

ダラキューロ配合皮下注 に関する資料

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1.5 起原又は発見の経緯及び開発の経緯

1.5.1 全身性 AL アミロイドーシス

全身性免疫グロブリン軽鎖（AL）アミロイドーシスは異常形質細胞より産生されるモノクローナル免疫グロブリン（M 蛋白）の軽鎖（L 鎖）に由来するアミロイド蛋白が多臓器に沈着し、多様な臨床症状を示す、予後不良の疾患である。全身性 AL アミロイドーシスの病態は多発性骨髄腫（MM）と類似しているため、悪性形質細胞を標的とする薬物療法（抗形質細胞療法）が実施されている。海外では、シクロホスファミド水和物、ボルテゾミブ及びデキサメタゾンの併用（CyBorD）療法が全身性 AL アミロイドーシスの標準治療の 1 つとしてガイドラインで推奨され^{1) 2) 3)}、日本でも CyBorD 療法の有用性がガイドライン等で報告されている^{4) 5)}。しかしながら、CyBorD 療法も含めた抗形質細胞療法は、いずれも十分な臨床的エビデンスは得られていないため、国内外で全身性 AL アミロイドーシスの適応を有する治療法は現時点でなく、新規薬剤開発の医療的必要性が高い。そこで、抗形質細胞療法の中で推奨、汎用されている CyBorD 療法にダラツムマブ（遺伝子組換え）（以下ダラツムマブ）を上乗せしたダラツムマブ、シクロホスファミド水和物、ボルテゾミブ及びデキサメタゾン（DCyBorD）療法を全身性 AL アミロイドーシスに対する治療法として開発した。

ダラツムマブは、CD38 を特異的に認識する免疫グロブリン G1 kappa (IgG1κ) 完全ヒト型モノクローナル抗体である。CD38 は MM、リンパ腫、白血病を含む造血器腫瘍において、高い発現を呈し、その他の様々な細胞や組織でも発現が確認されている細胞表面抗原蛋白質である。CD38 は正常組織にも発現するが、MM 細胞と比べ、その発現量ははるかに少ない。非臨床薬理試験の結果、ダラツムマブは MM 細胞を含むヒト細胞で発現している CD38 に特異的に結合し、CD38 を発現する腫瘍細胞の増殖を *in vivo* で強力に阻害することが示された。補体依存性細胞傷害（CDC）及び抗体依存性細胞傷害（ADCC）がダラツムマブの主要な作用機序である。

ダラツムマブ点滴静注製剤は、日本において、「多発性骨髄腫」を効能・効果として承認されている。しかしながら、infusion related reaction のリスクや、長時間の投与による患者及び医療従事者の負担を軽減するため、ダラツムマブとボルヒアルロニダーゼ アルファ（遺伝子組換え）（rHuPH20）を配合したダラツムマブ皮下注製剤の開発に着手し、2020 年 4 月に「多発性骨髄腫」を効能・効果として製造販売承認を申請した。

全身性 AL アミロイドーシスの病態生理は、MM と類似しており、全身性 AL アミロイドーシス患者の骨髄においても CD38 陽性形質細胞のモノクローナルな増殖が報告されている^{6) 7)}。したがって、MM に治療効果が認められるダラツムマブが全身性 AL アミロイドーシスにも治療効果を有すると考え、皮下注製剤での開発に着手した。

シクロホスファミド水和物は、ナイトロジェンマスタード系の抗悪性腫瘍剤で、アルキル化剤に分類され、腫瘍細胞の DNA 合成を阻害し、抗腫瘍作用を示すことが認められている。現在、米国及び欧州を含む約 100 カ国で「悪性リンパ腫」、「多発性骨髄腫」、「進行性自己免疫疾患」等の適応で承認されている。日本では、「多発性骨髄腫」、「悪性リンパ腫」、「乳癌」、「慢性リンパ性白血病」、「慢性骨髄性白血病」、「咽頭癌」、「胃癌」、「膀胱癌」、「肝癌」、

「結腸癌」等の悪性腫瘍，「全身性エリテマトーデス」，「全身性血管炎」等のリウマチ性疾患及びネフローゼ症候群に関する適応が承認されている^{8) 9)}。

ボルテゾミブはユビキチン化によって制御を受ける多数の蛋白がプロテアソームで分解されるのを阻害し，それによって細胞増殖抑制及び抗腫瘍作用を示すプロテアソーム阻害剤である。ボルテゾミブは動物細胞に存在する 26S プロテアソームのキモトリプシン様活性を強力かつ可逆的に阻害することにより，多様ながん細胞に対し *in vitro* で細胞毒性を示し，更に *in vivo* の非臨床腫瘍モデルにおいて MM 等の腫瘍の増殖を抑制する。特に，Nuclear Factor-kappa-B (NF-κB) の活性化阻害，骨髄ストローマ細胞のインターロイキン 6 (IL-6) 産生を抑制することによる細胞増殖の抑制，サイクリン及びサイクリン依存性キナーゼを介する細胞周期の停止，直接的なアポトーシス誘導作用及び血管新生抑制作用等を介し，MM に対し治療効果を発揮する^{10) 11) 12)}。ボルテゾミブは腫瘍細胞の細胞内シグナル伝達経路に作用するだけでなく，MM の病態に重要な腫瘍微小環境に対しても作用する。現在，米国及び欧州を含む約 110 の国と地域で「多発性骨髄腫」及び「マントル細胞リンパ腫」に関する適応で承認されており，日本では，「多発性骨髄腫」，「マントル細胞リンパ腫」及び「原発性マクログロブリン血症及びリンパ形質細胞リンパ腫」の適応が承認されている¹³⁾。

