822
162	161 not 160	11685384
163	155 and 159	3699
164	163 not 162 [Remove Animals]	3399

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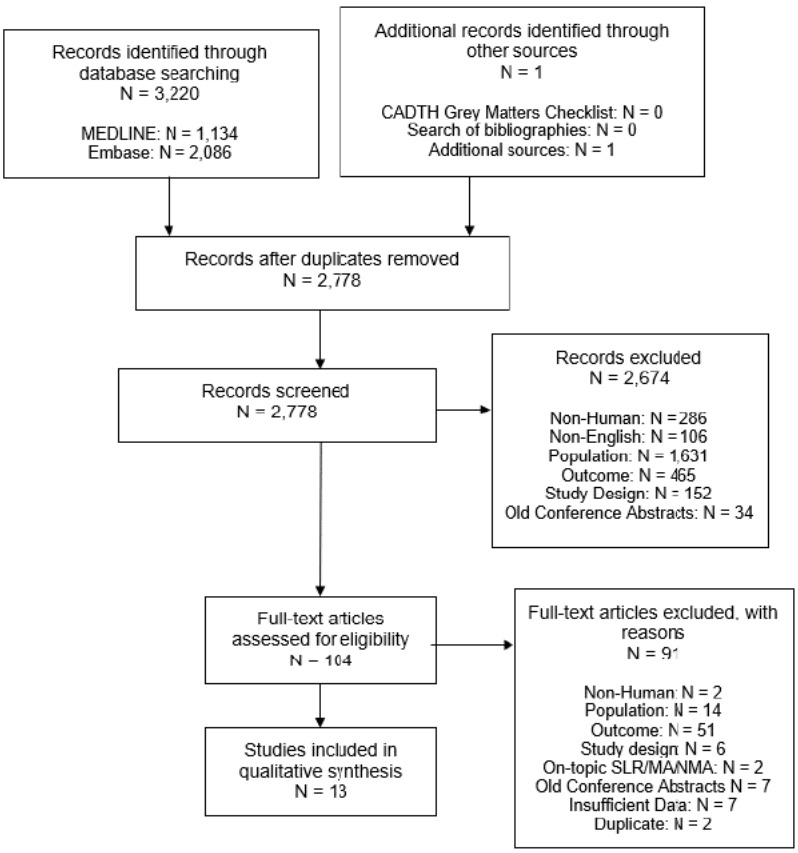
165	164 use oemezd	2297
166	(address or autobiography or bibliography or biography or comment or dictionary or directory or editorial or "expression of concern" or festschrift or historical article or interactive tutorial or lecture or legal case or legislation or news or newspaper article or patient education handout or personal narrative or portrait or video-audio media or webcast or (letter not (letter and randomized controlled trial))).pt.	4552052
167	78 not 166 [remove Opinion pieces - MEDLINE]	1159
168	(editorial or letter or note or short survey or tombstone).pt.	4882904
169	165 not 168 [remove Opinion pieces - Embase]	2206
170	167 or 169	3365
171	limit 170 to yr="2021 -Current" [Medline, Embase - All results - 2021 - Current]	328
172	limit 171 to dt="20210401-20211231" [Limit not valid in Embase; records were retained]	276
173	172 use ppez	53
174	limit 171 to dc="20210401-20211231"	196
175	174 use oemezd	196
176	173 or 175 [Medline, Embase - All results - Apr 2021 - Current]	249
177	remove duplicates from 176 [Medline, Embase - All results Deduplicated - Apr 2021 - Current]	208

