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FDA Briefing Document

BLA# 761145/S-029
Darzalex Faspro (daratumumab hyaluronidase)
Applicant: Janssen Therapeutics

Oncologic Drugs Advisory Committee Meeting

May 20, 2025

Division of Hematologic Malignancies II/Office of Oncologic Diseases

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4 Abbreviations

ACTM	Active Monitoring
AL	Immunoglobulin Light Chain
BMPC	Bone Marrow Plasma Cell
CCO	Clinical Cutoff
CI	Confidence Interval
Dara	Dara SC
EU	European Union
ECOG	Eastern Cooperative Oncology Group
FA	Final Analysis
FDA	Food And Drug Administration
FLC	Free Light Chain
g	Gram
HR	Hazard Ratio
IA	Interim Analysis
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IMWG	International Myeloma Working Group
INV	Investigator
IRC	Independent Review Committee
K-M	Kaplan Meier
ITT	Intention To Treat
L	Liter
M	Monoclonal
MDE	Myeloma Defining Events
mg	Milligram
MM	Multiple Myeloma
MRI	Magnetic resonance imaging
NA	North America
ORR	Overall Response Rate
OS	Overall Survival
P	P-value

PA	Primary Analysis
PD	Progressive Disease
PFS	Progression Free Survival
PFS2	Progression Free Survival on Firstline Treatment for Multiple Myeloma
PRO	Patient Reported Outcome
SAP	Statistical Analysis Plan
SD	Standard Deviation
SC	Subcutaneous
SMM	Smoldering Multiple Myeloma
TEAE	Treatment Emergent Adverse Event
TTP	Time to Progression
US	United States

1 Introduction

1.1 Proposed Indication

The proposed indication for daratumumab hyaluronidase (Dara SC) is as monotherapy for the treatment of adult patients with high-risk smoldering multiple myeloma (SMM).

The proposed dosing regimen is Dara SC weekly from Weeks 1 to 8, then every 2 weeks from Weeks 9 to 24, and then every 4 weeks from Week 25 onwards until disease progression or a maximum of three years.

1.2 Executive Summary

SMM is an asymptomatic precursor plasma cell disorder without evidence of myeloma defining events (MDE) as defined by the International Myeloma Working Group (IMWG) 2014 criteria (Appendix 12.1). Patients have a variable risk for progression to multiple myeloma (MM) based on the presence of specific features. While multiple models have been developed to identify patients at high-risk of progression, the current consensus guidelines recommend stratification based on the 20/2/20 Mayo 2018 model (1). Based on the Mayo 20/2/20 model, it is estimated that patients with high-risk SMM have a 2-year risk of progression to MM of 47% and a 5-year risk of progression of 82% (2).

Two Phase 3 trials have been conducted evaluating whether intervention in this precursor condition can improve outcomes. The QuiREDEX trial evaluated lenalidomide and dexamethasone compared to observation in participants with high-risk SMM and demonstrated a progression-free survival (PFS) and overall survival (OS) benefit (3). The ECOG E3A06 trial evaluated lenalidomide alone compared to observation in participants with intermediate- or high-risk SMM and demonstrated a PFS benefit and no OS benefit (4). Depending on the risk categorization, observation, lenalidomide treatment, or enrollment in a clinical trial testing early therapy is recommended (5). Observation is considered an appropriate control arm for clinical trials evaluating patients with high-risk SMM.

Study SMM3001 (AQUILA) is a randomized, phase 3, open-label trial that evaluated Dara SC compared to active monitoring (ACTM). The AQUILA trial enrolled 390 participants with a diagnosis of SMM per IMWG 2014 criteria ≤ 5 years with measurable disease who met the protocol-defined high-risk criteria. Participants had clonal bone marrow plasma cells (BMPC) ≥10% and at least one of the following protocol-defined high-risk factors: serum monoclonal (M) protein ≥30 gram (g)/Liter (L), Immunoglobulin A (IgA) SMM, immunoparesis with reduction of 2 uninvolved Ig isotypes, serum involved:uninvolved free light chain (FLC) ratio ≥8 and <100, or clonal BMPC >50% to <60% with measurable disease.

Participants were randomized to ACTM or Dara SC until 39 cycles or 36 months, whichever occurred first. The primary endpoint was PFS defined as time from the date of randomization to the date of initial documented progression to MM according to the IMWG diagnostic criteria (6) or date of death, whichever occurred first as assessed by an Independent Review Committee (IRC). Key secondary endpoints in the order of testing included overall response rate (ORR), progression-free survival on first-line treatment for MM (PFS2), and OS.

The Food and Drug Administration (FDA) conducted an efficacy and safety evaluation of Study AQUILA trial based on a data cut-off date of May 1, 2024. Analysis of efficacy is based on the 390 randomized participants (Intention to treat [ITT]); Dara SC (n=194) and ACTM (n=196). Analysis of safety is based on all participants who were randomized and received at least one dose of Dara SC (n=193) or were monitored on the ACTM arm (n=196). The percentages presented are based on rounding.

Efficacy:

- At the time of the primary efficacy analysis, a total of 166 PFS events per IRC assessment (Dara SC 67 [35%]; ACTM 99 [51%]) were observed. The median PFS was not reached (95% Confidence Interval [CI]: 66.7, NE) in the Dara SC arm and was 41.5 months (95% CI: 26.4, 53.3) in the ACTM arm. The hazard ratio (HR) was 0.49 (95% CI: 0.36, 0.67; 2-sided p<0.0001).
- The most common reason for progression to MM was serum free FLC ratio increase criteria, (Dara SC 17%, ACTM 17%).
- The ORR was 63% in the Dara SC arm compared to 2% in the ACTM arm. The odds ratio was 83.8 (95% CI: 29.7, 236.5), with a 2-sided p-value <0.0001 crossing the prespecified type I error rate of 0.05.
- The median PFS2 was not reached in either arm. PFS2 was not statistically significant at the time of the primary analysis. The HR was 0.58 (95% CI: 0.35, 0.96; 2-sided p=0.0318), which did not cross the prespecified stopping boundary of 0.0235.
- The trial was not adequately powered to demonstrate a significant improvement in OS. At the time of the primary PFS analysis, the OS data were not mature. Only 41 events out of the planned 107 events for death were observed, (Dara SC [8%], ACTM [13%]). The median OS was not reached for both arms. The HR was 0.52 (95% CI: 0.27, 0.98). The OS results are descriptive only as PFS2 did not cross the prespecified boundary.

Safety

- Nearly all participants, 97%, on the Dara SC arm experienced treatment emergent adverse events (TEAE) compared to 83% on the ACTM arm.
- The rate of fatal TEAEs were not different; 1% on the Dara SC arm compared to 2% on the ACTM arm.
- There was a higher incidence of Grade 3-4 TEAEs on the Dara SC arm compared to the ACTM arm (Dara SC 40% ACTM 30%)
- The incidence of serious adverse events (SAEs) were higher in the Dara SC arm compared to the ACTM arm (Dara SC 29%, ACTM 19%)
- Dose discontinuations due to TEAEs were reported in 6% and dose modifications due to TEAEs were reported in 47% of the Dara SC arm.
- The most common TEAEs (≥20%) were musculoskeletal pain, upper respiratory tract infection, fatigue, diarrhea, nasopharyngitis, sleep disorder, rash, and sensory neuropathy.

1.3 Purpose of the ODAC meeting

FDA is convening this Oncologic Drug Advisory Committee meeting to discuss the results of the pivotal Phase 3 trial, AQUILA, a randomized, multicenter study comparing ACTM and Dara SC in subjects with high-risk SMM.

Specifically, the FDA seeks the committee's opinion on the following topics:

- Discuss applicability of trial results to the high-risk SMM population.
- Discuss considerations for appropriate endpoints in SMM, based on the AQUILA trial results.
- Discuss the overall benefit-risk of Dara SC for the intended high-risk SMM population in context of the results from the AQUILA trial.

2 Brief Description of Issues for Discussion at the AC

2.1 Applicability of AQUILA results to patients with high-risk SMM

Several SMM models are available to assess the risk of progression to MM, to identify patients who may need closer observation or intervention prior to experiencing end organ damage.

Two models developed prior to the revised classification in 2014, Mayo 2008 and PETHEMA evaluated risk of progression to end-organ damage based on progression to CRAB (hyperCalcemia, Renal insufficiency, Anemia, and Bone Disease) criteria. Subsequently, with the 2014 updates to the definition of SMM and MM, additional models were developed for risk stratification of patients with SMM. These include the 20/2/20 Mayo 2018 model and the subsequent IMWG 2020 model.

The AQUILA trial protocol definition of high-risk SMM was not based on standard SMM risk stratification models (Section 12.2). The trial included a heterogenous population of high-, intermediate- and low-risk patients based on the available models for risk stratification. While the AQUILA trial was initiated in 2017, prior to the development of the 20/2/20 Mayo 2018 model, the protocol defined criteria were not consistent with the Mayo 2008 or PETHEMA model which were available at the time of trial initiation. Applying the current consensus 20/2/20 Mayo 2018 risk model retrospectively to the AQUILA trial population, only 41% of participants were categorized as high-risk, with 39% of participants as intermediate risk and 20% as low-risk. This raises concerns regarding the applicability of the trial results to a population with high-risk SMM, as currently defined.

2.2 Appropriateness of the endpoints for high-risk SMM population.

Overall survival is the ultimate clinical benefit endpoint as it is a measure of both safety and efficacy. PFS has been used as a primary endpoint for clinical trials in hematologic malignancies. PFS can be assessed earlier than OS and usually requires a smaller sample size. Additionally in patients with active cancer, PFS defined as time to progression or death is considered clinically meaningful depending on the magnitude of benefit observed. PFS is thought, or in some instances, has been shown, to predict overall survival.

SMM is a precursor condition and patients are usually asymptomatic from their disease. There are no therapies approved currently and the clinically relevant endpoints that can support approvals have not been established. There are also uncertain implications of early treatment prior to the development of MM vs. treatment at the time of MM diagnosis particularly as the diagnosis of MM can now be based on biochemical parameters alone (SLiM criteria: Sixty percent or greater clonal BMPC, a FLC ratio of 100 or more, and more than one focal bone lesion on MRI) prior to the development of end-organ damage. Trial endpoint considerations are

different for patients with SMM compared to patients with active malignancy and it is important to ensure that these endpoints are clinically meaningful for this population.

The primary endpoint in the AQUILA trial was PFS; defined as the time from date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurred first, as assessed by an IRC. PFS, as defined in the AQUILA trial, has not supported approval of therapies for this patient population and has not been shown to correlate with improved OS or been validated as a regulatory endpoint. While the primary endpoint of PFS was met, the PFS improvement was primarily due to delay in progression to MM based on the biochemical or lab parameters (SLiM criteria:30%) as opposed to end organ damage.

In total, 12% of participants progressed based on end organ damage related CRAB criteria. Additionally, although the data are not mature, there was no significant effect on PFS2, defined as the time from the date of randomization to the date of documented PD assessment on the first-line treatment for MM or death, whichever occurs first. With no proven improvement in progression after development of active multiple myeloma, the value of treatment prior to development of disease is questionable.

In the AQUILA trial, OS was one of the key secondary endpoints. In patients with a precursor condition such as SMM, an improvement in OS would represent a meaningful therapeutic benefit. The AQUILA trial was not adequately powered to demonstrate a significant OS efficacy benefit and the difference between the arms at 5 years was about 5%. In patients with a precursor condition such as SMM, there may be challenges in conducting an adequately powered trial for OS due to the long survival durations and availability of effective subsequent anti-myeloma therapies. However, there is uncertainty whether the available OS results are sufficient to support a positive benefit-risk in this asymptomatic patient population.

2.3 Uncertain benefit-risk of Dara SC in patients with high-risk SMM

Interpreting a drug's benefit-risk requires an examination of the clinical trial evidence and understanding its limitations.

As discussed previously, the study endpoints, as defined in the AQUILA trial, are of uncertain clinical meaningfulness in SMM. While the trial met its primary PFS endpoint there is uncertainty in the benefit of delaying progression to MM in the absence of a significant improvement in OS. Additionally, the observed difference in progression was primarily due to differences observed in the biochemical or lab parameters (SLiM criteria). FDA has concerns with generalizing the results observed in the AQUILA trial to a high-risk SMM patient population as the majority of participants enrolled would be classified as intermediate and low-risk based on the current risk-stratification definitions.

When considering the risks associated with the AQUILA trial, participants received Dara SC as monotherapy for up to three years. More participants on the Dara SC arm experienced TEAEs, Grade 3-4 TEAEs, serious adverse events, and dose discontinuations and modifications compared to the ACTM arm. Several symptomatic AEs, musculoskeletal pain (Dara SC 59%, ACTM 42%), upper respiratory tract infection (Dara SC 52%, ACTM 17%), fatigue (Dara SC 42%, ACTM 21%), diarrhea (Dara SC 27%, ACTM 5%), nasopharyngitis (Dara SC 28%, ACTM 12%), sleep disorder (Dara SC 24%, ACTM 5%), Rash (Dara SC 24%, ACTM 5%), and sensory neuropathy (Dara SC 20%, ACTM 8%) were higher in the Dara SC arm compared to the ACTM arm. Additionally, there were several limitations to the patient reported outcomes (PRO)

assessments, such as infrequent assessment. With limited and sparse collection, PRO data were not informative for determination of the benefit-risk.

Overall, given the limitations of the clinical meaningfulness of the efficacy findings and the toxicity observed with three years of treatment with Dara SC, there is uncertainty regarding the benefit-risk profile of Dara SC for patients with high-risk SMM.

3 Background

3.1 Smoldering Multiple Myeloma

SMM is an asymptomatic, precursor condition, characterized by plasma cell proliferation in the bone marrow without end-organ damage in contrast to MM which is a life-threatening hematologic malignancy. The current definition of SMM updated in 2014 is serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein >500 milligram (mg) per 24 hour, and/or clonal bone marrow plasma cells 10-60%, and the absence of MDE or amyloidosis (6).

The definition of SMM and MM have evolved over the years. Prior to 2014, the diagnosis of MM required the presence of end organ damage or tissue impairment as defined by CRAB criteria - hypercalcemia, renal insufficiency, anemia, or bone disease. With advances in imaging, with ability to detect asymptomatic bone lesions, sensitive tests for MM related serum markers, and advances in treatment options for MM, the IMWG (Appendix 12.1) updated the definition of multiple myeloma in 2014. Based on the updated criteria, MM can be diagnosed based on the presence of 10% or greater plasma cells in the bone marrow and any one of the specified laboratory/imaging based parameters referred to as SLiM criteria or CRAB criteria. The updates in 2014 resulted in some patients who would have, prior to 2014, been classified as having high-risk SMM being now classified as having MM without end organ damage. The new definition of MM impacted the various risk classifications for SMM in use at the time.

3.1.1 Risk stratification

While SMM is an asymptomatic precancerous condition, there is a risk of progressing to active MM. In general, progression to malignancy is 10% per year for the first 5 years with the risk declining after 5 years to 3% and less than 1% per year for the last 10 years (7). The rate of progression is variable depending on the presence or absence of specific features. Several models have been proposed to identify patients at a high-risk for progression to identify a population that could benefit from closer monitoring or early intervention.

Four models (Appendix12.2) have been used to define patients at high-risk for progression to MM.

The PETHEMA model and the Mayo 2008 model were developed prior to the 2014 revision to the MM definition and assessed progression to MM based on the CRAB criteria. The PETHEMA model utilized percentage of aberrant bone marrow plasma cells based on flow cytometry and immunoparesis to define high-risk SMM (8). The Mayo 2008 model was developed based on a retrospective cohort of 276 patients during a 26-year period between 1970 to 1995 and added serum biomarkers such as M-protein spike and sFLC ratio to the bone marrow plasma cell infiltration criteria (9). The Mayo 20/2/20 Model was published after the 2014 update to the IMWG Multiple Myeloma criteria and is based on M protein >2 g/dL, clonal BMPCs >20%, and sFLC ratio >20 (2). The most recent, 2020 IMWG Score, added high-risk features such as high-

risk cytogenetics and includes a more detailed risk model resulting in a new risk score with 4 risk groups (10).