デキサメタゾン は，合成糖質コルチコステロイドであり，抗炎症作用，抗アレルギー作用，免疫抑制作用等の作用がある。世界中で内分泌疾患，リウマチ性疾患，膠原病，皮膚疾患，アレルギー性疾患，悪性腫瘍性疾患等に関連する適応で承認されている。日本では，「慢性副腎皮質機能不全」や「急性副腎皮質機能不全」等の内分泌疾患，「関節リウマチ」等のリウマチ性疾患，「エリテマトーデス」等の膠原病，「気管支喘息」，「喘息性気管支炎」等のアレルギー性疾患，「悪性リンパ腫（リンパ肉腫症，細網肉腫症，ホジキン病，皮膚細網症，菌状息肉症）」，「乳癌の再発転移」等の悪性腫瘍，「多発性骨髄腫」に対する他の抗悪性腫瘍剤との併用療法，抗悪性腫瘍剤（シスプラチン等）投与に伴う消化器症状（悪心・嘔吐）等，様々な疾患領域の適応で承認されている^{14) 15)}。

未治療の全身性 AL アミロイドーシス患者を対象とした 54767414AMY3001 試験（以下 AMY3001 試験）において，主要評価項目の complete response (CR) 率で統計学的に有意な改善が認められ，CyBorD 療法に対するダラツムマブの上乗せ効果が検証された。感度分析，補足的解析，部分集団解析，及び主な副次評価項目である主要な臓器機能低下－無増悪生存期間 (MOD-PFS) の結果からも DCyBorD 療法の有効性が確認された。日本人集団でも，主要評価項目である CR 率で全体集団との一貫性が示され，主な副次評価項目である MOD-PFS も全体集団と同様の結果であり，日本人患者でも有効性が期待できると考えられた。

DCyBorD 療法の安全性については，原疾患である全身性 AL アミロイドーシスの合併症を考慮するとダラツムマブ，ボルテゾミブ，シクロホスファミド水和物及びデキサメタゾンの既知の安全性プロファイルと比較したときと大きな差はないと考えられた。また，DCyBorD 療法の安全性プロファイルに日本人集団と全体集団で明らかな違いはないと考えられた。

このように AMY3001 試験では，DCyBorD 療法の良好なベネフィット・リスクプロファイルが全体集団及び日本人集団のいずれでも認められた。

海外のガイドラインでは、再発した全身性 AL アミロイドーシス患者に対しては、初回治療レジメンでの再治療、又はこれまでに投与していない代替併用レジメンでの治療が選択肢となるため^{1) 2) 3)}、未治療の全身性 AL アミロイドーシス患者で有効性が検証された治療レジメンは、再発した全身性 AL アミロイドーシス患者での治療選択肢の 1 つとなると考える。

以上より、ダラツムマブ皮下注製剤、ボルテゾミブ、シクロホスファミド水和物及びデキサメタゾンの各薬剤で、効能・効果に全身性 AL アミロイドーシスを追加することを目的とした製造販売承認申請を行うこととした。なお、ダラツムマブ皮下注製剤は、ボルテゾミブ、シクロホスファミド水和物及びデキサメタゾンの併用療法で、米国及び欧州でも 2020 年 9 月及び 11 月に AMY3001 試験成績を基に製造販売承認申請を行った。

起原又は発見の経緯及び開発の経緯については、平成 13 年 6 月 21 日付医薬審発第 899 号厚生労働省医薬局審査管理課長通知「新医薬品の製造又は輸入の承認申請に際し承認申請書に添付すべき資料の作成要領について」の別紙 2 の 5 (1) 項の記述をもとに、当該内容を主に第 2 部 (5) に記載した (表 1.5-1)。また、本申請に関する臨床試験の開発経緯を表 1.5-2 に示す。

表 1.5-1 CTD1.5 項の内容の記載場所

CTD 1.5 項の内容	CTD 第 2 部の記載場所
起原又は発見の経緯	2.5.1 製品開発の根拠
全身性 AL アミロイドーシスの病態及び疫学	2.5.1.2.1 全身性 AL アミロイドーシス
全身性 AL アミロイドーシスの治療	2.5.1.2.2 全身性 AL アミロイドーシスの治療法
開発の経緯	2.5.1.3 臨床開発経緯
申請効能・効果に対する有用性	2.5.6 ベネフィットとリスクに関する結論

表 1.5-2 臨床試験の開発経緯

相	実施地域	対象	試験番号等	実施時期
III	国際共同	未治療の全身性 AL アミロイドーシス患者	54767414AMY3001 (評価資料)	2017 年 10 月～継続中
Ib	海外	PI 及び IMiD を含む前治療を 2 ライン以上受けたことがある再発又は難治性の MM 患者	54767414MMY1004 ^a (参考資料)	2015 年 10 月～継続中
I	国内	PI 及び IMiD を含む前治療を 2 ライン以上受けたことがある再発又は難治性の日本人 MM 患者	54767414MMY1008 (参考資料)	2017 年 8 月～継続中

IMiD：免疫調節薬，PI：プロテアソーム阻害剤

a MMY1004 試験では Part 1, Part 2 及び Part 3 を設定したが、本申請までに結果が得られていない Part 3 については省略した。