The database searches for the AL amyloidosis HRQoL evidence identified 3,220 citations. One additional record from the clinical evidence review was noted to contain relevant HRQoL data and was thus included and discussed in this review. No additional records were identified from the grey literature search using the CADTH Grey Matters Checklist. Thus, the literature search for AL amyloidosis HRQoL evidence identified 3,221 citations through database and grey literature searches and from reviewing citation lists from on-topic SLRs identified during the screening process. After the removal of duplicate citations, 2,778 citations underwent title and abstract screening, resulting in the exclusion of 2,674 articles that did not meet pre-specified inclusion criteria (see PICOS). Studies reporting any type of HRQoL outcome were included at the title and abstract screening phase, but only studies reporting EQ-5D, EORTC QLQ-C30, SF-36, SF-6D, or HUI values were included at the full-text screening phase. Among the 104 citations remaining after title and abstract screening, 91 were excluded during full-text screening and 13 studies underwent data extraction. The PRISMA flow diagram for the selection of these studies is presented in Figure 37.

Figure 38: PRISMA flow diagram



Abbreviations: CADTH = Canadian Agency for Drugs and Technologies in Health; MA = meta-analysis; N = number; NMA = network meta-analysis; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR = systematic literature review.

The HRQoL SLR identified 13 relevant studies for which data extraction was performed. None of the included studies reported utility values or mapping algorithms. However, all studies reported survey scores with potential for mapping to utility values. The HRQoL studies included in the review consisted of 3 RCTs (including the ANDROMEDA trial27) and 10 observational studies. All studies involved an AL amyloidosis patient population, with six studies reporting on newly diagnosed or treatment-naïve populations. Only five studies reported HRQoL outcomes as a result of intervention administration; these interventions included high-dose melphalan with stem cell transplant (HDM/SCT), nutritional counselling, and bortezomib-based chemotherapy (VCd, D-VCd, VMd, and Md). The five relevant studies are detailed in Table 54.

Table 54: Summary of studies included in the health-related quality of life review

Author, Publication Date	Study Design	Country	Population	Intervention	Utility Instrument	External Source of Data[a]
Caccialanza, 2015	Two-arm (parallel assignment), open-label RCT	Italy	Treatment-naïve AL amyloidosis	Nutritional counselling Usual care	SF-36v1[b]	NCT02055534
Sanchorawala, 2017	Retrospective data analysis	US	AL amyloidosis	HDM/SCT Non-SCT chemotherapy	SF-36v1	NA

Author, Publication Date	Study Design	Country	Population	Intervention	Utility Instrument	External Source of Data[a]
Seldin, 2004	Retrospective analysis	US	AL amyloidosis	HDM/SCT	SF-36v1[b]	NA
Sanchorawala, 2020	RCT	Various	Newly diagnosed AL amyloidosis	VCd D-VC[d]	EORTC QLQ-C30 EQ-5D-5L VAS SF-36v2	NA
Kastritis, 2020	RCT	Italy	Previously untreated AL amyloidosis	VM[d] M[d]	EORTC QLQ-C30 SF-36v2	NA

[a] Indicates whether the analyses were conducted with data collected directly from patients enrolled in the study or whether analyses were performed using an existing data set from another study.

[b] Version number was not explicitly stated in publication and was inferred from bibliography.

[c] EQ-5D values were predicted based on SF-36 scores using an algorithm published by Rowen *et al.*, (2009).

[d] Known countries of residence included US, UK, Canada, and Australia.

[e] Known regions of residence included North America and Europe.

Abbreviations: AL = amyloid light-chain; D-VCd = daratumumab (subcutaneous) + VELCADE® (bortezomib) + cyclophosphamide + dexamethasone; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D-5L = European Quality of Life Five Dimensions Questionnaire (five levels); HDM = high-dose melphalan; Md = melphalan + dexamethasone; NR = not reported; RCT = randomized controlled trial; SCT = stem cell transplant; SF-36 = Short Form 36-Item Health Survey; US = United States; UK = United Kingdom; VAS = visual analogue scale; VCd = VELCADE® (bortezomib) + cyclophosphamide + dexamethasone; VMd = VELCADE® (bortezomib) + melphalan + dexamethasone.