Consensus guidelines recommend the Mayo 20/2/20 for risk stratification. Using the consensus Mayo 20/2/20 model, the risk of progression at 2 years for patients with low-, intermediate-, and high-risk SMM is 10%, 26%, and 47%, respectively (2). The risk of progression at 5 years using the Mayo 20/2/20 model was 23%, 47% and 82% for the low-, intermediate-, and high-risk groups, respectively (11). There is variation in the risk stratification based on the model used (12). In a concordance study of the PETHEMA, Mayo 2008 and Mayo 2018 models, significant discordance was found between the models. Patients were categorized into low-, intermediate-, and high-risk based on the three models and the overall global rate of agreement across all 3 models for all 3 categories was only 16.6% (13).

3.1.2 Treatment landscape

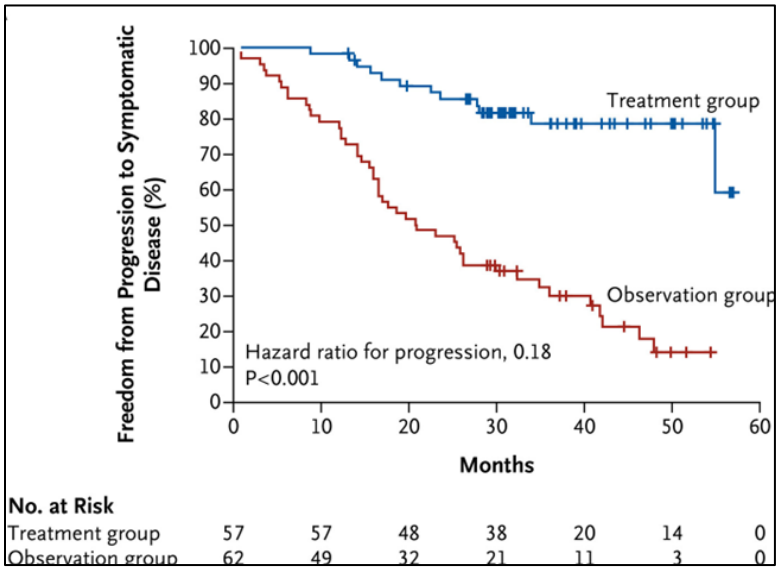
There are no FDA approved therapies for high-risk SMM. For patients with low-, and intermediate-risk SMM, observation remains the standard of care. There is no consensus in the field as to one standard approach to treatment of patients with high-risk SMM, and commonly used approaches include observation, lenalidomide-based therapy, or enrollment in a clinical trial (5). The treatment landscape for this asymptomatic, precursor condition, has not drastically changed over the last decade despite the results of two large, randomized trials evaluating therapies for this condition being available, as described below.

3.1.2.1 QuiREDEX Trial

The QuiREDEX trial was a phase 3 study that randomized (N=125) patients to a combination regimen of lenalidomide plus dexamethasone or observation. The trial enrolled patients with high-risk defined as either bone-marrow plasma cell infiltration of at least 10% and presence of monoclonal component (IgG ≥3 g/dL or IgA ≥2 g/dL, or Bence Jones proteinuria >1 g/24 h), or only one of these 2 criteria and ≥ 95% abnormal bone marrow plasma cells by flow cytometry and immunoparesis (>25% reduction in 1 or 2 uninvolved immunoglobulins) (4). The primary endpoint was time to progression to symptomatic disease defined by CRAB criteria in the protocol. Secondary endpoints were overall survival, response rate, and safety.

After a median follow up time of 40 months, median time to progression was longer (Figure 1) in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18 (95% CI: 0.09, 0.32, p<0.001).

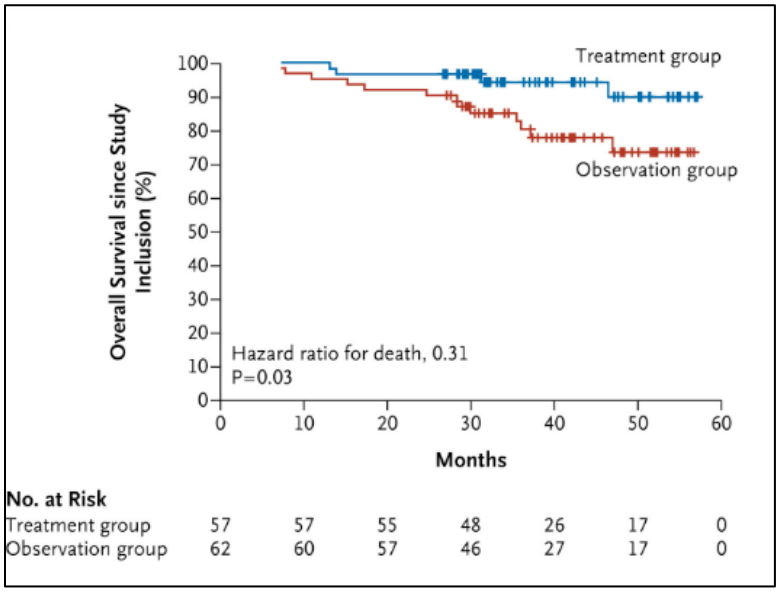
Figure 1. QuiREDEX KM Curve-Time to Progression to Symptomatic Disease



Source: Mateos et al N Engl J Med 2013

The median OS was not reached in either arm. The HR for death was 0.31 (95% CI: 0.10, 0.91; P=0.03) (Figure 2).

Figure 2 QuiREDEX KM Curves- OS



Source: Mateos et al N Engl J Med 2013

Despite the improvement in TTP and OS benefit reported in the QuiREDEX trial, lenalidomide and dexamethasone did not become standard of care for the treatment of patients with high-risk SMM for the following reasons:

- Forty percent of the participants on the trial were included on the basis of flow cytometry criteria (based on the PETHEMA risk stratification method) which are not widely available (14).

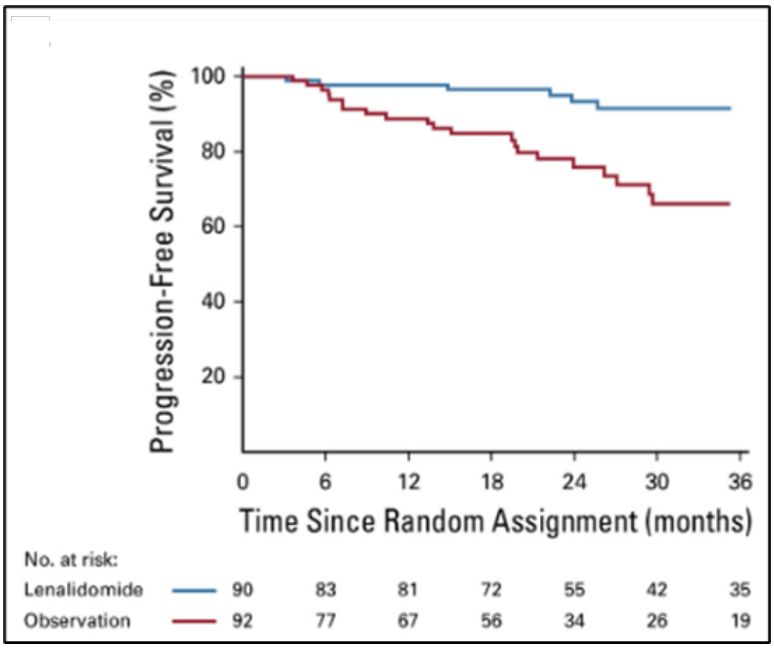
- As the QuiREDEX trial began enrollment in 2007, prior to the revised diagnostic classification of MM and the availability of advanced imaging techniques, a substantial number of the patients in this trial were likely diagnosed with MM at study entry using the updated criteria (15). This limited the applicability of the trial results.
- The trial design did not isolate the relative contribution of the 2 drugs to the observed benefit (14).
- Further, although an OS benefit was shown for those receiving lenalidomide and dexamethasone, the trial was not powered for OS analysis.
- Lenalidomide was received by only 28% of patients in the control arm upon progression to MM (15).

3.1.2.2 ECOG E3A06 Trial

The second phase 3 trial was the ECOG E3A06. Eligible patients had intermediate or high-risk SMM bone marrow plasmacytosis with 10% or more plasma cells- or sheets of plasma cells and an abnormal serum FLC ratio (<0.26 or >1.65). The trial randomized patients to single-agent lenalidomide or observation. The primary endpoint was PFS, with disease progression requiring the development of end-organ damage due to MM and biochemical progression as defined by the IMWG criteria for MM.

One hundred and eighty-two patients were randomly assigned in this trial; 92 patients were assigned to the observation arm and 90 to the lenalidomide arm. PFS was significantly improved in the lenalidomide arm compared with the observation arm (HR: 0.28, 95% CI, 0.12 to 0.62; p-0.002), Figure 3.

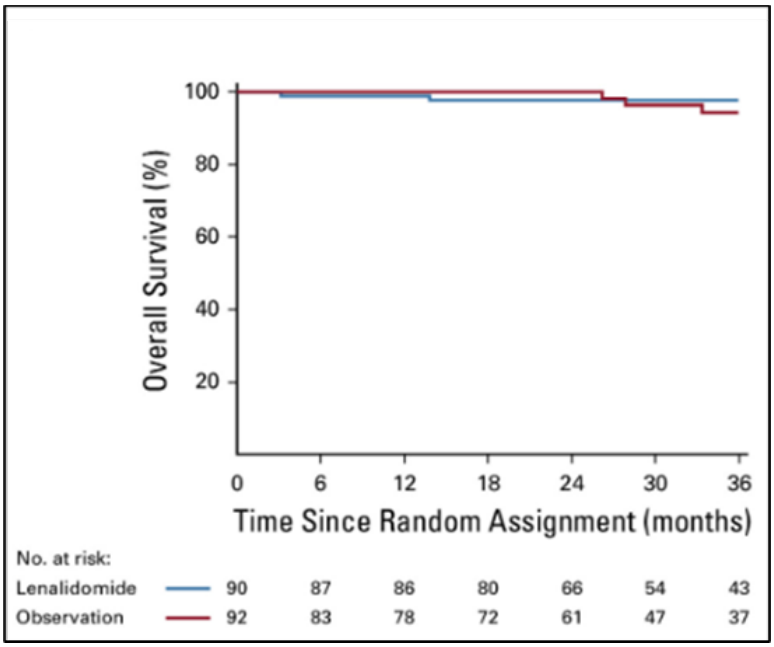
Figure 3 ECOG AE03 PFS K-M Curves



Source: Lonial et al J Clin Oncol 2019.

No OS improvement was observed, Figure 4**.** There were 6 deaths reported, two in the lenalidomide arm versus four in the observation arm (HR for death: 0.46; 95% CI: 0.08 to 2.53) (4).

Figure 4 ECOG E3A06 OS K-M Curves



Source: Lonial et al J Clin Oncol 2019.

A key limitation of ECOG E3A06 was that it included a heterogenous patient population that included patients with high-, intermediate-, and low-risk based on Mayo 2008 and Mayo 2018 risk stratification model. Also, 41% of the patients on the lenalidomide arm experienced grade 3 or 4 hematologic and non-hematologic adverse events while 5% of the patients on the observation arm experienced grade 3 or 4 hematologic and non-hematologic adverse events. Forty percent of patients receiving lenalidomide discontinued therapy because of AEs (4). Another key limitation of the trial was the PFS endpoint included biochemical progression and progression to CRAB criteria. There was uncertainty regarding the clinical meaningfulness of biochemical progression.

3.2 Newly diagnosed MM

With the revisions to the 2014 criteria, patients with MM can now be diagnosed in an asymptomatic stage based on laboratory or imaging parameters prior to the onset of organ impairment or symptomatic end-organ damage. In contrast to SMM, the treatment landscape for patients with MM has changed substantially over the past decade. For patients with a newly diagnosed MM, standard of care includes triplet or quadruplet combination regimens that include CD38 monoclonal antibodies (including Dara SC) with or without autologous stem cell transplantation based on patient eligibility. These therapies are the standard of care for patients with newly diagnosed MM. The median survival for patients with newly diagnosed MM exceeds a decade (16). For patients who progress on frontline therapies or do not respond, there are multiple therapies approved with varying mechanisms of action including bispecific antibodies and chimeric antigen T-cell receptor therapies (Appendix 12.3).

4 Drug Description

Dara SC is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, an endoglycosidase. Dara SC is administered subcutaneously.

Dara SC is FDA approved as monotherapy and in combination with other standard therapies for several MM indications including for the treatment of adult patients with MM and newly diagnosed AL amyloidosis.

For patients with newly diagnosed MM, Dara SC is approved for the following indications:

- in combination with bortezomib, lenalidomide, and dexamethasone for induction and consolidation in newly diagnosed patients who are eligible for autologous stem cell transplant
- in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- in combination with lenalidomide and dexamethasone in newly diagnosed patients who are ineligible for autologous stem cell transplant and in patients with relapsed or refractory multiple myeloma who have received at least one prior therapy
- in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant

5 Regulatory History

The regulatory interactions between the Applicant and the FDA are listed below.

Table 1 Key Regulatory Interactions Relevant to the Application

Date	Regulatory Interactions
January 2016	Applicant proposed randomized, open-label 3 arm study (Arm A-observation; Arm B - Dara intermediate dosing schedule; Arm C- Dara short intense dosing schedule* Agency noted that that PFS may be an appropriate endpoint given diagnostic criteria of MM at that time. Agency cautioned that there is no consensus on the definition of high-risk. Applicant cancelled meeting with FDA after receiving preliminary comments.
May 2017	Agency recommended Dara monotherapy compared to an observation arm. Agency stated that PFS as primary endpoint when defined as progression to active MM or death due to any cause may be reasonable. Applicant cancelled meeting with FDA after receiving preliminary comments.
October 2017	Applicant submitted revised protocol (2 arm study design) for high-risk SMM (AQUILA trial, SMM3001)
September 2024	Applicant submitted proposal for planned supplemental Biologic License Application based on data from AQUILA trial and supportive CENTAURUS trial Agency stated that proposal to submit AQUILA trial results was reasonable with issues foreseen regarding: • Heterogenous population enrolled in the AQUILA trial based on current high-risk definition • Concerns with PFS2 as an endpoint to support regulatory approval • Higher rates of safety events in participants treated with Dara SC • Immature OS data leading to uncertainty of overall benefit-risk

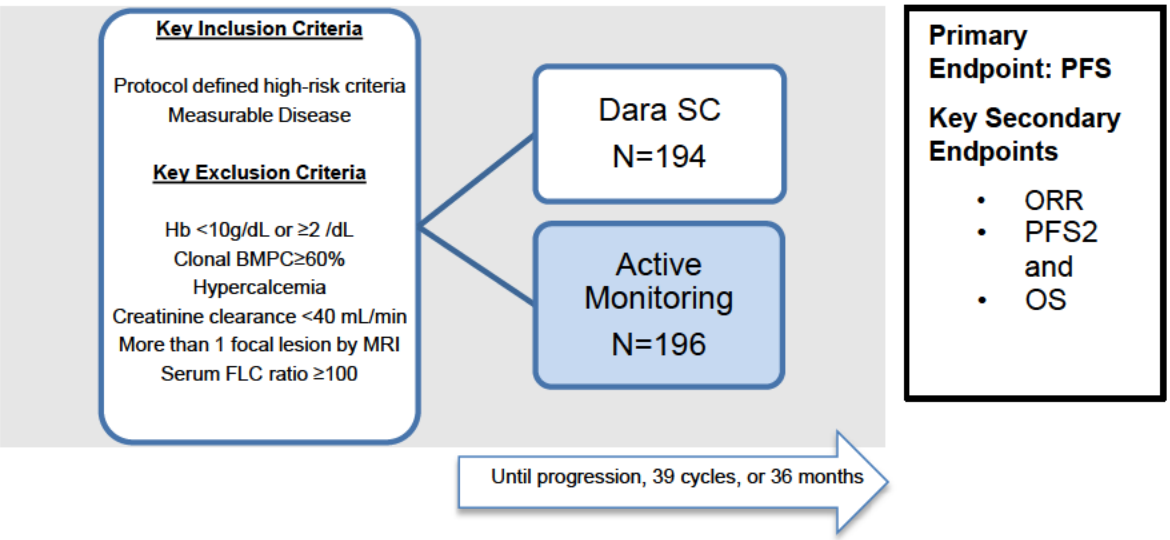
**Intermediate dosing schedule: Dara IV 8 week cycles, then Q8 weeks for up to 3 years; short intense dosing schedule: Dara IV for 8 weeks*

6 Trial

6.1 AQUILA overview

AQUILA is a Phase 3, randomized, open-label, 2-arm, multicenter trial evaluating the safety and efficacy of Dara SC versus ACTM in patients with high-risk SMM. In total, 390 patients were randomized 1:1 to receive Dara SC or ACTM. Dara SC was administered as a fixed duration for 39 cycles or 36 months (3 years) or until confirmed PD. Participants in the ACTM arm were followed for 36 months without disease specific treatment. Disease evaluations in both arms were conducted at screening and every 12 weeks until progressive disease (PD).