参考文献

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- 2) Wechalekar AD, Gillmore JD, Bird J, et al. Guidelines on the management of AL amyloidosis. Br J Haematol. 2015;168:186-206.
- 3) The Risk Adapted Approach to Management of Multiple Myeloma and Related Disorders [homepage on the Internet]. Mayo clinic; [update 2019 August]. Treatment Guidelines: Amyloidosis. Available from: <https://static1.squarespace.com/static/5b44f08ac258b493a25098a3/t/5d7fd7bd27708631a437368f/156865939>
- 4) 造血器腫瘍診療ガイドライン 2018 年補改訂 [2020 年 4 月] 一般社団法人 日本血液学会
- 5) Kikukawa Y, Yuki H, Hirata S, et al. Combined use of bortezomib, cyclophosphamide, and dexamethasone induces favorable hematological and organ responses in Japanese patients with amyloid light-chain amyloidosis: a single-institution retrospective study. Int J Hematol. 2015;101(2):133-9.
- 6) Matsuda M, Gono T, Shimojima Y, et al. Phenotypic analysis of plasma cells in bone marrow using flow cytometry in AL amyloidosis. Amyloid. 2003 Jun;10(2):110-6.
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- 8) 注射用シクロホスファミド水和物 注射用エンドキサン®100 mg/注射用エンドキサン®500mg インタビューフォーム 2013 年 4 月改訂 第 8 版
- 9) シクロホスファミド錠 エンドキサン®錠 50 mg/シクロホスファミド水和物散 経口用エンドキサン®原末 100 mg インタビューフォーム 2015 年 12 月改訂 第 16 版
- 10) Hideshima T, Richardson P, Chauhan D, et al. The proteasome inhibitor PS-341 inhibits growth, induces apoptosis, and overcomes drug resistance in human multiple myeloma cells. Cancer Res. 2001 Apr 1;61(7):3071-6.
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- 12) Sherr CJ. Cancer cell cycles. Science. 1996 Dec 6;274 (5293):1672-7.
- 13) ベルケイド®注射用 3 mg インタビューフォーム 2019 年 8 月 第 12 版
- 14) 副腎皮質ホルモン製剤 デカドロン®錠 0.5 mg/デカドロン®錠 4 mg/デカドロン®エリキシル 0.01% インタビューフォーム 2020 年 8 月改訂 第 13 版

- 15) 副腎皮質ホルモン製剤 デカドロン[®]注射液 1.65 mg/デカドロン[®]注射液 3.3 mg/デカドロン[®]注射液 6.6 mg インタビューフォーム 2020年8月改訂 第14版

1.6 外国における使用状況等に関する資料

ダラツムマブ（遺伝子組換え）（以下本剤）は、2021年6月現在、静脈内投与製剤として多発性骨髄腫に対する適応にて、米国及び欧州を含む世界 60 以上の国と地域で承認されている。皮下注射製剤の最新の承認国及び地域の一覧を表 1.6-1、全身性 AL アミロイドーシスに係る最新の承認状況を表 1.6-2 に示す。

皮下注射製剤としては 2020 年 5 月に米国において、2020 年 6 月に欧州において、4 試験（MMY3012 試験、MMY2040 試験、MMY1004 試験、MMY1008 試験）の成績に基づき、静脈内投与製剤と同様の適応及び用法で承認されている。また、AMY3001 試験の成績に基づき「AL アミロイドーシス」の適応で米国においては 2021 年 1 月に承認取得し、欧州においては 2020 年 11 月に承認申請した。

米国の承認状況は表 1.6-3、欧州の承認状況は表 1.6-4 に示す。

外国の添付文書として、米国及び欧州の添付文書、並びに企業中核データシート（CCDS）を添付する。

表 1.6-1 皮下注製剤の海外承認国及び地域一覧

国	承認日
United States	2020 年 5 月 1 日
European Union / EEA (31 countries)	2020 年 6 月 3 日
Canada	2020 年 7 月 30 日
Korea	2020 年 6 月 29 日
Switzerland	2020 年 8 月 13 日
Israel	2021 年 4 月 18 日
Brazil	2020 年 8 月 24 日
Australia	2020 年 9 月 8 日
Singapore	2020 年 10 月 27 日
Taiwan	2020 年 9 月 25 日
Qatar	2021 年 4 月 7 日

表 1.6-2 全身性 AL アミロイドーシスの海外承認国及び地域一覧

国	承認日
United States	2021 年 1 月 15 日
Canada	2021 年 4 月 12 日
Switzerland	2021 年 4 月 14 日
Brazil	2020 年 11 月 30 日

表 1.6-3 米国のダラツムマブ皮下注製剤承認状況

販売名	DARZALEX FASPRO 皮下注射剤
承認時期	<ul style="list-style-type: none"> 2020年5月
剤形・含量	<ul style="list-style-type: none"> 15mL バイアル中, ダラツムマブ 1,800mg 及びボルヒアルロニダーゼアルファ 30,000 単位含有
効能・効果	<p><多発性骨髄腫></p> <p>併用療法</p> <ul style="list-style-type: none"> 自家造血幹細胞移植非適応な未治療の多発性骨髄腫患者に対する本剤, ボルテゾミブ, メルファラン及びプレドニゾンとの併用療法 自家造血幹細胞移植非適応な未治療の多発性骨髄腫患者及び少なくとも1レジメン以上の前治療歴を有する再発又は難治性の多発性骨髄腫患者に対する本剤, レナリドミド及びデキサメサゾンとの併用療法 自家造血幹細胞移植適応な未治療の多発性骨髄腫患者に対する本剤, ボルテゾミブ, サリドマイド及びデキサメサゾンとの併用療法 少なくとも1レジメン以上の前治療歴を有する多発性骨髄腫患者に対する本剤, ボルテゾミブ及びデキサメタゾンとの併用療法 <p>単剤療法</p> <ul style="list-style-type: none"> プロテアソーム阻害剤及び免疫調節薬を含む3レジメン以上の前治療歴を有する, 又はプロテアソーム阻害剤及び免疫調節薬の両剤に難治性の多発性骨髄腫患者に対する治療 <p><ALアミロイドーシス></p> <ul style="list-style-type: none"> 未治療のALアミロイドーシス患者に対する本剤, ボルテゾミブ, シクロフォスファミド及びデキサメタゾンとの併用療法。この適応症は奏効率に基づく迅速承認である。検証的試験で臨床的ベネフィットが検証され, 説明されることを条件に, 本適応の承認を継続することが出来る。 <p>【使用制限】</p> <p>NYHA 心機能分類クラス IIIB もしくはクラス IV の心疾患, 又は Mayo 病期 IIIB の ALアミロイドーシスを有する患者の治療には, 臨床試験にて確認されていないため DARZALEX FASPRO は適応とならず推奨されない。</p>
用法・用量	<p><重要な投与情報></p> <ul style="list-style-type: none"> DARZALEX FASPRO は皮下投与のみとすること。 DARZALEX FASPRO の投与前後に以下の薬剤を投与すること, 投与に伴う反応を最小限にすること。 DARZALEX FASPRO の投与開始前に患者のタイプを入力し, スクリーニングを行うこと。 <p><多発性骨髄腫における推奨用量及びスケジュール></p>