22.1.2 Quality assessment and generalizibility of estimates

Quality assessments of included publications were conducted using the quality assessment and relevance criteria presented in NICE Decision Support Unit (DSU) Technical Support Document (TSD) 9(Papaioannou 2010) and Papaioannou *et al.*, (2013).(Papaioannou 2013) The assessments were performed independently by two reviewers; evaluations were then compared to ensure a consensus was reached.

22.1.3 Unpublished data

N/A

23. Appendix J - Mapping of HRQoL data

Danish tariff for the EQ-5D-5L was applied in estimating the health state utility values (Janssen 2021d). This approach is in accordance with the Danish Medicines Council (DMC) guidelines, which refer to the use of EQ-5D-5L for patient reported outcomes data as the preferred outcome measure [2]. The utility analysis was based on descriptive statistics where 6-months ITT pooled utility values were used to inform health state utility values. Alternative approaches of using data that was not pooled or using a mixed model approach yielded predictions of utility values not clinically reliable in that utility values for patients not responding to treatment were higher than utility values for patients responding to treatment. It should be noted however that the assumption of normality underpinning the mixed model was not met.

Missing data

The analysis included only complete cases, so missing values were not treated specifically (e.g., using imputation) at this stage. Although, the multilevel modelling that was used for the analyses is assumed that accounts for the missing data. This is the approach that was taken previously in the analyses scripts you shared with us.

After the base case analyses are presented, we presented a summary of the missing values. In particular we presented some descriptive statistics for the level of missingness in the data set, and then we also applied a simple imputation method (last observation carried forward) and did the analyses again. The base case and the analyses with the imputation have some differences but they are generally aligned.

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24. Appendix K - Probabilistic sensitivity analyses

The objective of the PSA was to assess the variation in model results stemming from the uncertainty around each individual parameter used in the model.

To conduct a PSA, probabilistic distributions were assigned to each input in the model and used to randomly select new plausible values. Each new sampled value was applied in the model, with the results of the model under each new value being recorded. This process was then repeated for a large number of iterations. The series of results recorded in the PSA can be used to quantify the overall variation in results.

The key parameters in the PSA included:

- Clinical data
- Cost data
- Utility data

A summary of the distributions applied in the PSA is provided in Table 55. The distributions selected follow the recommendations outlined in the handbooks in health economic evaluation.

Table 55: Summary of the distributions applied in the probabilistic sensitivity analysis

Parameter cluster	Parameters	Distribution
Clinical data	Survival distributions	Multivariate normal distribution, with correlation between the parameters
	Transition probabilities	Dirichlet distribution
Cost data	Disease management costs Administration cost Monitoring cost Adverse event cost Other direct costs	Gamma distribution
Utility data	Utility weights assigned to health states	Beta distribution
	Disutility of AEs	Normal distribution

Abbreviations: AE: Adverse event

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The CIs, standard errors, and Cholesky decomposition of the variance-covariance matrices used to sample new values in the PSA are available in the " PSA Inputs" tab in the Excel file.

25. Appendix L - Company-specific appendices

Calculation of health state transition probabilities

Transition probability matrices were used to estimate the number of alive patients that would progress to another health state (except death) in the Markov model. The transition probabilities between the Markov model health states (i.e. the health states in the orange box as shown in the model structure diagram in Figure 26) varied by hematologic response but were assumed to be the same between treatment groups; that is, hematologic response drives the progression to other health states rather than being directly impacted by the treatment received. These transition probabilities were generated using pooled patient-level data for D-VCd and VCd from the ANDROMEDA trial and are described further below. Moreover, it was necessary to assume that these transition probabilities would be constant over time and is a reflection of the current data availability from the trial.