Figure 5 AQUILA Trial Schema



Participants were stratified at randomization by number of factors associated with progression to MM (<3 vs ≥3) as defined by the protocol inclusion criteria for high-risk.

6.2 Key eligibility criteria

Participants were required to have a diagnosis of smoldering multiple myeloma per IMWG criteria for ≤5 years with measurable disease at the time of randomization defined as serum M protein ≥10 g/L or urine M protein ≥200 mg/24 hours or involved serum FLC ≥1(00 mg/L and abnormal serum FLC ratio) and clonal BMPC≥10%; and at least 1 of the following risk factors:

- Serum M protein ≥ 30 g/L
- IgA SMM
- Immunoparesis with a reduction of 2 uninvolved immunoglobulin isotypes (only IgA, IgM and IgG should be considered in determination for immunoparesis; IgD and IgE are not considered)
- Serum involved: uninvolved FLC ratio ≥8 and <100
- Clonal BMPCs >50% to 60% with measurable disease.

Key exclusion criteria included absence of MM requiring treatment as defined in the protocol (Appendix 12.4)

6.3 Administration and monitoring

For participants randomized to the Dara SC arm, Dara SC was administered weekly in Cycles 1 and 2, then every 2 weeks for Cycle 3 to Cycle 6, and every 4 weeks thereafter until 39 cycles or up to 36 months or until progressive disease or unacceptable toxicity. The dose for the AQUILA trial was based on the results from the Phase 2, randomized trial, CENTAURUS (Appendix 12.5). CENTAURUS evaluated 16 mg/kg IV regimens of increasing intensity in participants with intermediate or high-risk SMM. The Long-intense frequency is most similar to

the proposed dosing for the AQUILA trial. However, the duration of treatment in the CENTAURUS trial was twenty 8-week cycles.

For participants randomized to ACTM (active monitoring), no disease-specific treatment was administered.

6.4 Statistical Analysis Plan

Primary Endpoint

The primary endpoint of the trial was PFS, defined as the time from the date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurs first. PFS based on IRC assessment was considered as the primary analysis endpoint. The key censoring scheme included censoring subjects at randomization if multiple myeloma was diagnosed at baseline based on central imaging review, censoring subjects at randomization if they had no post-baseline disease assessments and censoring at the initiation of any subsequent anti-cancer therapy prior to documented disease progression or death.

Key Secondary endpoints (In the hierarchical testing order)

- ORR, defined as, the proportion of participants with a PR or better response, per the IMWG response criteria, before the start of subsequent anti-myeloma therapy.
- PFS2, defined as, the time from the date of randomization to the date of documented PD assessment on the first-line treatment for MM or death, whichever was first (Appendix 12.6). Disease progression for the PFS2 endpoint determination was based on investigator assessment.
- OS, defined as, the time from the date of randomization to the date of death.

Sample Size Justification.

The AQUILA study was designed with a planned sample size of 360 patients (180 per arm). The sample size calculation was based on an 85% power to detect a PFS hazard ratio (HR) of 0.625 (Dara SC vs ACTM), with a 5% type I error rate (2-sided). This assumed an increase in median PFS from 30 months in the ACTM arm to 48 months in the Dara SC arm. Based on these parameters, the target number of PFS events was set at 165. At the end of the study, the predicted number of events was 134 for PFS2 and 107 for OS in both arms.

For PFS2, with 134 events, the probability of showing a positive trend, (i.e., estimated HR < 1), was more than 95% assuming a true HR of 0.75 (median PFS2 of 72 months in ACTM arm vs 96 months in the Dara SC arm). For OS, with 107 events, the probability of showing a positive trend (i.e., estimated HR<1) was more than 85% assuming the true HR is 0.80 (median OS: 100 months in ACTM arm vs 125 months in Dara SC arm).

Points to consider:

- The longer projected median PFS of 30 months for the ACTM arm compared to the published 24 months was chosen to account for the fact that high-risk SMM subjects, who were included in earlier studies, were now considered to have symptomatic MM according to the updated IMWG criteria, and to account for the additional risk factors included to identify high-risk SMM for this study.
- In clinical trials with time-to-event endpoints, the target number of events was typically determined based on the assumed hazard ratio and other pre-specified design parameters, such as the Type I error rate and statistical power. As the trial was designed to test HR < 1

(i.e., a positive trend) for PFS2 and OS, AQUILA trial was not adequately powered for PFS2 or OS to demonstrate the efficacy.

Interim and Final Analyses

Three analyses were pre-planned.

Interim Analysis (IA) for Futility: an Independent Data Monitoring Committee (IDMC) was established to review data at the interim analysis prior to the primary endpoint analysis. The IA was planned to occur after about 99 PFS events (60% of targeted events) had occurred. The purpose of this analysis was to evaluate cumulative interim safety and efficacy data.

Primary Analysis (PA): Planned to occur after approximately 165 PFS events (100% of targeted events). It was performed when 166 PFS events had occurred, with a clinical cutoff date of May 1, 2024. The key secondary endpoints, ORR and PFS2, were formally tested according to the hierarchical testing procedure. OS was analyzed descriptively, as the PFS2 result was not statistically significant. The discussions in this briefing document will be based on this analysis.

Final Analysis (FA): To be performed at the end of the study, with an expected total of 134 PFS2 events and 107 OS events. Per protocol, the end of the study was expected to occur approximately 8 years after the first subject was randomized, or when the sponsor would decide to stop the study. Given that the first patient was randomized in December 2017, the planned study completion date is December 2025. See Table *22* in Appendix 12.7 for additional details including plan for multiplicity control.

7 Trial Results

The data cut-off date for the FDA analysis was May 1, 2024.

7.1 Patient Population

7.1.1 Demographics

Baseline demographics were balanced between the two arms, as shown in Table 2. However, participants on the AQUILA trial were younger than patients with SMM in the U.S. The median age of participants enrolled on the trial was 65 years while the median age of patients with SMM in the United States is 67 years and the prevalence increases with age (17).

Additionally, although the trial enrolled 15% of the participants from the United States, only 2% of the participants on the Dara SC arm and 4% of the participants on the ACTM arm were Black. The prevalence of MM precursor conditions is approximately two-fold higher amongst Blacks compared to Whites in the United States (18).

Table 2 AQUILA- Baseline Demographics

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)	Overall N = 390 N(%)
Age			
Median (Range)	63.0 (31.0- 86.0)	64.5 (36.0-83.0)	64.0 (31.0- 86.0)
Age group (Years)			
18 - <65	106 (55)	98 (50)	204 (52)
65 - <75	67 (35)	74 (38)	141 (36)
≥75	21 (11)	24 (12)	45 (12)
Sex			
Male	95 (49)	93 (47)	188 (48)
Female	99 (51)	103 (53)	202 (52)
Race			
White	161 (83)	162 (83)	323 (83)
Black or African American	4 (2)	7 (4)	11 (3)
Asian	18 (9)	13 (7)	31 (8)
American Indian or Alaska Native	0 (0)	3 (2)	3 (1)
Native Hawaiian or Pacific Islander	0 (0)	2 (1)	2 (0.5)
Multiple	1 (0.5)	0 (0)	1 (0.3)
Not Reported	10 (5)	9 (5)	19 (5)
Ethnicity			
Hispanic or Latino	14 (7)	9 (5)	23 (6)
Not Hispanic or Latino	169 (87)	176 (90)	345 (88)
Not Reported	11 (6)	11 (6)	22 (6)
Geographic Enrollment			
United States	30 (15)	27 (14)	57 (15)
Israel	28 (14)	28 (14)	56 (14)
United Kingdom	18 (9)	17 (9)	35 (9)
Japan	15 (8)	13 (7)	28 (7)
Spain	10 (5)	14 (7)	24 (6)
Australia	5 (3)	10 (5)	15 (4)
Others †	88 (45)	87 (44)	175 (45)

Source: FDA review. † Other countries include Argentina, Belgium, Brazil, Canada, China, Czech Republic, Germany, Denmark, France, Greece, Hungary, India, Italy, Mexico, Netherlands, Norway, Poland, Romania, Russian Federation, Sweden, Turkey, and Taiwan.

7.1.2 Baseline Disease Characteristics

Baseline disease characteristics, including key features, that could impact the PFS results such as time from randomization to initial diagnosis of SMM to randomization, baseline hemoglobin, lytic bone lesions and focal bone lesions were balanced amongst the two arms. Despite being classified as high-risk, participants generally had favorable MM prognostic features. The majority of participants had standard cytogenetics (60%) and ISS Stage I (80%) which are generally considered as favorable prognostic features in participants with MM. (Table 3)

Table 3 AQUILA -Baseline Disease Characteristics

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)	Overall N = 390 N(%)
Type of SMM			
IgG	127 (65)	138 (70)	265 (68)
IgA	55 (28)	42 (21)	97 (25)
IgM	1 (0.5)	0 (0)	1 (0.3)
IgD	0 (0)	2 (1)	2 (0.5)
IgE	0 (0)	0 (0)	0 (0)
Light chain	9 (5)	9 (5)	18 (5)
Kappa	6 (3)	7 (4)	13 (3)
Lambda	3 (2)	2 (1)	5 (1)
Biclonal	1 (0.5)	5 (3)	6 (2)
Serum FLC only	1 (0.5)	0 (0)	1 (0.3)
Not detected	0 (0)	0 (0)	0 (0)
Time from initial diagnosis date of SMM to randomization (years)			
≤1 year	108 (56)	114 (58)	222 (57)
>1 year	86 (44)	82 (42)	168 (43)
Mean (SD)	1.2 (1.2)	1.3 (1.3)	1.2 (1.2)
Median (range)	0.8 (0.0-4.7)	0.7 (0.0 - 5.0)	0.7 (0.0-5.0)
ISS Stage			
I	154 (79)	155 (79)	309 (79)
II	33 (17)	33 (17)	66 (17)
III	4 (2)	4 (2)	8 (2)
Missing	3 (2)	4 (2)	7 (2)
ECOG Score			
0	165 (85)	160 (82)	325 (83)

1	29 (15)	36 (18)	65 (17)
Cytogenetic Risk§			
High-risk	29 (15)	22 (11)	51 (13)
Standard Risk	116 (60)	118 (60)	234 (60)
Unevaluable	49 (25)	56 (29)	105 (27)
Hemoglobin (g/dL) †			
Median	12.7	12.6	12.7
Range	9.3-16.2	9.3-16.7	9.3-16.7
Lytic bone lesions			
0	194 (100)	193 (98)	387 (99)
1	0 (0)	3 (2)	3(1)
Focal bone lesions			
0	172 (89)	179 (91)	351 (90)
1	20 (10)	15 (8)	35 (9)
> 1	2(1)	2 (1)	4 (1)

Source: FDA review. The percentages are based on ITT analysis set. ECOG = eastern cooperative oncology group; FLC = free light chain; SD = standard deviation; SMM = smoldering multiple myeloma. § For cytogenetic risk, del17, t(14;16) and t(4;14) were considered. Subjects were considered not evaluable if: a) they had missing results for all FISH abnormalities considered, or b) they had no abnormal test results and missing results for other abnormalities. † Excluding 2 participants with missing baseline hemoglobin values.

7.1.3 Protocol Defined High-risk Criteria

Nearly 75% of the participants met the protocol defined criteria for involved: uninvolved FLC ratio≥8 (Table 4). The next most common criteria was immunoparesis, in approximately 60% of participants on each arm. The rates of individual criteria were generally balanced across the arms with the exception of IgA, which was slightly higher in the Dara SC arm compared to the ACTM arm.

Table 4 Protocol Defined High-Risk Criteria

High-risk Criteria § (Protocol-defined)	Dara SC N=194 N(%)	ACTM N=196 N(%)	Overall N = 390 N(%)
Serum M protein ≥ 30g/L	34 (18)	40 (20)	74 (19)
Involved: Uninvolved FLC ratio ≥8 and < 100	135 (70)	147 (75)	282 (72)
BMPCs >50% to <60%	6 (3)	4 (2)	10 (3)
IgA SMM	55 (28)	42 (21)	97 (25)
Immunoparesis †	116 (60)	116 (59)	232 (59)
Number of High-Risk Factors			
0	5 (3)	0 (0)	5 (1)
1	72 (37)	81 (41)	153 (39)
2	80 (41)	80 (41)	160 (41)
3	34 (17)	32 (16)	66 (17)
4	3 (2)	3 (2)	6 (2)
Number of High-Risk Criteria			
<=2	157 (81)	161 (82)	318 (82)
>2	37 (19)	35 (18)	72 (18)

Source: FDA Review. § Participants may meet one or more risk criteria (See Appendix, *Figure* 15). † Immunoparesis with reduction of 2 uninvolved Ig isotypes, only IgA, IgM, and IgG were considered). BMPC = bone marrow plasma clone; FLC = free light chain; SMM = smoldering multiple myeloma.

7.1.4 AQUILA trial participants based on available risk stratification models for high-risk SMM

As noted in Section 1, multiple risk models were developed for SMM risk stratification risk of progression to multiple myeloma at 2 years and 5 years. Consensus guidelines recommend the use of the Mayo 2018 model for risk stratification.

The AQUILA protocol defined high-risk SMM population was not based on the available SMM risk stratification models. Additionally, the IgA SMM criteria and clonal BMPCs >50% to <60% with measurable disease used in the protocol's eligibility criteria are not included in the SMM risk stratification models.

Analysis of the trial participants based on the available risk stratification criteria are shown in Table 5. More than half of the participants on the trial were assessed as intermediate- or low-risk. Based on the consensus Mayo 2018 risk model less than half the AQUILA trial participants (41%) were categorized as high-risk for progression to MM, 39% of participants were intermediate-risk and 20% low-risk.

A majority of the participants enrolled in the AQUILA trial were intermediate- or low-risk based on the current risk models. There is uncertainty regarding the generalizability of the AQUILA trial results to patients with high-risk SMM.

Table 5 AQUILA Population Based on Different High-Risk Models

Risk Models	Dara SC N = 194 N(%)	ACTM N = 196 N(%)	Overall N = 390 N(%)
Mayo 2018			
High	72 (37)	86 (44)	158 (41)
Intermediate	77 (40)	76 (39)	153 (39)
Low	45 (23)	34 (17)	79 (20)
Mayo 2008			
High	26 (13)	28 (14)	54 (14)
Intermediate	121 (62)	131 (67)	252 (65)
Low	47 (24)	37 (19)	84 (22)
IMWG 2020§			
High	12 (6)	6 (3)	18 (5)
Intermediate	32 (16)	38 (19)	70 (18)
Low/intermediate	66 (34)	65 (33)	131 (34)
Low	30 (15)	27 (14)	57 (15)
Not evaluable	54 (28)	60 (31)	114 (29)

Source: FDA Analysis. § For the IMWG2020 criteria, the AQUILA trial did not collect deletion 13q information at enrollment. t(4;14), t(14;16) and 1P1Q were considered in this evaluation. Participants were considered not evaluable if (a) results were missing for all three abnormalities, or (b) all available results were normal and the rest were missing. The 1P1Q result was considered missing if the recorded result is not equal to 'Normal' or 'Abnormal'. PETHEMA model was not evaluated as a key flow cytometry criteria was not collected in the AQUILA trial.