販売名	DARZALEX FASPRO 皮下注射剤																
	<p>DARZALEX FASPRO の推奨用量は 1,800 mg/30,000 単位（ダラツムマブ 1,800 mg とヒアルロニダーゼ 30,000 単位）で、約 3~5 分かけて皮下投与する。</p> <p>DARZALEX FASPRO を単剤療法又は併用療法として投与する場合の推奨投与スケジュールを表 1,2 及び 3 に示す。</p> <p><u>単剤療法及びレナリドミド及びデキサメタゾンとの併用療法(D-Rd)</u></p> <p>DARZALEX FASPRO を投与する場合は表 1 に記載された投与スケジュールを使用すること。</p> <p>レナリドミド及びデキサメタゾンとの併用（4 週間サイクル）又は単剤療法</p> <p>表 1：レナリドミド及びデキサメタゾンとの併用投与及び単剤療法の投与スケジュール（4 週間サイクル）</p> <table border="1" data-bbox="440 813 1323 1010"> <thead> <tr> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>1~8 週</td> <td>毎週（計 8 回投与）</td> </tr> <tr> <td>9~24 週^a</td> <td>2 週間隔（計 8 回投与）</td> </tr> <tr> <td>25 週以降，疾患進行まで^b</td> <td>4 週間隔</td> </tr> </tbody> </table> <p>a. 2 週間隔投与スケジュールの初回投与は 9 週目</p> <p>b. 4 週間隔投与スケジュールの初回投与は 25 週目</p> <p>DARZALEX FASPRO を併用療法の一部として投与する場合，臨床成績の項及び他剤の推奨用法・用量は添付文書を参照すること。</p> <p><u>ボルテゾミブ，メルファラン及びプレドニゾンとの併用療法（D-VMP）</u></p> <p>DARZALEX FASPRO をボルテゾミブ，メルファラン及びプレドニゾンと併用投与する場合は，表 2 に示す投与スケジュールに従うこと（6 週間サイクル）。</p> <p>表 2：ボルテゾミブ，メルファラン及びプレドニゾンとの併用投与スケジュール（6 週間サイクル）</p> <table border="1" data-bbox="450 1536 1313 1733"> <thead> <tr> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>1~6 週</td> <td>毎週（計 6 回投与）</td> </tr> <tr> <td>7~54 週^a</td> <td>3 週間隔（計 16 回投与）</td> </tr> <tr> <td>55 週以降，疾患進行まで^b</td> <td>4 週間隔</td> </tr> </tbody> </table> <p>a. 3 週間隔投与スケジュールの初回投与は 7 週目</p> <p>b. 4 週間隔投与スケジュールの初回投与は 55 週目</p> <p>DARZALEX FASPRO を併用療法の一部として投与する場合，臨床成績の項及び他剤の推奨用法・用量は添付文書を参照すること。</p> <p><u>ボルテゾミブ，サリドマイド及びデキサメタゾンとの併用療法（D-VTd）</u></p>	週	スケジュール	1~8 週	毎週（計 8 回投与）	9~24 週 ^a	2 週間隔（計 8 回投与）	25 週以降，疾患進行まで ^b	4 週間隔	週	スケジュール	1~6 週	毎週（計 6 回投与）	7~54 週 ^a	3 週間隔（計 16 回投与）	55 週以降，疾患進行まで ^b	4 週間隔
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販売名	DARZALEX FASPRO 皮下注射剤																							
	<p>DARZALEX FASPRO をボルテゾミブ、サリドマイド及びデキサメタゾンと併用投与する場合は、表 3 の投与スケジュールに従うこと（4 週間サイクル）。</p> <p>表 3：ボルテゾミブ、サリドマイド及びデキサメタゾンとの併用投与スケジュール（4 週間サイクル）</p> <table border="1" data-bbox="375 477 1386 723"> <thead> <tr> <th>治療期</th> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>導入療法</td> <td>1～8 週</td> <td>毎週（計 8 回投与）</td> </tr> <tr> <td>導入療法</td> <td>9～16 週^a</td> <td>隔週（計 4 回投与）</td> </tr> <tr> <td colspan="3">大量化学療法及び自家造血幹細胞移植のため投与中止する</td> </tr> <tr> <td>地固め療法</td> <td>1～8 週^b</td> <td>隔週（計 4 回投与）</td> </tr> </tbody> </table> <p>a. 隔週投与スケジュールでの初回投与は 9 週目 b. 隔週投与スケジュールでの再開は自家造血幹細胞移植後 1 週目</p> <p>DARZALEX FASPRO を併用療法の一部として投与する場合は、他剤の推奨用法・用量は添付文書を参照すること。</p> <p><u>ボルテゾミブ及びデキサメタゾンとの併用療法 (D-Vd)</u></p> <p>DARZALEX FASPRO をボルテゾミブ及びデキサメタゾンと併用投与する場合は、表 4 の投与スケジュールに従うこと（3 週間サイクル）。</p> <p>表 4：ボルテゾミブ及びデキサメタゾンとの併用投与スケジュール（3 週間サイクル）</p> <table border="1" data-bbox="456 1249 1305 1447"> <thead> <tr> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>1～9 週</td> <td>毎週（計 9 回投与）</td> </tr> <tr> <td>10～24 週^a</td> <td>3 週間隔（計 5 回投与）</td> </tr> <tr> <td>25 週以降，疾患進行まで^b</td> <td>4 週間隔</td> </tr> </tbody> </table> <p>a. 3 週間隔投与スケジュールの初回投与は 10 週目 b. 4 週間隔投与スケジュールの初回投与は 25 週目</p> <p>DARZALEX FASPRO を併用療法の一部として投与する場合は、他剤の推奨用法・用量は添付文書を参照すること。</p> <p><AL アミロイドーシスにおける推奨用量及びスケジュール></p> <p><u>ボルテゾミブ、シクロフォスファミド及びデキサメタゾンとの併用療法 (D-VCd)</u></p> <p>DARZALEX FASPRO をボルテゾミブ、シクロフォスファミド及びデキサメタゾンと併用投与する場合は、表 5 の投与スケジュールに従うこと（4 週間サイクル）。</p>	治療期	週	スケジュール	導入療法	1～8 週	毎週（計 8 回投与）	導入療法	9～16 週 ^a	隔週（計 4 回投与）	大量化学療法及び自家造血幹細胞移植のため投与中止する			地固め療法	1～8 週 ^b	隔週（計 4 回投与）	週	スケジュール	1～9 週	毎週（計 9 回投与）	10～24 週 ^a	3 週間隔（計 5 回投与）	25 週以降，疾患進行まで ^b	4 週間隔
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	<p>表 5 : ボルテゾミブ, シクロフォスファミド及びデキサメタゾンとの併用投与スケジュール (4 週間サイクル)</p> <table border="1" data-bbox="456 333 1307 580"> <thead> <tr> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>1~8 週</td> <td>毎週 (計 8 回投与)</td> </tr> <tr> <td>9~24 週^a</td> <td>隔週間隔 (計 8 回投与)</td> </tr> <tr> <td>25 週以降, 疾患進行又は最長 2 年間まで^b</td> <td>4 週間隔</td> </tr> </tbody> </table> <p>a. 隔週間隔投与スケジュールの初回投与は 9 週目 b. 4 週間隔投与スケジュールの初回投与は 25 週目</p> <p>DARZALEX FASPRO を併用療法の一部として投与する場合, 他剤の推奨用法・用量は添付文書を参照すること。</p> <p><DARZALEX FASPRO を投与できなかった場合> 予定どおり DARZALEX FASPRO を投与できなかった場合は, できる限り早くその投与を行い, 投与スケジュールを適宜調整して投与間隔を維持すること。</p> <p><推奨併用薬> 前投薬 DARZALEX FASPRO の各投与 1~3 時間前に以下の前投薬を行うこと。 ・アセトアミノフェン 650~1,000mg 経口投与 ・ジフェンヒドラミン 25~50mg (又は同等品) の経口または静脈内投与 ・コルチコステロイド (長時間又は中時間作用型)</p> <p>単剤療法 メチルプレドニゾロン 100 mg (又は同等品) を経口又は静脈内投与する。2 回目の投与後は, メチルプレドニゾロン 60 mg (又は同等品) に減量することを検討すること。</p> <p>併用療法 DARZALEX FASPRO の毎回の投与前にデキサメタゾン 20 mg (又は同等品) を経口又は静脈内投与すること。 デキサメタゾンが併用療法に特異的なコルチコステロイドである場合, 併用療法の一部であるデキサメタゾンの用量を DARZALEX FASPRO 投与日の前投薬として使用すること。 患者が前投薬としてデキサメタゾン (例:プレドニゾン) の投与を受けていた場合は, DARZALEX FASPRO の投与日に基礎療法としてコルチコステロイド (又は同等品) を投与しないこと。</p>	週	スケジュール	1~8 週	毎週 (計 8 回投与)	9~24 週 ^a	隔週間隔 (計 8 回投与)	25 週以降, 疾患進行又は最長 2 年間まで ^b	4 週間隔
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	<p>後投薬</p> <p>以下のとおり後投薬を行うこと。</p> <p>単剤療法</p> <p>DARZALEX FASPRO 投与の翌日からメチルプレドニゾロン 20 mg（又は同等量の中時間作用型又は長時間作用型コルチコステロイド）を 2 日間経口投与すること。</p> <p>併用療法</p> <p>DARZALEX FASPRO 投与の翌日から、メチルプレドニゾロン 20 mg（又は同等量の中時間作用型又は長時間作用型コルチコステロイド）以下の経口投与を検討すること。</p> <p>DARZALEX FASPRO の投与翌日に、基礎療法に特異的なコルチコステロイド（例:デキサメタゾン、プレドニゾン）を投与する場合、コルチコステロイドの追加は必要ない場合がある。</p> <p>DARZALEX FASPRO の最初の 3 回の投与後に全身投与に伴う重大な反応が認められない場合は、コルチコステロイドの投与中止を検討すること（基礎療法に特異的な副腎皮質ステロイドを除く）。</p> <p>慢性閉塞性肺疾患の既往がある患者には、短時間作用型及び長時間作用型の気管支拡張薬及び吸入コルチコステロイドの処方考慮する。DARZALEX FASPRO の最初の 4 回の投与後、患者に重大な全身投与関連反応が認められない場合は、これらの追加の後投薬の中止を検討すること。</p> <p>帯状疱疹の再燃予防</p> <p>帯状疱疹の再燃予防のため、抗ウイルス薬予防投与を DARZALEX FASPRO 投与開始後 1 週間以内に開始し、本治療終了後も 3 カ月間投与し続けること。</p> <p><用量調節></p> <p>DARZALEX FASPRO の減量は推奨されない。骨髄抑制が発現した場合に血球数を回復させるため、DARZALEX FASPRO の投与中断を検討すること。</p> <p><調製及び投与></p> <p>DARZALEX FASPRO は医療従事者が投与すること。</p> <p>投薬過誤を防止するため、バイアルのラベルを確認し、調製及び投与する薬剤が DARZALEX FASPRO 皮下投与用であることを確認すること。</p>