The transition probabilities were generated using ANDROMEDA IPD pertaining to time-to-MOD-PFS (which included hematologic progression and major organ deterioration events but excluded deaths according to the primary analysis; February 2020; median follow-up: 11.4 months) stratified by hematologic response irrespective of treatment arm. The time-to-MOD-PFS data were still immature at the time of primary analysis (87 out of 200 planned events had occurred); as such, the shapes of the MOD-PFS by hematologic response curves are unknown and any extrapolation of these data beyond 10-months would be highly uncertain due to the limited sample size and short follow-up. Furthermore, the plateau in all the KM curves from the lack of long-term events seemed clinically implausible; rather, a continuous decline in the curves would be expected given that AL amyloidosis is a progressive disease. Given that these curves appear generally linear, a constant transition probability was deemed reasonable as a simplistic and pragmatic assumption. Constant hazard rates were calculated from the curves (Figure 39) and converted to a per-cycle probability. The monthly probability for MOD-PFS stratified by hematologic response is presented in Table 56.

Because patients from 'Off Tx/FDT', and '2L Tx' can all transition to 'End-stage Organ Failure' at any given cycle, the monthly probability of MOD-PFS was stratified based on the distribution of MOD-PFS events (excluding deaths) that occurred by health state (Table 56). For example, the monthly probability of a MOD-PFS event (excluding deaths) for a patient with CR was determined to be [redacted] (Table 56).

Ideally, the transition probabilities would be based strictly on events pertaining to cardiac or renal failure; however, as there were too few such events observed in ANDROMEDA at the time of CUA development, MOD-PFS (excluding death) was used to allow for sufficiently robust re-analyses. Although a potential limitation of using MOD-PFS is the risk of overestimating the transition probabilities to 'End-stage Organ Failure', this was considered a simplistic assumption implemented due to data immaturity.

All remaining patients in CR and VGPR transitioned to the 'Off Tx/FDT' health state, whereas all remaining patients in PR/NR transitioned to the '2L Tx' health state.

[redacted]

Table 56: Values informing transition probabilities to 'End-stage Organ Failure'

[redacted]

Patients in CR and VGPR in the 'Off Tx/FDT' health state may transition to '2L Tx' or 'End-stage Organ Failure'. The transition to the 'End-stage Organ Failure' health state was generated using ANDROMEDA IPD (pooled from both treatment groups) pertaining to MOD-PFS (primary analysis; February 2020; median follow-up: 11.4 months) stratified by hematologic response, as described above. The transition from 'Off Tx/FDT' to '2L Tx' was generated using the time to subsequent

non-cross resistant anti-plasma cell therapy curves from ANDROMEDA IPD (12-month landmark analysis; November 2020; median follow-up: 20.3 months) stratified by CR or VGPR hematologic responses (note that the 3-month stratification of hematologic response, rather than stratification at 6-months, was selected due to larger sample size for generating the curves).

Follow-up data for this outcome was still immature from the trial, as shown by the low numbers at risk after ~10 months. Extrapolation of these curves would, therefore, introduce unnecessary complexity and uncertainty to the model at this time. Given that these curves appear generally linear, a constant transition probability was therefore deemed reasonable as a simplistic and pragmatic assumption. Moreover, as the plateau in the KM curves (from the lack of long-term events), particularly in the CR curve, would favour patients in the D-VCd arm, the use of a constant transition probability would also be a conservative assumption. The constant hazard rate was calculated from the CR and VGPR time to subsequent non-cross resistant anti-plasma cell therapy curves and then converted to a per-cycle probability. The per-cycle transition probabilities from 'Off Tx/FDT' to '2L Tx' were [redacted] for CR and [redacted] for VGPR.