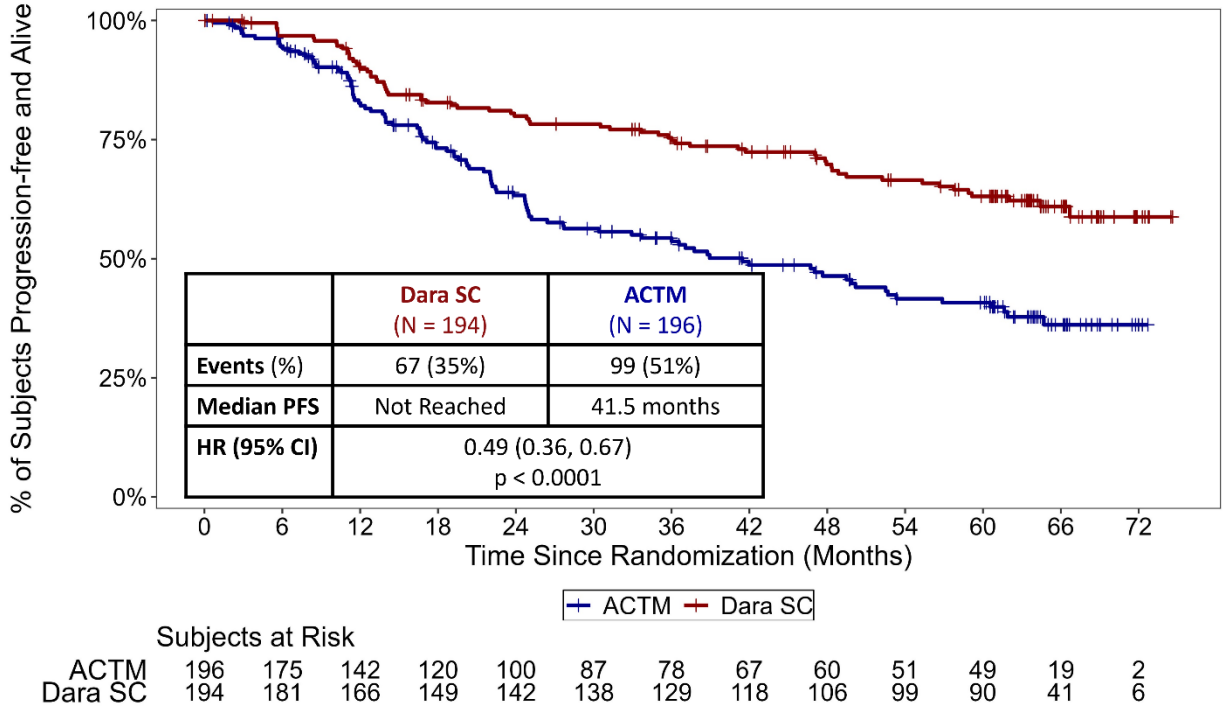
7.2 Efficacy Results

7.2.1 Primary Endpoint- PFS

The primary endpoint was PFS, defined as the time from the date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurred first.

As of the clinical cutoff (CCO) date of May 1, 2024, with a median follow up of 65.2 months, a total of 166 PFS events per IRC assessment (Dara SC 67 [35%]; ACTM 99 [51%]) were observed. The stratified HR for PFS per IRC was 0.49 (95% CI: 0.36, 0.67), with a 2-sided p-value of <0.0001,Figure 6. Median PFS was not reached in the Dara SC arm and was 41.5 months (95% CI: 26.4, 53.3) in the ACTM arm (60-month PFS rate: Dara SC 63%; ACTM 41%)

Figure 6 AQUILA KM Curve- PFS



Source: FDA analysis. ITT analysis based on IRC assessment. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; PFS = progression-free survival; ITT = intent-to-treat; IRC = independent review committee.

The landmark PFS rates are shown in Table 6.

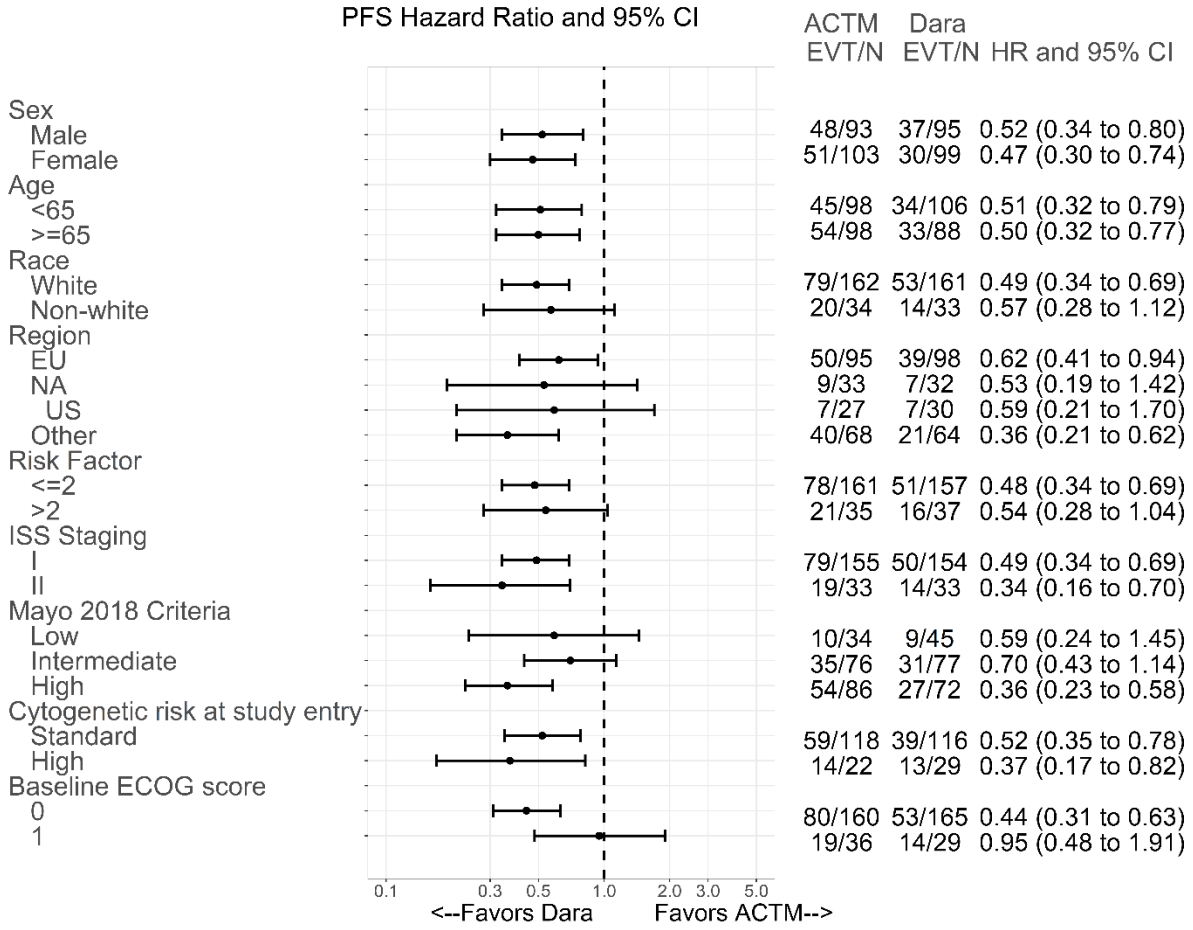
Table 6 Landmark PFS Rates

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)
12-month PFS rate % (95% CI)	90 (85, 93)	83 (76, 88)
24-month PFS rate % (95% CI)	80 (73, 85)	63 (56, 70)
36-month PFS rate % (95% CI)	75 (68, 81)	54 (46, 62)
48-month PFS rate % (95% CI)	70 (62, 76)	46 (38, 54)
60-month PFS rate % (95% CI)	63 (55, 70)	41 (33, 49)

Source: FDA analysis. ITT Analysis based on IRC assessment. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; PFS = progression-free survival; ITT = intent-to-treat; IRC = independent review committee.

Overall, the results across the different subgroups were consistent with the primary PFS analysis. In the Mayo 2018 Model groups; the greatest PFS benefit was observed in the Mayo 2018 high-risk group (Figure 7 and Appendix Figure 16).

Figure 7 AQUILA Forest Plot – PFS Subgroup Analyses



Source: FDA analysis. PFS based on IRC assessment. Median follow-up was 65.2 months. Risk Factor was based on protocol defined risk factors at baseline. The subgroups with less than 10 participants were suppressed in the plot.
ACTM = active monitoring; CI = confidence interval; Dara = Dara SC; ECOG = Eastern Cooperative Oncology Group; EU = European Union; EVT = event; HR = hazard ratio; PFS = progression-free survival; IRC = independent review committee; ISS = International staging system; ITT = intent-to-treat; NA = north American; US = United States.

7.2.1.1 Considerations for the PFS Endpoint

For the AQUILA trial, PFS was defined as the time from date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for MM or the date of death, whichever occurred first, as assessed by the Independent Review Committee (IRC). Although the definition of PFS on the trial included deaths, the rate of death events was very low, 3% and equal on both arms. Improvement in PFS was primarily due to delay in progression to MM.

The reasons for PD on the AQUILA trial can be seen in Table 7. About 30% of the participants on the AQUILA trial progressed based on laboratory or imaging based SLiM criteria and only 12% of participants progressed based on end organ damage related CRAB criteria. The most common reason for progression on both arms (17% in both arms) was asymptomatic elevation of serum free light chain ratio >100. There were few events of hypercalcemia (<1%) and no participants had progression related to renal end organ damage.

Table 7 Reasons for Progressive Disease

	Dara SC N= 194 N(%)	ACTM N = 196 N(%)	Overall N = 390 N(%)
Subjects with progression-free survival event	67 (35)	99 (51)	166 (43)
Subjects with progressive disease	62 (32)	94 (48)	156 (40)
Reason for progressive disease[a]			
Calcium elevation	0 (0)	2 (1)	2 (0.5)
Renal insufficiency	0 (0)	0 (0)	0 (0)
Anemia	2 (1)	14 (7)	16 (4)
Bone disease	10 (5)	18 (9)	28 (7)
Clonal BM plasma cells	5 (3)	16 (8)	21 (5)
Serum FLC	33 (17)	33 (17)	66 (17)
Focal lesion by MRI	12 (6)	16 (8)	28 (7)
Subjects died without progressive disease	5 (3)	5 (3)	10 (3)

a Progression to MM is based on the SLiM CRAB criteria, defined as, ≥60% bone marrow plasma cells, free light chain involved/uninvolved ratio ≥100, > 1 focal bone lesions on MRI, calcium elevation, renal insufficiency by creatinine clearance, anemia, or bone disease due to lytic bone lesions.

Source: FDA analysis. ITT Analysis based on IRC assessment. Denominator for the percentages is based on the ITT population. Median follow-up was 65.2 months. A participant may show progressive disease based on more than one criterion. BM = bone marrow; FLC = free light chain; IRC = independent review committee; ITT = intent-to-treat; MRI = magnetic resonance imaging.

The definition for anemia as per CRAB criteria is defined as Hb <10g/dL or >2g/dL below the lower limit of normal or both, unless the anemia was attributed to another cause. Per protocol, before progressive disease was declared on the basis of anemia without CRAB signs or symptoms, additional diagnostic tests (iron, ferritin, transferrin, manual smear review, Coombs testing, lactate dehydrogenase, vitamin B12, and folate) were recommended to rule out other underlying cause of anemia. However, the results of these diagnostic tests to evaluate other causes of anemia not attributed to progression to MM were not collected by the Applicant.

The hemoglobin levels at baseline and at the time of progression are shown in Table 8.

Table 8 Hemoglobin Levels at Study Entry and at PD

Treatment	Hemoglobin (g/dL) Study Entry	Hemoglobin (g/dL) At Progression
ACTM	11.1	10.3
ACTM*	11.2	9.8
ACTM	10.0	8.6
ACTM*	13.2	8.8
ACTM	13.4	10.1
ACTM	11.6	9.7
ACTM	11.0	9.6
ACTM	12.6	10.4
ACTM	11.5	8.7
ACTM	11.2	9.7
ACTM*	11.4	9.8
ACTM	11.8	9.5
ACTM	12.2	9.8
ACTM	11.7	10.2
Dara SC	11.3	9.5
Dara SC	10.0	9.9

Source: FDA Analysis based on ADCRAB dataset. *Reported as Grade 1 anemia in the ADAE dataset

Fourteen participants on the ACTM arm and 2 participants on the Dara SC arm met progressive disease criteria for anemia. The majority of participants had PD based on minor changes in Hb levels (Table 8). The median change in hemoglobin was 1.7 g/dL. Additionally, only three participants with PD reported due to anemia had a clinician reported AE of anemia. All three had grade 1 anemia. For reference, Common Toxicology Criteria for Adverse Events (CTCAE) Grade 2 anemia is Hemoglobin <10.0-8.0 g/dL and CTCAE Grade 3 anemia is Hemoglobin <8 g/dL with transfusion indicated (19). None of the participants who were assessed as having PD on the basis of anemia received transfusions. None of the participants had an AE of fatigue reported.

In terms of bone lesions in the CRAB criteria, these lesions were detected primarily by imaging. In total, 3 participants had bone disease as PD, had bone symptoms (pain/fracture) with bone lesions at the time of PD assessment.

- (b) (6) (Dara SC arm): had bone lesions confirmed as PD (16 March 2022) and AE Grade 3 Costal cartilage fracture (09 Aug 2021 – 19 Jan 2022). Also had bone pain reported as AE (16 March 2022) with PD based on Bone Lesions on 16 March 2022 identified on disease evaluation imaging (CT scan) performed on the same day.

- (b) (6) (Dara SC arm): had bone lesions confirmed as PD (07 Dec 2020) and AE Grade 3 Rib fracture (26 May 2019 – 04 Jun 2019).
- (b) (6) (ACTM arm): had bone lesions confirmed as PD (03 April 2020) and AE Grade 3 Osteoporotic fracture (11 Dec 2018 – 12 Dec 2019).

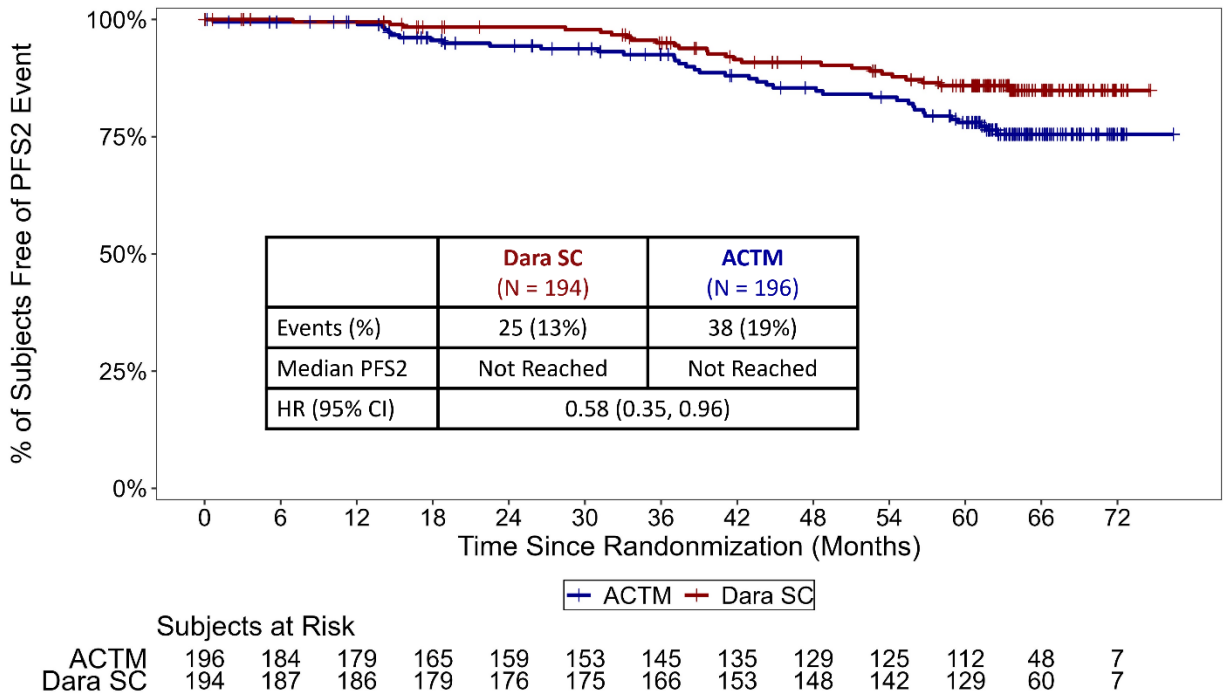
Based on our review of the data, bone disease was primarily asymptomatic and were identified primarily based on imaging.