販売名	DARZALEX FASPRO 皮下注射剤
	<p>DARZALEX FASPRO は静脈内投与しないこと。 DARZALEX FASPRO はすぐに使用できる状態である。</p> <p>調整</p> <ul style="list-style-type: none"> • DARZALEX FASPRO バイアルを冷蔵保管から取り出し [2~8°C (36° F~46° F)] , 室温に平衡化する [15~30°C (59° F~86° F)] 。未穿刺のバイアルは、周囲温度及び周囲光下で最長 24 時間保管する。直射日光を避けて保管すること。振盪しないこと。 • バイアルからシリンジに 15 mL 採取すること。 • DARZALEX FASPRO はポリプロピレン又はポリエチレン製シリンジに適合する。ポリプロピレン、ポリエチレン又はポリ塩化ビニル (PVC) の皮下注入セット;ステンレス製の移送用針及び注射針。直ちに使用すること。 • DARZALEX FASPRO の溶液をシリンジに吸引した後、トランスファーニードルをシリンジクローズドキャップと交換する。医療施設の基準に従って、投与経路を含むようシリンジに適切なラベルを貼付する。シリンジに剥離ラベルを貼付すること。 • 注射針の詰りを避けるため、注射直前に皮下注射針又は皮下注入セットをシリンジに装着すること。 • 非経口製剤は投与前に、溶液及び容器が許す限り、粒子状物質及び変色がないか目視検査すること。不透明な粒子、変色、その他の異物がある場合は使用しないこと。 <p>貯法</p> <p>DARZALEX FASPRO が入ったシリンジをすぐに使用しない場合は、DARZALEX FASPRO 溶液を室温及び外光下で最長 4 時間保管すること。使用しない場合は 4 時間後に廃棄すること。</p> <p>投与</p> <ul style="list-style-type: none"> • DARZALEX FASPRO 15 mL を腹部の皮下組織左右約 3 インチ [7.5 cm] の臍に約 3~5 分かけて注入すること。その他の部位への投与に関するデータは得られていない。 • 注射部位を順番に変えること。 • 皮膚が赤くなったり、青あざができたり、圧痛があったり、硬くなったり、傷あとがあったりする部位には絶対に注射しないこと。 • 患者に疼痛がある場合は注入を中断又は注入速度を遅らせる。注入を中断又は注入速度を遅くしても疼痛が軽減しない場合、2 回目の注射部位を腹部の