Notably, curves for time to next treatment based on hematologic response were available from a UK observational study of a large cohort of 915 patients with AL amyloidosis treated with upfront bortezomib (Manwani 2019). Patient baseline characteristics reported in this study were generally aligned with those from the ANDROMEDA trial. For example, the two patient populations had similar median age, proportion of male subjects, median number of organs involved, proportion of patients with cardiac involvement, and dFLC values. The most notable difference between the patient populations in Manwani et al., (2019) and the ANDROMEDA trial was the proportion of patients classified as Mayo Stage IIIB (ANDROMEDA: 2.1%; Manwani et al., (2019): 13.7%) (Manwani 2019, Janssen Research and Development 2020b). In this respect, time to next treatment results from Manwani et al., (2019) may be considered conservative estimates when compared with results from ANDROMEDA. The article by Manwani et al., (2019) was used to assess validity of the transition probabilities derived from the ANDROMEDA study. The per-cycle transition probability for CR was very similar to the estimated value using data from Manwani et al., (2019) (i.e. 0.495% for Manwani et al., (2019) and 0.420% for ANDROMEDA). The per-cycle transition probability for VGPR calculated using ANDROMEDA data was slightly higher (1.523%) than the calculated value from the publication (0.741%); the steeper VGPR curve from the ANDROMEDA data could be due to the fact that clinical trial patients are more routinely assessed and might be considered for a subsequent therapy sooner than patients reflected in the real-world data from Manwani et al. (Manwani 2019).

Since patients with PR/NR would immediately switch to second-line treatment after exiting the decision tree, no transition probability for 'Off Tx/FDT' to '2L Tx' was calculated.
All remaining patients that did not transition to another health state and did not die, remained in the 'Off Tx/FDT' health state until the next cycle.

Patients in the '2L Tx' health state can transition to 'End-stage Organ Failure'. The transition from '2L Tx' to 'End-stage Organ Failure' was generated using ANDROMEDA IPD (pooled data from both treatment groups) pertaining to MOD-PFS stratified by hematologic response (independent of treatment), as was previously described and done for the other health states transitioning to 'End-stage Organ Failure'. All remaining patients remained in the '2L Tx' health state until the next cycle.

All patients who are alive in the 'End-stage Organ Failure' health state will stay within this health state until the next cycle.

Transition probabilities

A summary of transition probabilities for patients with CR, VGPR, and PR/NR is presented in Table 57, Table 58, and Table 59, respectively.

Table 57: CR transition probabilities (D-VCd and VCd)

Table 58: VGPR transition probabilities (D-VCd and VCd)

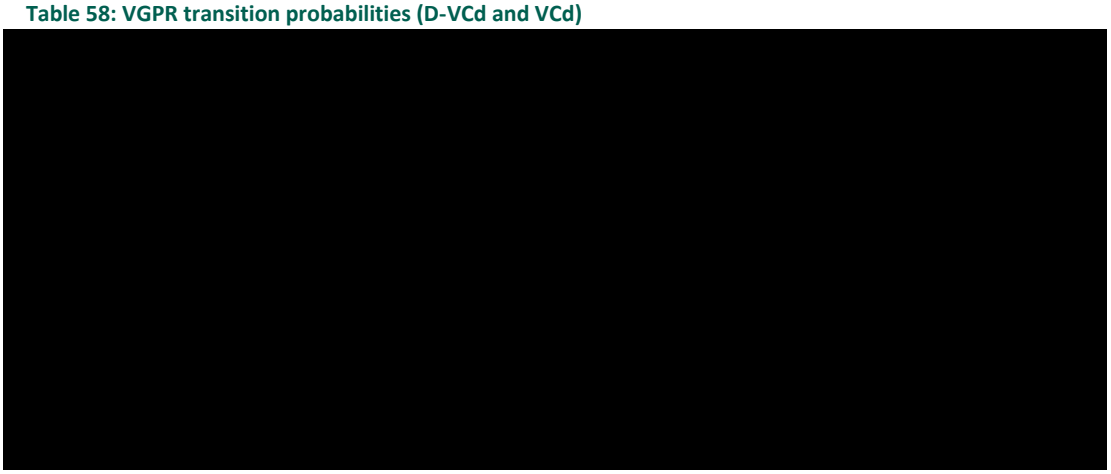

Table 59: PR/NR transition probabilities (D-VCd and VCd)

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