In summary, while the trial met the primary endpoint of PFS as defined, this was primarily based on delaying progression to MM. The majority of the PD events were based on serum FLC criteria, MRI detected bone lesions and asymptomatic changes in hemoglobin and low rates of renal insufficiency, hypercalcemia, or deaths. The clinical meaningfulness of the observed improvement in PFS is unclear.

7.2.2 Secondary Endpoint- PFS2

At the time of the CCO (May 1, 2024), the PFS2 data were not yet mature, with 63 PFS2 events per investigator assessment were observed (Dara SC 25 [13%]; ACTM 38 [19%]). The HR of PFS2 (Dara SC vs ACTM) was 0.58 (95% CI: 0.35, 0.96) with a 2-sided p-value of 0.0318, which did not cross the prespecified stopping boundary of 0.0235. With a median follow-up of 65.2 months, the median PFS2 was not reached in either arm, Figure 8.

Figure 8 AQUILA KM Curve- PFS2



Source: FDA analysis. ITT Analysis based on investigator assessment. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; PFS2 = progression-free survival on first line therapy; ITT = Intent-to-treat.

The landmark PFS2 rates are shown in Table 9. The 60-month PFS2 rate for Dara SC was 86% (95% CI: 80%, 90%) in the ACTM was 78% (95% CI: 71%, 84%).

Table 9 Landmark PFS2 Rates

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)
12-month PFS2 rate % (95% CI)	99 (96, 100)	99 (96, 100)
24-month PFS2 rate % (95% CI)	98 (95, 99)	94 (90, 97)
36-month PFS2 rate % (95% CI)	95 (91, 97)	93 (87, 96)
48-month PFS2 rate % (95% CI)	91 (85, 94)	85 (79, 90)
60-month PFS2 rate % (95% CI)	86 (80, 90)	78 (71, 84)

Source: FDA analysis. ITT Analysis based on investigator assessment. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; PFS2 = progression-free survival on first line therapy.

7.2.2.1 PFS2 Considerations

PFS2 has not supported approval of therapies for patients with cancer in the US. There are challenges with the use of this endpoint as it is largely impacted by factors not related to the initial therapy: decisions regarding when to start subsequent therapy, which therapies to administer, healthcare access and patient discretion.

However, in patients with precursor conditions, PFS2 can provide some information about the impact of precursor condition treatment on active disease outcomes.

In the AQUILA trial, PFS2 was defined as the time from the date of randomization to the date of documented progression of disease by investigator on the first-line treatment for MM or death, whichever came first (Appendix12.6). While the trial was not adequately powered to demonstrate significant improvement in PFS2, the assumptions for the PFS2 endpoint was based on the assumed median PFS2 of 72 months in ACTM arm vs 96 months in the Dara SC arm.

As noted above in Section 4.5.2.1.2 despite delaying progression to development of active MM in the Dara SC arm, the time to next progression on the first-line treatment or death was not statistically different between the arms.

However, there are some caveats to interpreting these results. The decision to initiate first line therapy and type of first line therapy was left to the discretion of the individual investigator and was not stipulated by the trial's protocol. As shown in Table 10 there was an imbalance among the treatment arms in terms of the types of first line therapy that was administered. Overall, 16% of the participants on the ACTM arm and 7% in the Dara SC received daratumumab based first line therapy which is now considered the standard of care for patients with newly diagnosed multiple myeloma. Less than half of the participants received commonly used non-daratumumab containing triplet regimens (bortezomib with lenalidomide and dexamethasone or with cyclophosphamide with dexamethasone). Among participants who had PD determined by investigator, about 20% did not receive a subsequent therapy (Appendix 12.10).Additional limitations are noted in Appendix 12.11.

Table 10 First Line Subsequent Therapies for MM

	Dara SC N = 194 n (%)	ACTM N = 196 n (%)	Overall N = 390 n (%)
Participants with first line therapy	65 (34)	105 (54)	170 (44)
VRd	19 (10)	29 (15)	48 (12)
VCd	6 (3)	14 (7)	20 (5)
VTd	9 (5)	8 (4)	17 (4)
DVRd	4 (2)	10 (5)	14 (4)
DRd	3 (2)	10 (5)	13 (3)
Rd	5 (3)	7 (4)	12 (3)
DVMP	1 (0.5)	5 (3)	6 (2)
KRd	3 (2)	3 (2)	6 (2)
DVTd	2 (1)	2 (1)	4 (1)
Isa-VRd	1 (0.5)	3 (2)	4 (1)
Vd	2 (1)	1 (0.5)	3 (1)
Daratumumab	2 (1)	0 (0)	2 (0.5)
IRd	0 (0)	2 (1)	2 (0.5)
R	1 (0.5)	1 (0.5)	2 (0.5)
RCd	1 (0.5)	1 (0.5)	2 (0.5)
VMP	1 (0.5)	1 (0.5)	2 (0.5)
VMP-DRd	0 (0)	2 (1)	2 (0.5)
D-VTCd	0 (0)	1 (0.5)	1 (0.3)
Dara-Iber-d	1 (0.5)	0 (0)	1 (0.3)
DKRd	1 (0.5)	0 (0)	1 (0.3)
DVd	0 (0)	1 (0.5)	1 (0.3)
Elo-KRd	0 (0)	1 (0.5)	1 (0.3)
Isa	0 (0)	1 (0.5)	1 (0.3)
KCd	0 (0)	1 (0.5)	1 (0.3)
Venetoclax+VTd	0 (0)	1 (0.5)	1 (0.3)
VTCd	1 (0.5)	0 (0)	1 (0.3)
VRd, Isa-Kd, transplant	1 (0.5)	0 (0)	1 (0.3)
VRTd + melphalan, transplant	1 (0.5)	0 (0)	1 (0.3)
Any Daratumumab-containing regimen	14 (7)	31 (16)	45 (12)

Source: FDA Review. Daratumumab-containing regimen includes D-VTCd, Dara-Iber-d, Daratumumab, DKRd, DRd, DVd, DVMP, DVRd, DVTd, and VMP-DRd. The denominator for the % is the ITT analysis set. The distribution of subsequent antimyeloma therapy by treatment regimen is similar among participants who had progressive disease per investigator and initiated first-line therapy. C=cyclophosphamide; d=dexamethasone; D=daratumumab; Elo=elotuzumab; Iber=iberdomide; I=ixazomib; K=carfilzomib; M=melphalan; P=prednisone; R=lenalidomide; T=thalidomide; V=bortezomib.

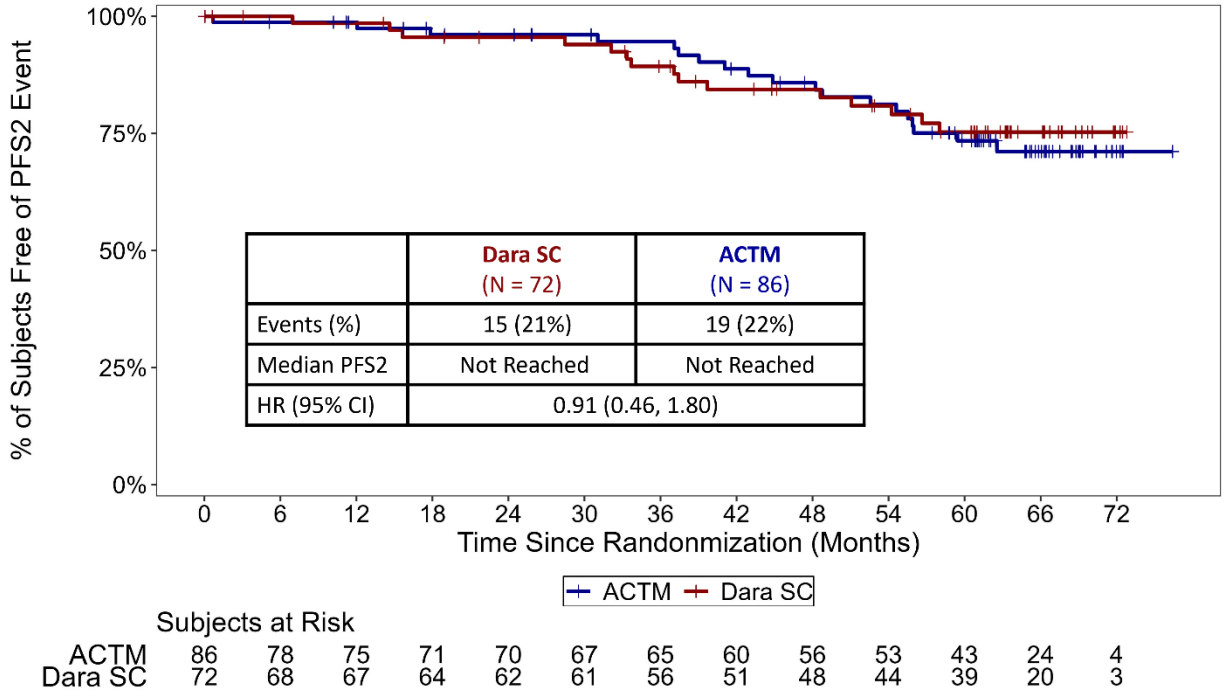
Because a substantial proportion of participants did not receive therapies or regimens that would be considered standard of care for patients with newly diagnosed MM currently there is

uncertainty regarding the PFS2 results. A small percentage in the Dara SC arm (or the ACTM arm) received subsequent Daratumumab or a CD-38 monoclonal antibody. Given that CD38 treatment has shown an overall survival improvement when given as part of initial combination therapy for MM, the impact of pre-emptive treatment on long-term outcomes and ability to respond to CD38 treatment as part of initial treatment is unclear. The impact of the treatment of high-risk SMM versus treatment at MM diagnosis has not been established.

7.2.2.2 PFS2 in the Mayo 2018 high-risk subgroup

Additionally, in the high-risk group defined by the Mayo 2018 Model, there were 15 PFS2 events in the Dara SC arm and 19 events in the ACTM. The unstratified HR was 0.91 (95% CI: 0.46-1.80). While the point estimate is less than 1, the CI crosses 1 (Figure 9).

Figure 9 AQUILA KM Curve PFS2 Mayo 2018 High Risk Subgroup

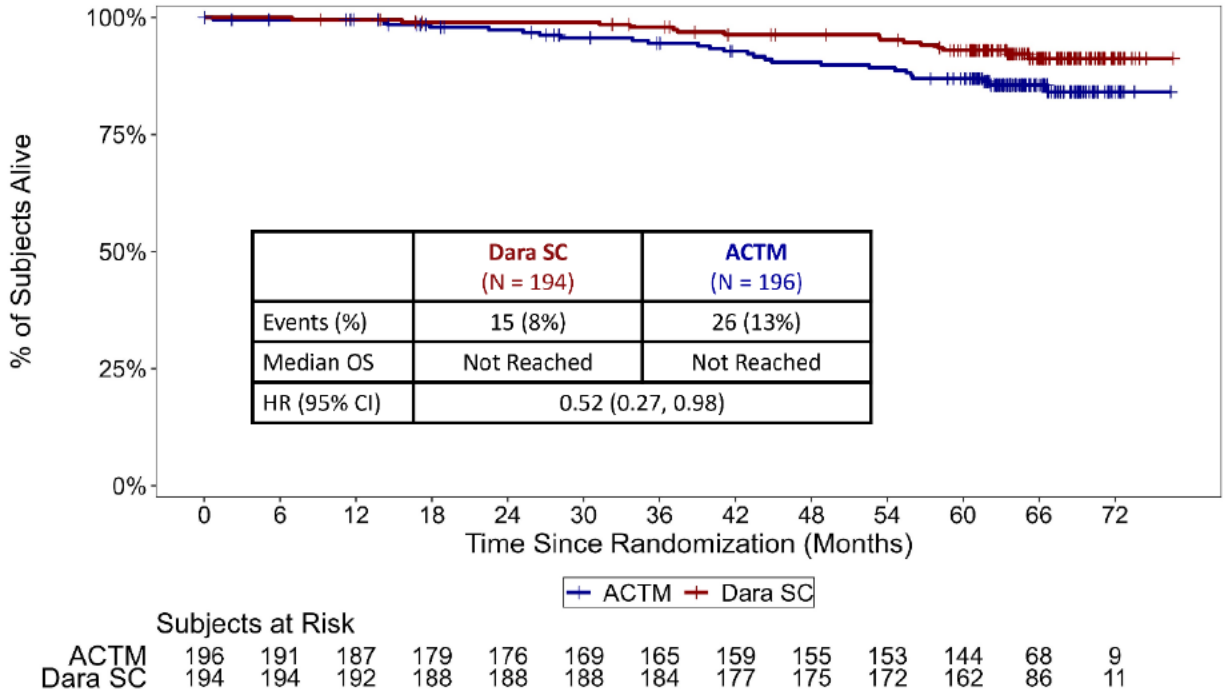


Source: FDA Analysis. Clinical cutoff was May 1, 2024. ACTM = active monitoring; CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; PFS2 = progression-free survival on first-line treatment for multiple myeloma.

7.2.3 Secondary Endpoint- OS

OS was a key secondary endpoint on the trial and was tested after ORR and PFS2. Interim OS analysis was conducted at the time of the primary PFS analysis with a median follow up of 65.2 months. There were 41 OS events, 15 (8%) in the Dara SC arm and 26 (13%) in the ACTM. The OS HR was 0.52 (95% CI: 0.27,0.98). Figure 10 depicts the OS KM curves.

Figure 10 AQUILA KM Curve-OS



Source: FDA analysis. ITT Analysis. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; ITT = Intent-to-treat; OS = overall survival.

The landmark OS rates are presented in Table 11. At 5-years landmark time, the difference in OS rates was about 5%.

Table 11 Landmark OS Rates

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)
12-month survival rate % (95% CI)	99 (96, 100)	99 (96, 100)
24-month survival rate % (95% CI)	99 (96, 100)	97 (94, 99)
36-month survival rate % (95% CI)	98 (95, 99)	95 (90, 97)
48-month survival rate % (95% CI)	96 (92, 98)	90 (85, 94)
60-month survival rate % (95% CI)	93 (88, 96)	87 (81, 91)

Source: FDA analysis. ITT Analysis based on investigator assessment. Median follow-up was 65.2 months. ACTM = active monitoring; CI = confidence interval; OS = overall survival.

7.2.3.1 Overall Survival Considerations in the AQUILA trial

The AQUILA study was not adequately powered to assess OS efficacy.

The OS results were immature. At the time of the primary PFS analysis, it was anticipated that there would be 64 OS events (60%), but only 41 (38% of the planned 107 events) were observed (Dara SC15 [8%]; ACTM 26 [13%]). Overall survival was not formally tested at the primary analysis because PFS2 did not cross the prespecified stopping boundary according to the prespecified hierarchical testing order.

Given the limitations noted above with the endpoints on the AQUILA trial, FDA conducted additional analysis to evaluate the OS results on the AQUILA trial to inform benefit-risk assessment.

7.2.3.1.1 Review of Deaths

FDA evaluated the cause of deaths to assess impact on the treatment on myeloma specific survival. There were very few deaths within 30 days or 60 days of treatment or active monitoring period. There were no deaths related to progressive disease during this period. (Table 12).

When considering all deaths on the AQUILA study, the majority of deaths were categorized as “other” with few death events related to progression of disease or adverse events. Upon further clarification for narratives to confirm cause of death, the Applicant indicated that individual sites were asked to provide to details to further clarify the reason for death, but detailed information was not available.

Table 12 AQUILA- Overview of Deaths

	Dara SC N=194 N(%)	ACTM N=196 N(%)
Deaths	15 (8)	26 (13)
AEs	2 (1)	4 (2)
PD	3 (2)	9 (5)
Other	10 (5)	13 (7)
Death within 30 days	0	4
Death Within 60 days	3	0
AEs	2 (1)	4 (2)
Other (Unknown)	1 (0.5)	0

Source: FDA Analysis; ITT Population

More than 75% of the deaths in the ACTM arm and more than half of the deaths in the Dara SC arm occurred following receipt of subsequent therapy. As a result, the confirmation of cause of death (PD or adverse event) was not possible (Table 13).