販売名	DARZALEX FASPRO 皮下注射剤
	<p>反対側に選択し、残りの投与を行うことができる。</p> <ul style="list-style-type: none"> • DARZALEX FASPRO の投与中は、同じ部位に他の皮下投与用の薬剤を投与しないこと。
禁忌	<p>DARZALEX FASPRO は、ダラツムマブ、ヒアルロニダーゼ又は本剤の成分に対し重度の過敏症の既往歴のある患者には投与しないこと</p>
警告及び使用上の注意	<p><過敏症及びその他の投与反応></p> <p>DARZALEX FASPRO では、重度又は生命を脅かす反応を含む全身投与に伴う反応及び局所注射部位反応のいずれも発現する可能性がある。</p> <p>全身反応</p> <p>DARZALEX FASPRO の単剤療法又は併用療法を受けた 683 例（多発性骨髄腫の患者=490 例，AL アミロイドーシスの患者=193 例）の安全性解析対象集団を併合したところ，10%の患者に全身投与に伴う反応が発現した（グレード2：3.5%，グレード3：1%）。全身投与に伴う反応は，初回投与患者の9%，2回目投与患者の0.4%に発現し，その後の投与では累積1%に発現した。発現までの時間の中央値は3.2時間（範囲:9分~3.5日）であった。DARZALEX FASPRO 投与日に発現した全身性の副作用は，117例66人中100件（85%）であった。遅発性全身投与関連反応の発現率は1%であった。</p> <p>重度の反応として，低酸素症，呼吸困難，高血圧及び頻脈が認められた。全身投与に伴う反応のその他の徴候及び症状には，気管支痙攣，鼻閉，咳嗽，咽喉刺激感，アレルギー性鼻炎及び喘鳴などの呼吸器症状のほか，アナフィラキシー反応，発熱，胸痛，そう痒症，悪寒，嘔吐，悪心及び低血圧がある。</p> <p>ヒスタミン1受容体拮抗薬，アセトアミノフェン及び副腎皮質ステロイドの前投与を行うこと。全身投与に伴う反応について，特に初回及び2回目の注射後に患者をモニタリングすること。アナフィラキシー反応又は生命を脅かす（グレード4）投与関連反応が発現した場合は，DARZALEX FASPRO の投与を直ちに中止し，永続的に中止すること。遅発性（投与翌日に発現したもの）の全身投与関連反応のリスクを最小限にするため，投与方法及び既往歴に応じて，DARZALEX FASPRO 投与後のコルチコステロイド及びその他の薬剤の投与を考慮すること。</p> <p>局所反応</p> <p>併合した安全性解析対象集団において，注射部位反応は9%の患者に発現し，Grade 2の反応は0.7%であった。主な注射部位反応（1%超）は注射部位紅斑であった。これらの局所反応は，DARZALEX FASPRO の投与開始から中央値5</p>

販売名	DARZALEX FASPRO 皮下注射剤
	<p>分（範囲:0分~4.7日）後に発現した。局所反応を観察し、対症療法を考慮すること。</p> <p><ALアミロイドーシス患者における心毒性></p> <p>DARZALEX FASPRO, ボルテゾミブ, シクロフォスファミド及びデキサメタゾンを併用投与したALアミロイドーシス患者において、重篤又は死亡に至った心臓関連の副作用が発現している。重篤な心障害は16%に発現し、致命的な心障害は10%発現した。NYHA心機能分類クラスIIIA又はMayo病期IIIAの患者はリスクがより高い可能性がある。NYHA心機能分類クラスIIIB又はIVの患者については検証されていない。</p> <p>ALアミロイドーシスの心臓病変を有する患者では、心臓の副作用をより頻繁にモニタリングし、必要に応じて支持療法を行うこと。</p> <p><好中球減少症></p> <p>ダラツムマブは、基礎治療により誘発される好中球減少症を悪化させる可能性がある。</p> <p>基礎療法に関する製造業者の処方情報に従って、投与中は全血球数を定期的にモニタリングすること。好中球減少症の患者では感染の徴候をモニタリングすること。好中球数が回復するまでDARZALEX FASPROを休薬することを検討する。DARZALEX FASPROの投与を受けた低体重患者では、グレード3~4の好中球減少症の発現率が高かった。</p> <p><血小板減少症></p> <p>ダラツムマブは、基礎治療により誘発される血小板減少症を悪化させる可能性がある。</p> <p>基礎療法に関する製造業者の処方情報に従って、投与中は全血球数を定期的にモニタリングすること。血小板が回復するまでDARZALEX FASPROを休薬することを検討する。</p> <p><胚・胎児毒性></p> <p>作用機序から、DARZALEX FASPROは妊婦に投与すると胎児に悪影響を及ぼす可能性がある。DARZALEX FASPROは、胎児の免疫細胞を枯渇させ、骨密度を低下させる可能性がある。妊婦には胎児への潜在的リスクについて説明すること。妊娠可能な女性には、DARZALEX FASPROの投与期間中及び最終投与後3カ月間は有効な避妊法を使用するよう指導すること。</p>