Table 13 AQUILA-Overview of Deaths Based on Receipt of Subsequent Therapy

	Dara SC N = 194 N(%)	ACTM N = 196 N(%)	Overall N = 390 N(%)
Death without any subsequent therapy use	6 (3)	6 (3)	12 (3)
AE	2 (1)	4 (2)	6 (2)
Other	4 (2)	2 (1)	6 (2)
Influenza	1 (0.5)	0 (0)	1 (0.3)
Respiratory failure	1 (0.5)	0 (0)	1 (0.3)
Sudden cardiac arrest	1 (0.5)	1 (0.5)	2 (0.5)
Unknown	1 (0.5)	1 (0.5)	2 (0.5)
Death following subsequent therapy use	9 (5)	20 (10)	29 (7)
Progressive disease	3 (2)	9 (5)	12 (3)
Other	6 (3)	11 (6)	17 (4)
1. pneumocystis jirovecci pneumonia 2. myeloma	0 (0)	1 (0.5)	1 (0.3)
Congestive heart failure	0 (0)	1 (0.5)	1 (0.3)
General deterioration	0 (0)	1 (0.5)	1 (0.3)
Intrinsic cardiac death	1 (0.5)	0 (0)	1 (0.3)
Patient was admitted to hospital with abdominal pain and passed away. no diagnosis stated.	1 (0.5)	0 (0)	1 (0.3)
Pneumonitis	0 (0)	1 (0.5)	1 (0.3)
Respiratory failure due to exacerbated chronic obstructive pulmonary disease and influenza symptoms	0 (0)	1 (0.5)	1 (0.3)
Sepsis	0 (0)	1 (0.5)	1 (0.3)
Sudden cardiac arrest	1 (0.5)	0 (0)	1 (0.3)
Sudden cardiac death	0 (0)	1 (0.5)	1 (0.3)
Sudden death	0 (0)	1 (0.5)	1 (0.3)
Unknown	3 (2)	3 (2)	6 (2)

Source: FDA Analysis. Percentages based on the ITT population.

The lack of details on the cause of death limits the ability to assess myeloma specific survival. This raises additional uncertainty regarding the clinical meaningfulness of delaying progression to MM.

7.2.3.1.2 OS as an efficacy endpoint in SMM

FDA further explored the feasibility of designing a trial adequately powered for OS efficacy. Based on FDA analysis, assuming a hazard ratio of 0.80, as in the AQUILA study, the target number of OS events for a trial powered for OS would be 686 from more than 2,000 participants (Table 14). This underscores the impracticality of OS as a primary efficacy endpoint in high-risk SMM.

Table *14* Sample Size Calculation for Efficacy

OS Hazard Ratio	Target Number of OS Events	Sample size	Median OS in Dara SC Arm (months) †
0.80	686	2487	125
0.75	413	1535	133
0.70	269	1026	143
0.65	184	722	154
0.60	131	529	167
0.52 (observed)	80	339	192

Source: FDA Analysis. Using 80% power and a 0.05 two-sided Type I error. The accrual period was set at 24 months, followed by a 40-month follow-up. The alpha spending at the primary analysis and the final analysis was determined by a linear alpha spending function. †Median overall survival in Dara SC arm was calculated under each hazard ratio assumption and the exponential distribution, with the assumption that the median OS in the active monitoring arm is 100 months.

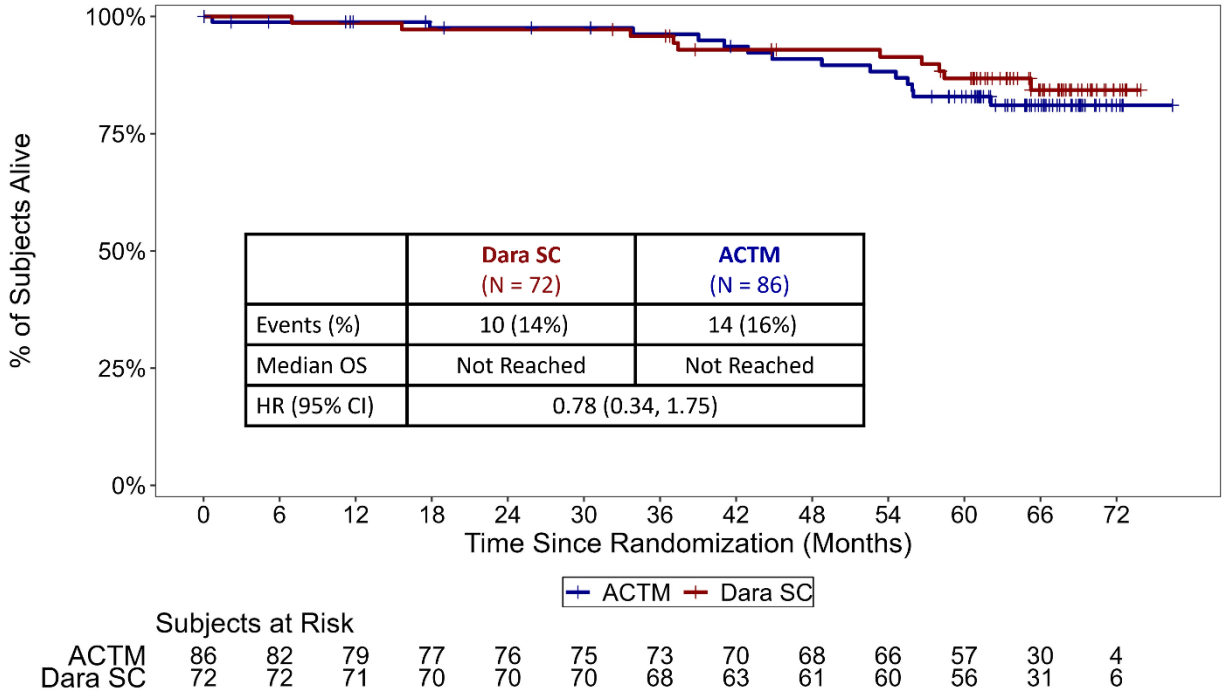
7.2.3.1.3 Overall Survival for Safety Monitoring

While the OS results indicate that treatment with Dara SC showed a trend towards a demonstration of no harm, the results were immature. The FDA conducted an analysis to monitor OS for potential harm associated with the treatment. The assessment was based on the observed HR of 0.52 and the 41 deaths observed at the primary analysis cutoff. To evaluate the risk of potential harm as more events accumulate, we estimated the conditional probability of observing an HR >1 (which would suggest potential harm), assuming a total of 107 deaths at the end of the trial. The results of OS monitoring analysis indicated a low probability of observing harm at final analysis with 107 deaths (Appendix12.12, Table 24).

7.2.3.1.4 OS results in the Mayo 2018 high-risk subgroup

In the high-risk group defined by the Mayo 2018 Model, there were 24 deaths (Dara SC 10 [14%]; ACTM: 14 [16%]). The unstratified HR was 0.78 (95% CI: 0.35-1.75). While the point estimate is less than 1, the CI crosses 1, we cannot definitively rule out harm. While this is an exploratory analysis and due to the small sample sizes and limited number of OS events, the results should be interpreted with caution (Figure 11), this subgroup is most reflective of the intended use population, so this analysis is important to consider.

Figure 11 AQUILA KM Curve-OS, Mayo 2018 High-Risk Group.



Source: FDA Analysis. Clinical cutoff was May 1, 2024. ACTM = active monitoring; CI = confidence interval; HR = hazard ratio; ITT = Intent-to-treat; OS = overall survival.

There is uncertainty regarding the clinical meaningfulness of the delay in progression to MM as evaluated by the PFS endpoint. There is lack of significant improvement in PFS2 based on the planned analysis. Additionally, there are several limitations noted in the PFS2 endpoint in the AQUILA trial as noted in Section7.2.2.1. This raises additional uncertainties regarding the clinical meaningfulness of delaying progression to MM as determined by the PFS endpoint. A significant improvement in OS could have provided robust estimate of the treatment effect and clinical benefit of Dara SC for the high-risk SMM population. However, the trial was not designed to show a significant improvement in OS efficacy and the data captured is inadequate to determine the impact on myeloma-specific survival. Additionally, the results in the Mayo 2018 high-risk subgroup where there is lack of robust data to definitely rule out harm, raises concerns regarding the benefit of Dara SC for a high-risk SMM population.

7.3 Safety Results

The safety populations included participants that received at least one dose of Dara SC (n=193) and all participants in the ACTM arm (n=196). The FDA's analysis of TEAEs were based on grouped terms for selected AEs as indicated.

7.3.1 Safety Overview

Nearly all participants (97%) on the Dara SC Arm experienced TEAEs. The rates of TEAEs were also high (83%) in the ACTM arm. Overall, 40% of the participants on the Dara SC experienced Grade 3 or 4 TEAEs compared to 30% on the ACTM arm. Although Dara SC was administered as monotherapy, nearly 50% of the participants experienced AEs that required dose modifications (Appendix 13) and 6% had clinically significant TEAEs leading to treatment discontinuation, as shown in Table 15.

Table 15 AQUILA Overview of TEAEs

Category	**Dara SC N=193 N(%)**	**ACTM N=196 N(%)**
Any TEAE Event	187 (97)	162 (83)
TEAE Grade 3 or 4	76 (40)	56 (29)
Grade 5 TEAE	2 (1)	4 (2)
Serious TEAE	56 (29)	38 (19)
TEAEs leading to discontinuation	11(6)	0
TEAE leading to dose modification	90 (47)	0

Source: FDA Analysis

7.3.2 Overview of Fatal TEAEs

Overall, the rate of fatal TEAEs were low in both the arms; 1% in the Dara SC arm and 2% in the ACTM arm.

Table 16 AQUILA Fatal TEAEs

Category	**Dara SC** (N=193) N(%)	**ACTM** (N=196) N(%)
Fatal TEAEs	2 (1.0)	4 (2.0)
Cardiac (GT)	0	2 (1.0)
COVID-19	1 (0.5)	0
Pneumonia (GT)	1 (0.5)	0
Pulmonary Embolism	0	1 (0.5)
Pulmonary Edema	0	1 (0.5)

Source: FDA Analysis

7.3.3 Serious Adverse Events

There were more participants with SAEs in the Dara SC arm (29%) compared to the ACTM arm (19%). Fracture and pneumonia were the most common SAEs reported in the Dara SC arm Table 17.

Table 17 AQUILA SAEs*

	DARA SC N=193 N(%)	ACTM N=196 N(%)
Any Serious TEAEs	56 (29)	38 (19)
Fractures (GT)	6 (3)	4 (2)
Pneumonia (GT)	12 (6)	4 (2)
Sepsis (GT)	4 (2)	4 (2)

Source: FDA Analysis*. SAEs≥2% on both arms.

7.3.4 Selected Adverse Events of Special Interest

Infusion related reactions (or systemic administration reactions) including fatal reactions and local injection site reactions can occur with administration of Dara SC. In the participants enrolled on the AQUILA trial, 17% of the participants experienced am infusion related reaction including 2 participants who developed Grade 3 infusion related reaction. Nearly one-third experienced injection site reactions, although none were Grade 3 or higher. The rate of infections were two times higher (80%) on the Dara SC arm compared with 45% in the ACTM arm. Notably, although anemia as a reason for PD was higher in the ACTM arm, there was no difference in the rates of laboratory-based anemia events between the arms.

Of the 4 participants with reported Grade 3 or higher anemia, for 2 participants anemia occurred in the setting of gastrointestinal hemorrhage and the other in the setting of ongoing sepsis. For the last patient, the Applicant clarified that there were discrepant results based on central and local testing and the investigator assessed the patient as not having Grade 4 anemia.

Table 18 AQUILA Selected AEs of Special Interest

	Dara SC N=193		ACTM N=196	
	All Grades	**Grade 3-5**	**All Grades**	**Grade 3-5**

	N(%)	N(%)	N(%)	N(%)
Systemic Administration Reactions	32 (17)	2 (1)	NA	NA
Injection Site Reactions (GT)	53 (28)	0	NA	NA
Infections and Infestations (SOC)	154 (80)	32 (17%)	88 (45%)	9 (5%)
Anemia*	80 (42)	0 (0%)	85 (43%)	4 (2%)
Neutropenia*	66 (34)	10 (5)	56 (29)	8 (4)
Thrombocytopenia*	36 (19)	1(0.5)	17 (9)	1 (0.5)

Source: FDA Analysis* Based on laboratory dataset

7.3.5 Common TEAES

TEAEs which occurred in 20% or more participants in either arm are listed in Table 19.

Overall, the rates of Grade 3-5 AEs were low (<5%) in both arms. Rates of all Grade TEAEs of musculoskeletal pain, upper respiratory infection (URI), fatigue, diarrhea, nasopharyngitis, rash, sleep disorder, and sensory neuropathy were higher (≥10% difference) in the Dara SC arm compared to the ACTM arm.

Table 19 AQUILA Common TEAEs

	Dara SC N=193		ACTM N=196	
	All Grades N(%)	**Grade 3-5 N(%)**	**All Grades N(%)**	**Grade 3-5 N(%)**
Any TEAE	**187 (97)**	**78 (40)**	**162 (83)**	**60 (31)**
Musculoskeletal pain (GT)	113 (59)	2 (1)	82 (42)	6 (3)
URI (GT)	100 (52)	1 (0.5)	33 (17)	0
Fatigue (GT)	81 (42)	5 (3)	41 (21)	1 (0.5)
Diarrhea (GT)	53 (27)	4 (2)	10 (5)	1 (0.5)
Nasopharyngitis	49 (25)	0	23 (12)	0
Rash (GT)	47 (24)	1 (0.5)	10 (5)	1 (0.5)
Sleep Disorder (GT)	46 (24)	1 (0.5)	9 (5)	0
Sensory Neuropathy (GT)	39 (20)	0	15 (8)	0

Source: FDA Analysis

7.3.6 Patient Reported Outcomes

In the AQUILA trial, patient-reported outcomes (PROs) were sparsely collected using the EORTC-QLQ-C30 and EORTC-MY-20. PROs were collected at baseline, week 12, week 24, week 60, week 112 and at the end of treatment. Although the data quality was amenable to analysis, with >70% compliance rate through week 60, FDA considers the PRO data from AQUILA to be non-informative for many reasons.

1) Infrequent PRO assessment is inadequate to demonstrate tolerability.

As described above regarding common TEAEs, participants in the Dara SC arm did have more clinician reported AEs. With only two post-baseline PRO assessments in the first year, the PRO assessment frequency was too sparse to adequately capture patient-reported symptoms related to treatment at the timepoints they were likely to occur.

2) The PRO measures used in AQUILA may be inappropriate for this trial population.

SMM is an asymptomatic disease, and as discussed above, most progression events in both arms were driven by biochemical events (e.g. FLC worsening) which are asymptomatic. Furthermore, the PRO measures utilized in AQUILA are more appropriate for those patients with active MM undergoing treatment.

3) The trial was not designed to detect differences between arms in regard to PROs.

PRO endpoints were non-ranked secondary endpoints without prespecified hypotheses, and it is unclear whether the AQUILA trial sample size was adequate to detect differences between arms. The open label design in an asymptomatic condition could also lead to potential bias in responses.

Although patient-reported outcomes can be a valuable source of information about tolerability and disease symptom improvement in cancer trials, the FDA disagrees with the Applicant regarding any interpretation regarding PRO results. Similar PRO scores between arms are not evidence of tolerability due to the limitations noted above. Based on the collected PRO data, FDA could not draw meaningful conclusions from the AQUILA PRO results.

8 Issues

8.1 Applicability of the AQUILA trial results to a high-risk SMM population

As presented in section 7.1.4, the AQUILA trial used protocol-specific criteria to define a population at high-risk for progression instead of the available high-risk models. Multiple scoring models are available to define SMM patients at high risk for progression to active MM, including the Mayo 2008 and the PETHEMA model that were available at the time of the AQUILA trial initiation and the more recent Mayo 2018 model and the IMWG 2020 (Appendix 12.2). Regardless of the model used, less than half of the participants on the AQUILA trial met criteria for high-risk for progression to MM. Specifically, based on the current Mayo 2018 model, only 41% of the AQUILA trial's patient population would meet the definition for high-risk, with a majority of participants classified as intermediate (39%) and low-risk (20%). It is important to note that for patients who are classified as low-risk, the risk of progression to MM is low (23% at 5 years).

Randomized clinical trials, provide the highest level of evidence to support the safety and efficacy of the products. An important aspect of this evidence is whether the results from the trial are generalizable to the population that will ultimately use the therapy. Based on the population enrolled in the AQUILA trial, there is uncertainty regarding the applicability of the trial results to the current high-risk SMM population.

8.2 Appropriateness of the endpoints for a high-risk SMM population

There are no approved therapies for SMM and the appropriate clinically relevant endpoint to support regulatory approval has not been established.

In the AQUILA trial, the primary efficacy endpoint was progression-free survival (PFS), as assessed by the Independent Review Committee (IRC), defined as the time from the date of randomization to the date of initial documented progression to MM in accordance with the IMWG diagnostic criteria for multiple myeloma or the date of death, whichever occurred first. While PFS is a widely used endpoint in clinical trials for hematologic malignancies, whether the PFS as defined in the AQUILA is a clinically meaningful endpoint is unknown, as PFS in this disease setting has not been shown to correlate with improved OS.

While a PFS benefit was observed in the Dara SC arm, the delay in progression to MM was driven by PFS events related to the SLiM criteria and there were a limited number of symptomatic CRAB (organ dysfunction) events. Even the observed differences in the CRAB

criteria were related to asymptomatic changes in hemoglobin and asymptomatic bone disease. The clinical relevance of PFS improvement alone is unclear. In AQUILA, the PFS2 endpoint was not statistically significant. Furthermore, the assessment of PFS2 and clinical meaningfulness is inherently limited due to the type of subsequent therapy the participants received. The lack of a significant improvement as it pertains to the PFS2 assessment in AQUILA raises additional uncertainty regarding the clinical relevance of delaying progression to MM.

The OS results were immature. There was no formal testing to demonstrate OS efficacy benefit. The analysis of myeloma-specific survival was limited by lack of detailed narratives for death cause. At the time of primary analysis, the HR observed at the time of primary analysis suggested no harm and the FDA analysis indicates that there is low likelihood of harm at the completion of the trial and large trials may be required to establish OS benefit, which may not be feasible. However, in the setting of the limitations noted with the other endpoints evaluated, the OS results do not provide robust evidence for benefit of the therapy in this asymptomatic precursor condition.

There is uncertainty regarding the clinical meaningfulness of the efficacy results measured by the endpoints in the AQUILA trial.

8.3 Safety concerns

Administration of Dara SC was associated with significant toxicities in this precursor population. There was a higher incidence of Grade 3-4 TEAEs on the Dara SC arm compared to the ACTM arm (Dara SC 40% ACTM 30%). The incidence of serious adverse events (SAEs) was higher in the Dara SC arm compared to the ACTM arm (Dara SC 29%, ACTM 19%). Dose discontinuations due to TEAEs were reported in 6% and dose modifications due to TEAEs were reported in 47% of the Dara SC arm. TEAEs of musculoskeletal pain, upper respiratory infection (URI), fatigue, diarrhea, nasopharyngitis, rash, sleep disorder, and sensory neuropathy were higher (≥10% difference) in the Dara SC arm compared to the ACTM arm. The rate of infections was two times higher (80%) on the Dara SC arm compared with 45% in the ACTM arm.

The PROs in the AQUILA trial were sparsely collected, insufficient to demonstrate tolerability, and may have been inappropriate for the trial population, hence the impact of the Dara SC side effects cannot be adequately assessed.

9 Benefit-risk conclusions

Benefit-risk assessment is an integral part of the FDA's review of a drug. It is an informed judgment as to whether the benefits of the drug outweigh the risks with their respective uncertainties. To make an informed decision, the disease condition, therapeutic context, evidence, and uncertainties are all taken into consideration.

For the current application there are several important points to consider.

Smoldering multiple myeloma, including high-risk SMM, is a precursor condition. Patients do not have symptoms from their disease and do not have end organ damage that is commonly associated with MM. As the risk of progression to MM varies, accurate identification of the appropriate target population is important to maximize the benefits of early intervention.

The Applicant is seeking an indication for Dara SC for the treatment of adult patients with high-risk SMM. However, less than half the participants enrolled on the trial would be considered

high-risk based on the current criteria. The AQUILA trial participants may not be reflective of the patient population for whom the drug is intended. This limits the generalizability of the trial results to current intended use population with high- risk SMM.

The endpoints used in the trial are an important aspect of determining benefit. While the magnitude of effect is important, the endpoints should measure outcomes that are clinically meaningful to the patients with the condition. A PFS benefit was observed in the Dara SC arm compared to the ACTM arm. However, there is uncertainty regarding the clinical meaningfulness of the PFS endpoint as the majority of PFS events were progression to the SLiM criteria (laboratory or imaging parameters, which were included in the definition of multiple myeloma after 2014) or asymptomatic changes in hemoglobin or on bone imaging. Clinical events relevant to MM such as fatigue and infections were higher in the Dara SC arm and there was no difference in the rate of serious clinical fractures between the two arms. The available evidence also does not demonstrate a meaningful impact on delaying the initiation of second line MM therapy (PFS2) which raises uncertainties regarding the clinical relevance of the observed PFS improvement and benefit of the treatment. Additionally, while there is no evidence of harm, given the limitations noted with the PFS endpoint and the PFS2 endpoint, the lack of robust OS results raises additional uncertainties regarding the benefit of the therapy. Notably, the limitations noted with the AQUILA trial population and the endpoints are similar to the limitations noted with the prior QuiREDEX and the ECOG E3A06 trials (Section 3.1.2)

The participants with high-risk SMM received treatment for 3 years. The toxicities observed, including higher rates of dose modification, drug discontinuation, infection, cytopenia, symptomatic side effects including URI, fatigue, and diarrhea, are concerning in the context of the noted limitations in the benefit of the therapy for patients with SMM.

Overall, the limitations of the endpoints to inform benefit and the noted safety concerns observed in the SMM patient population in the AQUILA trial raise uncertainties regarding a benefit-risk assessment for Dara SC for patients with high-risk SMM.

10 Draft Topics for Discussion

1. Discuss applicability of trial results to the high-risk SMM patient population.
2. Discuss the clinical meaningfulness of the efficacy endpoints assessed in the AQUILA trial.
3. Discuss the overall benefit-risk of Dara SC for the intended high-risk SMM population in context of the results from the AQUILA trial.

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12 Appendices

12.1 2014 IMWG Criteria for diagnosis of multiple myeloma

Panel
Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma

Definition of multiple myeloma

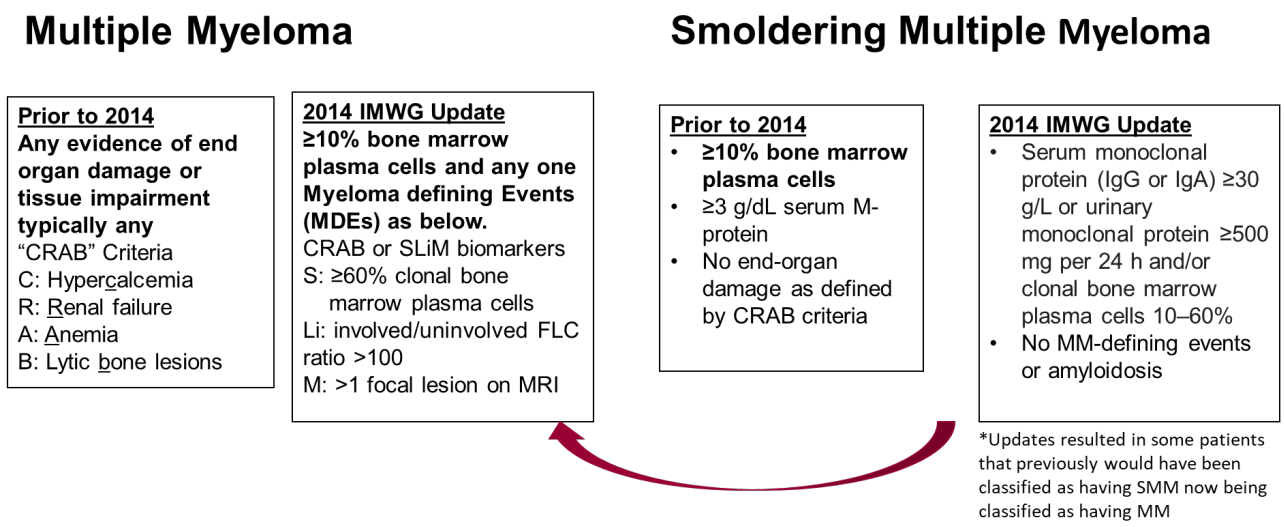
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
  - Hypercalcaemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40 mL per min† or serum creatinine >177 μmol/L (>2 mg/dL)
  - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT‡
- Any one or more of the following biomarkers of malignancy:
  - Clonal bone marrow plasma cell percentage* ≥60%
  - Involved:uninvolved serum free light chain ratio§ ≥100
  - >1 focal lesions on MRI studies¶

Source: Rajkumar S.V. ET AL. Lancet Oncol 2014

12.2 Revisions to MM and SMM Definitions

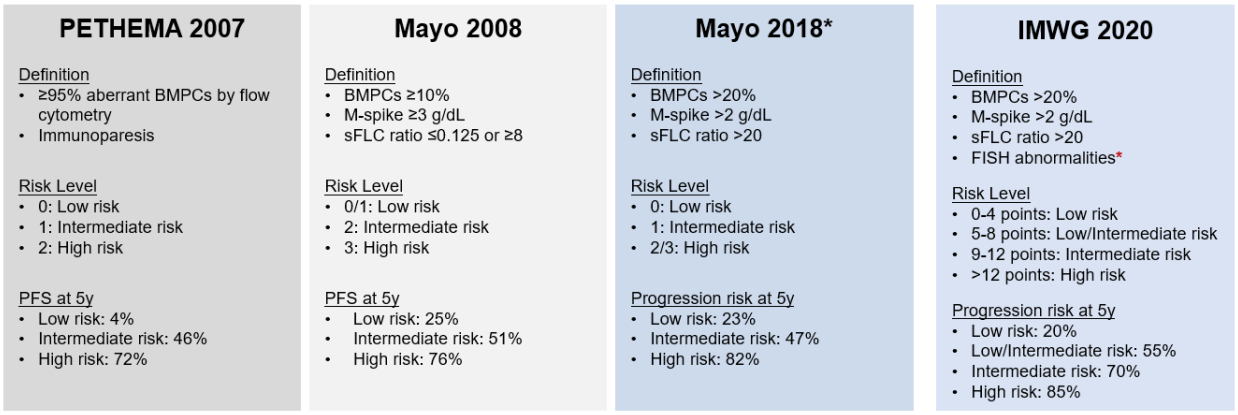
Figure 12 Definitions for SMM and MM



Source: FDA Adapted from Kyle RA et al Oncology 2011 (20)

12.3 SMM risk stratification models

Figure 13 Risk Stratification Models



(2) (5) (11) (21)

12.4 Treatment Options for Patients with MM

Table 20 MM Treatments

Approved Therapies and Combinations	
Newly Diagnosed Transplant Eligible	**D-VTd, D-VRd,** Rd, Td, VMP
Newly Diagnosed Transplant Ineligible	**DRd, D-VMP**, Isa- VRd, Rd, Td, VMP
Relapsed or Refractory MM	**DRd,** KRd, IRd, ERd, Vd, SVd, **DVd** EPd, IsaPd, **DPd, DKd,** IsaKd, Rd, Kd, Pd, V, **Daratumumab**, Cilta-cel, Ide-cel Teclistamab, Elranatamab, Talquetamab.

Proteasome Inhibitors V: Velcade (bortezomib); K: Kyprolis (carfilzomib), I: Ixazomib. Immunomodulatory Agents T: Thalidomide, R-Revlimid (lenalidomide), P-Pomalidomide. CD38 monoclonal antibodies Isa: Isatuximab, D: Daratumumab. SLAMF 7 antibody E: Elotuzumab. XPO1 inhibitor S: Selinexor. Chimeric T cell antigen cilta-cel: Ciltacabtagene autoleucel, Ide-cel: idecabtagene vicleucel. Bi-specifics Talquetamab, teclistamab and elranatamab. Other MP- Melphalan and prednisone, d-Dexamethasone. MM: Multiple Myeloma. ASCT: Autologous stem Cell Transplantation.

12.5 Protocol Eligibility Criteria (Protocol Version 14 January 2021)

Key Inclusion Criteria

1. ECOG performance status score of 0 or 1.
2. Pretreatment clinical laboratory values meet the following criteria during the Screening Phase:
    a) Absolute neutrophil count ≥1.0 x 109/L (ie, ≥1000/µL)
    b) Platelet count ≥50 x 109/L (not permissible to transfuse a subject within 2 weeks
    c) prior to the Screening platelet count to reach this level)
    d) Aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN)

Key Exclusion Criteria

1. Multiple myeloma, requiring treatment, defined by any of the following:
    a) Bone lesions (one or more osteolytic lesions on low-dose whole body computed tomography [LDCT], positron-emission tomography with computed tomography [PET-CT] or CT). Subjects who have benign/post-traumatic bone lesions visible on screening images as well as previous imaging, may be considered for inclusion. Details (diagnosis, location, duration) on benign/post-traumatic preexisting bone lesions that can

be seen on the screening images (e.g., old fractures) and were also present on previous imaging are to be reported in the CRF.

b) Hypercalcemia (serum calcium >0.25 mmol/L [>1 mg/dL] higher than ULN or >2.75 mmol/L [>11 mg/dL]). Subjects who have clinically stable hypercalcemia attributable to a disease other than multiple myeloma (ego, hyperparathyroidism) may be considered for inclusion after a case by case review by the medical monitor

c) Renal insufficiency, preferably determined by creatinine clearance <40 mL/min measured or estimated using the MDRD, or serum creatinine >177 μ mol/L. Subjects who have clinically stable renal insufficiency attributable to a disease other than multiple myeloma (eg, glomerulonephritis) may be considered for inclusion after a case by case review by the medical monitor

d) Anemia, defined as hemoglobin <10 g/dL or >2 g/dL below lower limit of normal or both; transfusion support or concurrent treatment with erythropoietin stimulating agents is not permitted. Subjects who have clinically stable anemia attributable to a disease other than multiple myeloma (e.g., thalassemia, vitamin B12 deficiency, iron deficiency) may be considered for inclusion after a case by case review by the medical monitor.

e) Clonal BMPC percentage ≥60%
f) Serum FLC ratio (involved: uninvolved) ≥100 (The involved FLC must be
g) ≥100 mg/L)
h) More than 1 focal lesion ≥5 mm in diameter by MRI.