販売名	DARZALEX FASPRO 皮下注射剤
	<p>DARZALEX FASPRO とレナリドミドの併用は、レナリドミドが先天異常を引き起こし、胎児を死亡させる可能性があるため、妊婦には禁忌である。妊娠中の使用に関するレナリドミドの添付文書を参照のこと。</p> <p><血清学的検査への干渉></p> <p>ダラツムマブは赤血球上の CD38 に結合し、間接抗グロブリン試験（間接クームス試験）で陽性となる。ダラツムマブを介する間接抗グロブリン試験陽性は、ダラツムマブ最終投与後 6 カ月まで持続する可能性がある。赤血球に結合したダラツムマブは、患者の血清中のマイナー抗原に対する抗体の検出を遮蔽する。患者の ABO 式及び Rh 式血液型の判定に影響しない。</p> <p>このような血清学的検査への干渉については、輸血センターに通知するとともに、DARZALEX FASPRO の投与を受けた患者について血液バンクに通知すること。DARZALEX FASPRO の投与開始前に患者の分類及びスクリーニングを行うこと。</p> <p><完全奏効の判定への干渉></p> <p>ダラツムマブは、内在性 M 蛋白の臨床モニタリングに使用される血清蛋白電気泳動及び免疫固定法の両方で検出可能なヒト IgGκ モノクローナル抗体である。この干渉は、IgGκ 型骨髄腫蛋白を有する一部の DARZALEX FASPRO 投与患者において、完全奏効及び疾患進行の判定に影響を及ぼす可能性がある。</p>

表 1.6-4 欧州におけるダラツムマブ皮下注製剤の承認状況

販売名	DARZALEX 1800 mg 注射液								
承認時期	• 2020 年 6 月								
剤形・含量	• 15mL バイアル中, ダラツムマブ 1,800mg 含有 (ダラツムマブ 120mg/mL)								
効能・効果	<p>併用療法</p> <ul style="list-style-type: none"> レナリドミド及びデキサメタゾンとの併用又はボルテゾミブ, メルファラン及びプレドニゾンとの併用で, 自家造血幹細胞移植非適応な未治療の多発性骨髄腫成人患者の治療 ボルテゾミブ, サリドマイド及びデキサメタゾンとの併用で, 自家造血幹細胞移植適応な未治療の多発性骨髄腫成人患者の治療 レナリドミド及びデキサメタゾン又はボルテゾミブ及びデキサメタゾンとの併用で, 1 レジメン以上の前治療歴を有する多発性骨髄腫成人患者の治療 <p>単剤療法</p> <ul style="list-style-type: none"> プロテアソーム阻害剤及び免疫調節薬を含む前治療歴を有し, 直近の治療に対して疾患進行を示した再発又は難治性の多発性骨髄腫成人患者の治療 								
用法・用量	<p>DARZALEX 皮下投与製剤は静脈内投与を目的としていないため, 規定された用量を皮下注射でのみ投与すること。</p> <p>DARZALEX の投与は医療従事者が行い, 初回投与は蘇生設備が整った環境で行うこと。</p> <p>バイアルのラベルを確認して, 処方通りに適切な製剤 (静脈内又は皮下投与製剤) 及び用量が患者に投与されていることを確認することが重要である。</p> <p>現在ダラツムマブ静脈内投与製剤の投与を受けている患者では, DARZALEX 皮下注射液を次の投与予定日からダラツムマブ静脈内投与製剤の代替として使用することができる。</p> <p>ダラツムマブの注入に伴う反応 (IRR) のリスクを低減するため, 注射前及び注射後に医薬品を投与すること。</p> <p>用量</p> <ul style="list-style-type: none"> 単剤療法及びレナリドミドとの併用療法の投与スケジュール (4 週サイクルレジメン) を表 1 に示す。DARZALEX 皮下注射液の推奨用量は 1800mg であり, 表 1 の投与スケジュールに従って約 3~5 分かけて投与する。 <p>表 1: レナリドミドとの併用療法 (4 週サイクルレジメン) 及び単剤療法の投与スケジュール</p> <table border="1"> <thead> <tr> <th>週</th> <th>スケジュール</th> </tr> </thead> <tbody> <tr> <td>1~8 週目</td> <td>毎週 (計 8 回投与)</td> </tr> <tr> <td>9~24 週目^a</td> <td>2 週間隔 (計 8 回投与)</td> </tr> <tr> <td>25 週目以降, 疾患進行まで^b</td> <td>4 週間隔</td> </tr> </tbody> </table> <p>a. 2 週間隔投与スケジュールの初回投与は 9 週目 b. 4 週間隔投与スケジュールの初回投与は 25 週目</p> <ul style="list-style-type: none"> ボルテゾミブ, メルファラン及びプレドニゾンとの併用療法投与スケジュール (6 週サイクルレジメン) を表 2 に示す。DARZALEX 皮下注射液の 	週	スケジュール	1~8 週目	毎週 (計 8 回投与)	9~24 週目 ^a	2 週間隔 (計 8 回投与)	25 週目以降, 疾患進行まで ^b	4 週間隔
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販売名	DARZALEX 1800 mg 注射液														
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	<ul style="list-style-type: none"> ボルテゾミブ，サリドマイド及びデキサメタゾンとの併用療法の投与スケジュール（4 週サイクルレジメン）を表 3 に示す。DARAZALEX 皮下注射液の推奨用量は 1800mg であり、表 3 の投与スケジュールに従って約 3~5 分かけて投与する。 														
<p>表 3：ボルテゾミブ，サリドマイド及びデキサメタゾンとの併用療法の投与スケジュール（4 週サイクルレジメン）</p>															
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<ul style="list-style-type: none"> ボルテゾミブとの併用療法の投与スケジュール（3 週サイクルレジメン）を表 4 に示す。DARAZALEX 皮下注射液の推奨用量は 1800mg であり、表 4 の投与スケジュールに従って約 3~5 分かけて投与する。 															
<p>表 4：ボルテゾミブとの併用療法の投与スケジュール（3 週サイクルレジメン）</p>															
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<p>投与漏れ 予定どおり DARZALEX を投与できなかった場合は、できる限り早くその投与を行い、投与スケジュールを適宜調整して投与間隔を維持すること。</p> <p>用量調節</p>															