2. Primary systemic AL (immunoglobulin light chain) amyloidosis.

12.6 Phase 2 Trial SMM2001 (CENTAURUS)

Table *21* CENTAURUS Dosing Regimens

Weeks	**Frequency**		
	Long-intense 16 mg/kg IV	**Intermediate** 16 mg/kg IV	**Short-intense** 16 mg/kg IV
Weeks 1 to 8	Weekly	Weekly	Weekly
Weeks 9 to 24	Every 2 weeks	Every 8 weeks	No dose
Week 25 to 56	Every 4 weeks		
Weeks 57 +	Every 8 weeks		

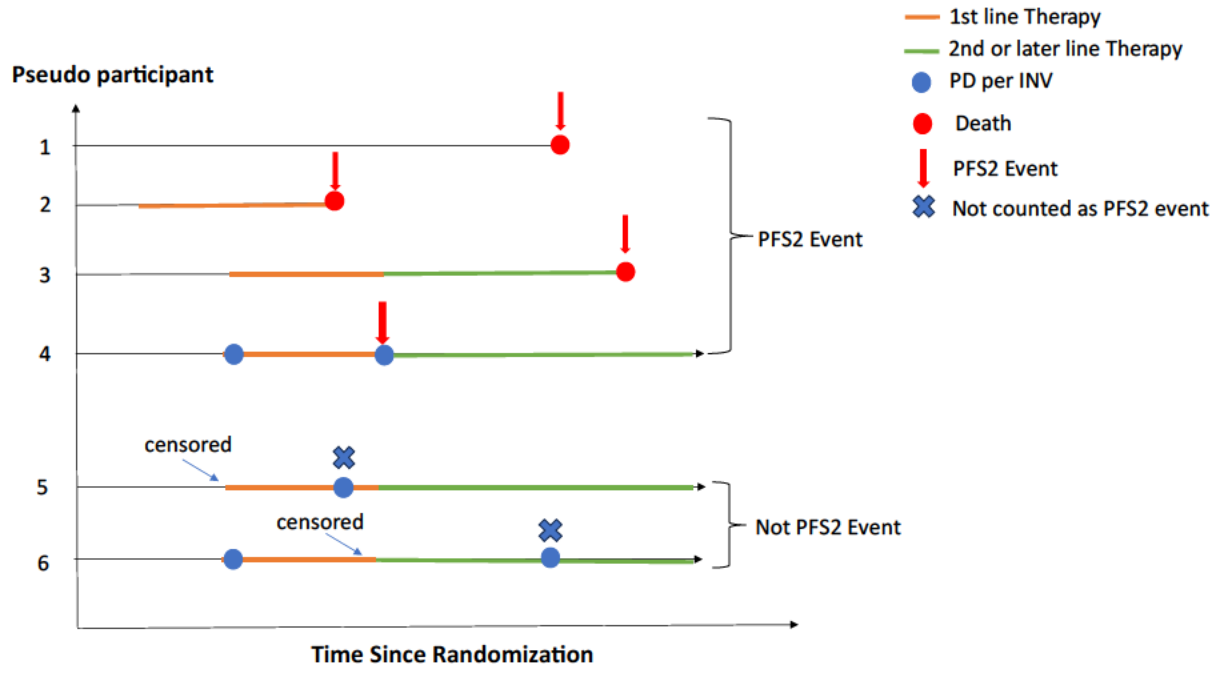
Source: FDA Review adapted from Phase 2 CENTAURUS protocol

12.7 Graphical Illustration of PFS2 Event

A participant is considered to have a PFS2 event if they meet either of the following criteria, whichever occurs first: 1) the participant experiences disease progression per investigator assessment while on study treatment, followed by progression per investigator assessment on first line of subsequent therapy; 2) the participant dies. Below is a graphical illustration using pseudo-participants to clarify how PFS2 events are defined.

- Participant 1, 2, 3 have PFS2 events due to death. Because all deaths count as PFS2 events, regardless of whether the death occurs prior to the initiation of first line therapy, on first-line therapy, or on later-line therapy.
- Participant 4 has a PFS2 event because the participant has an PD assessed by investigator (INV-PD) on study treatment, initiated a first-line therapy, and then had another INV-PD while on first line therapy.
- Participant 5 does not have PFS2 event because the participant does not have an INV-PD before initiation of subsequent therapy.
- Participant 6 does not have a PFS2 event because the second PD occurs during second or later line therapy, not on first line therapy.

Figure 14 Graphical Illustration of PFS2 Definition



Source: FDA analysis.

12.8 Summary of Interim and Final Analyses (AQUILA)

Table 22 Summary of Interim and Final Analyses (AQUILA)

Analysis Label	Planned Timing	Analysis Aim	Note
Interim Analysis for Futility (IA)	99 events (60%) PFS events ~ 8 months after the last subject is randomized	PFS Futility	To evaluate cumulative interim safety and efficacy data
Primary Analysis (PA) CCO: May 1, 2024 mF/U= 65.2 months	165 events (100%) PFS events ~ 2 years after the last subject is randomized	PFS per IRC	Planned 165 events (100%) Actual 166 events (100%)
		ORR per computerized algorithm	NA
		PFS2 per INV	Planned 81 events (60%) Actual 63 events (51%)
		OS	Planned 64 events (60%) Actual 41 events (38%)
Final Analysis (FA)	End of the study	PFS2 per INV	Planned 134 events (100%)
		OS	Planned 107 events (100%)

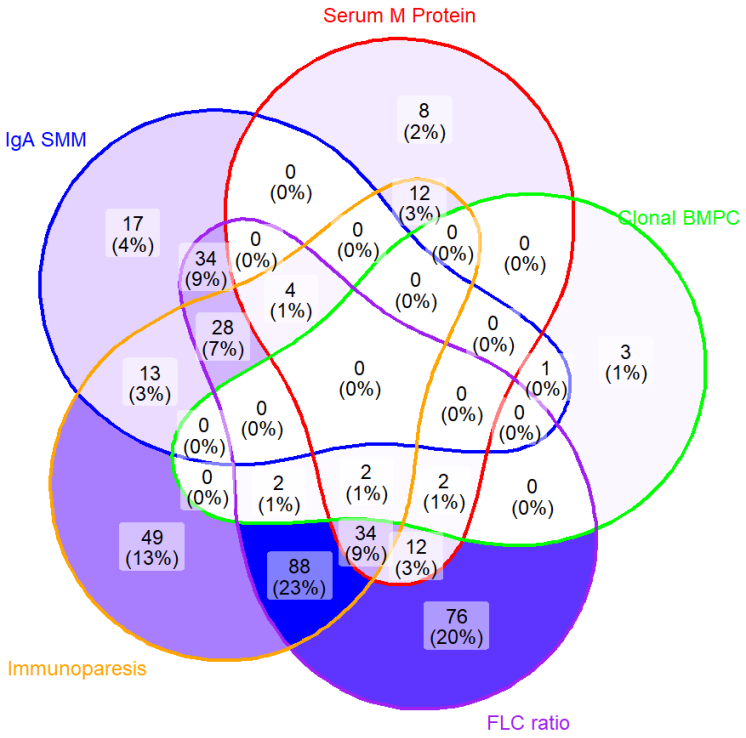
Source: FDA review adapted from AQUILA Statistical Analysis Plan. Percentages represents information fractions. CCO = clinical cutoff date; INV = investigator. IRC = independent review committee. mF/U = median follow up.

Multiplicity Control

The primary hypothesis for PFS was tested at a two-sided significance level of 0.05. Given that the PFS result was statistically significant at primary analysis cutoff, the key secondary endpoints—ORR, PFS2, and OS—were planned to be tested sequentially using a hierarchical testing approach, each with an overall two-sided alpha of 0.05. The ORR was planned to be tested only at the PA cut with a two-sided significance level of 0.05. For PFS2, and OS, alpha spending at the primary analysis and the final analysis time points was determined by a linear alpha spending function based on the observed number of the events at each time. The allocated alpha for PFS2 at the PA cutoff was 0.0235 (2-sided). Of note, since PFS2 did not reach statistical significance at PA, OS was not tested at the PA cutoff. During the pre-sBLA meeting in September 2024, the FDA raised concerns about considering PFS2 as an acceptable endpoint for regulatory approval. In response to this feedback, the Applicant followed the Agency's advice and excluded PFS2 from the hierarchical testing at the final analysis. OS was planned to be tested at the final analysis.

12.9 AQUILA Trial Population High Risk Criteria

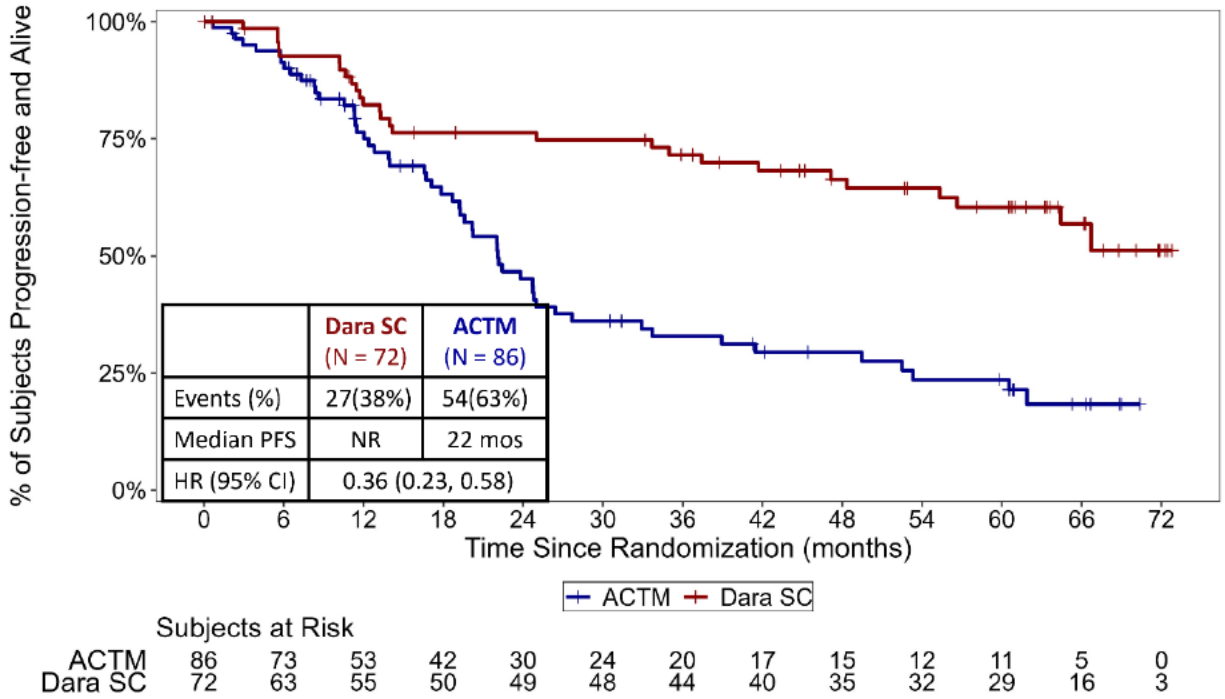
Figure 15 Venn Diagram of AQUILA Study Protocol-Defined Risk Factors.



Source: FDA analysis based on baseline values. Serum M Protein refers to serum M protein ≥30 g/L. IgA SMM denotes IgA smoldering multiple myeloma. Immunoparesis is defined as a reduction of two uninvolved immunoglobulin isotypes. FLC Ratio refers to a serum involved: uninvolved free light chain ratio of ≥8 and <100. Clonal BMPC denotes clonal bone marrow plasma cells >50% and <60%.

12.10 PFS Mayo 2018 High-Risk Subgroup

Figure 16 Aquila KM Curve PFS Mayo 2018 High-Risk Subgroup



Source: FDA review. Clinical cutoff was May 1, 2024. PFS based on IRC review. CI = confidence interval; HR = hazard ratio; KM = Kaplan Meier; PFS = progression-free survival. IRC = independent review committee.

12.11 Subsequent Therapy

Table 23 Receipt of First Line Subsequent Therapy Based on IRC or INV Assessed PD

	Dara SC N = 194 n (%)	ACTM N = 196 n (%)	Overall N = 390 n (%)
Participants with PD by INV †	68 (35)	112 (57)	180 (46)
Participants did not initiate first-line therapy ǂ	13 (19)	21 (19)	34 (19)
Participants initiated first-line MM therapy ǂ	55 (81)	91 (81)	146 (81)
Participants with PD by IRC †	62 (32)	94 (48)	156 (40)
Participants did not initiate first-line therapy §	14 (23)	19 (20)	33 (21)

Participants initiated first-line MM therapy §	48 (77)	75 (80)	123 (79)

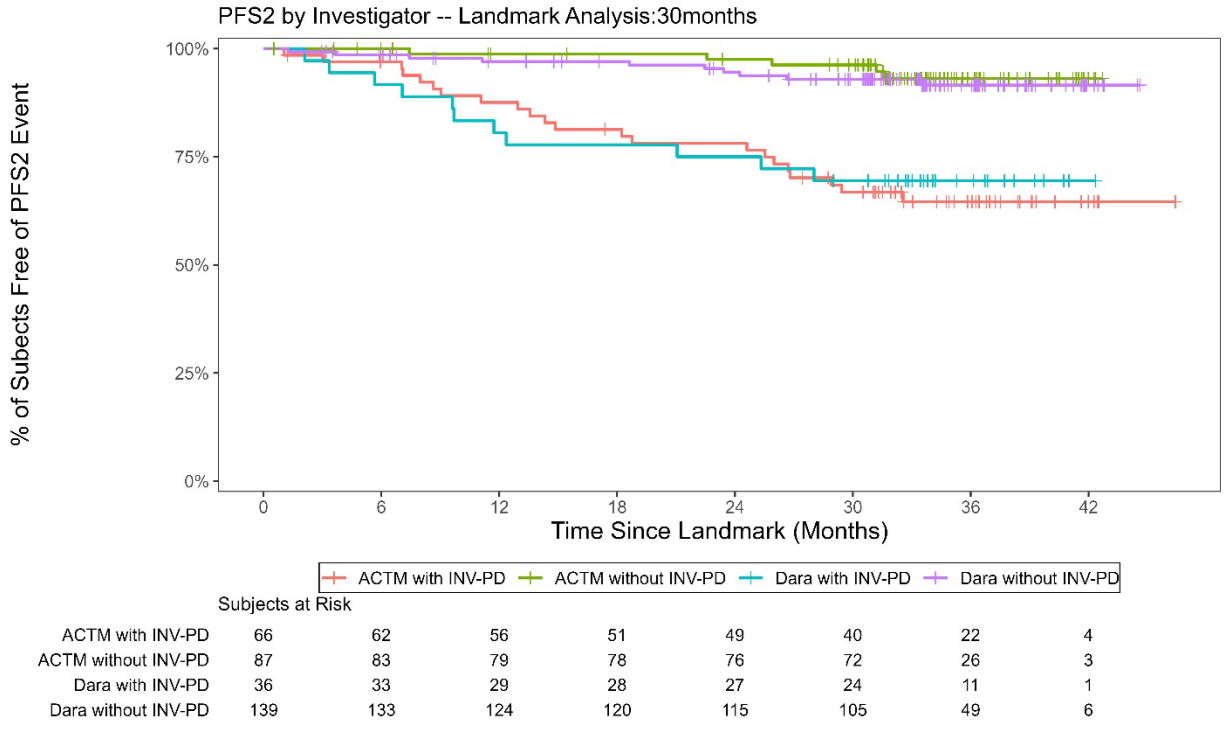
Source: FDA analysis. † Percentages are based on the participants in the ITT analysis set as the denominator. ǂ Percentages are based on participants with PD by INV. § Percentages are based on participants with PD by IRC. INV = investigator; IRC = independent review committee; MM = multiple myeloma; PD = progressive disease.

12.12 PFS2 Landmark Exploratory Analysis

The planned analyses for PFS2 may not be adequate as it does not consider the potential post baseline confounding, e.g. developing PD and subsequent anti MM therapy. So the estimated HR of 0.58 based on the planned analysis may be over-estimated.

We conducted an exploratory landmark analysis using 30 months as the landmark time to account for "guarantee-time bias" (22) and evaluate the treatment effect after considering the PD status prior to the landmark on the randomized treatments. The analysis was restricted to participants who had not experienced a PFS2 event or been censored before the landmark time. As shown in the plot below, among participants with progression by investigator assessment before the landmark time, the two arms show minimal separation (HR =0.91, 95% CI:0.44,1.87). Similarly, for those without progression by investigator assessment before the landmark time the KM curves closely overlapping (HR = 1.32, 95% CI: 0.45,3.85). Similar trend is observed using different landmark time point

Figure 17 Exploratory Landmark Analysis of PFS2 With and Without INV-PD Status



Source: FDA Analysis. Reference: Morgan, C.J., 2019. Landmark analysis: a primer. Journal of Nuclear Cardiology, 26, pp.391-393. ACTM = Active Monitoring; Dara = Dara SC; INV-PD; PD by investigator.

12.13 Conditional probability of harm at final analysis

Table 24 Conditional Probability for Harm

True HR Assumption	Probability (%) (HR at FA > 1 | HR at PA = 0.52)
0.5	< 0.1
0.6	< 0.1
0.7	0.1
0.8	0.5
0.9	2
1.0	5
1.1	10
1.2	18
1.3	28
1.4	39

Source: FDA Analysis. HR at FA denotes the estimated hazard ratio of overall survival at the end of the study. HR at PA denotes the observed hazard ratio of overall survival at primary analysis cutoff.

12.14 Dose Modification Criteria (Source: Protocol Section 6.5.2)

Daratumumab must be held if any of the following criteria are met, to allow for recovery from toxicity, regardless of relationship to study drug:

- Grade 4 hematologic toxicity, except for Grade 4 lymphopenia
- Grade 3 or higher thrombocytopenia
- Febrile neutropenia
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to antiemetic treatment within 7 days
    - Grade 3 vomiting that responds to antiemetic treatment within 7 days
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last
    - administration of daratumumab
    - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

Daratumumab administration should resumed when the toxicity has resolved to Grade 2