販売名	DARZALEX 1800 mg 注射液
	<p>DARZALEX の減量は推奨されない。血液毒性を発現した場合は血球数が回復するまで投与を待ってもよい。DARZALEX と併用する薬剤についての情報は、該当する医薬品の製品概要を参照すること。</p> <p>推奨併用薬</p> <p>前投薬</p> <p>Infusion reaction のリスクを軽減するため、毎回、本剤投与約 1～3 時間前に、以下のとおり前投薬を行うこと。</p> <ul style="list-style-type: none"> ・ コルチコステロイド（中時間作用型又は長時間作用型） <p>単剤療法：メチルプレドニゾン 100 mg 又は同等品を投与。2 回目の投与後は、メチルプレドニゾンを 60mg に減量してもよい。</p> <p>併用療法：デキサメタゾン 20 mg（又は同等品）を、毎回、本剤投与時に前投与する。デキサメタゾンは、本剤初回投与前には静脈内投与し、2 回目以降の前投与には経口投与を検討してもよい。デキサメタゾンが基礎療法に特異的なコルチコステロイドである場合にはデキサメタゾンを代わりに本剤投与前に使用する。追加の基礎療法に特異的なコルチコステロイド（例：プレドニゾン）を前投薬として本剤投与日には投与しないこと。</p> <ul style="list-style-type: none"> ・ 解熱剤（パラセタモール 650～1000 mg を経口投与） ・ 抗ヒスタミン剤（ジフェンヒドラミン 25～50 mg 又は相当量を経口又は静脈内投与） <p>後投薬</p> <p>遅発性 Infusion reaction のリスクを軽減するため、以下のとおり後投薬を行うこと。</p> <p>単剤療法：経口コルチコステロイド（メチルプレドニゾン 20 mg 又は同等量の中時間作用型又は長時間作用型コルチコステロイド（各地域の基準に従う））は、すべての注射後の 2 日毎に投与する（注射の翌日から）。</p> <p>併用療法：DARZALEX 注射の翌日に、低用量の経口メチルプレドニゾン（20 mg 以下）又は同等の薬剤の投与を検討すること。ただし、DARZALEX 注射の翌日に基礎療法として特定のコルチコステロイド（例：デキサメタゾン、プレドニゾン）を投与する場合は、追加の後投薬は必要ない場合がある。</p> <p>最初の三回の注射後に重大な IRR が発現しない場合は、注射後のコルチコステロイド（基礎療法としてのコルチコステロイドを除く）の投与を中止してもよい。</p> <p>慢性閉塞性肺疾患の既往を有する患者については、短時間作用型及び長時間作用型気管支拡張剤及び吸入コルチコステロイドといった後投与の使用について考慮すること。最初の 4 回を投与した後、患者に重大な Infusion reaction が発</p>

販売名	DARZALEX 1800 mg 注射液
	<p>現していない場合は、医師の判断により、これらの吸入による後投薬を中止してもよい。</p> <p>带状疱疹の再燃予防 带状疱疹の再燃予防のため、抗ウイルス薬の予防投与を検討すること。</p> <p>特殊集団</p> <p>腎障害患者への投与 腎機能障害患者を対象としたダラツムマブの正式な試験はこれまで実施されていない。母集団薬物動態（PK）解析に基づき、腎機能障害患者での用量調整は不要である。</p> <p>肝障害患者への投与 肝機能障害患者を対象としたダラツムマブの正式な試験はこれまで実施されていない。肝機能障害を有する患者での用量調整は不要である。</p> <p>高齢者への投与 高齢者での用量調整は不要と考えられる。</p> <p>小児への投与 18歳未満の小児患者に対するDARZALEXの安全性及び有効性は確立していない。データは得られていない。</p> <p>体重 (>120kg) 固定用量（1,800 mg）を用いた試験に参加した体重が120 kgを超える患者は限られている。DARZALEX 注射液の皮下投与及びこれらの患者に対する有効性は確率されていない。現在のところ、体重に基づく用量調節は推奨できない</p> <p>投与方法 DARZALEX 皮下投与製剤は静脈内投与を目的としていないため、規定された用量を皮下注射でのみ投与すること。 注射針の詰りを避けるため、注射直前に皮下注射針又は皮下注入セットをシリンジに装着すること。 DARZALEX 皮下注用 15 mL を腹部の皮下組織へその左右約 7.5 cm に 3~5 分かけて注射する。データがないためDARZALEX 注射液を他の部位に皮下注射してはならない。 連続して注射する場合は、注射部位を変えること。 DARZALEX 皮下注用注射液は、皮膚が赤くなっている部位、内出血している部位、圧痛のある部位、硬くなっている部位、瘢痕のある部位には決して注射しないこと。 患者に疼痛がある場合は中断又は注入速度を遅らせる。注入速度を遅くしても疼痛が軽減しない場合、2回目の注射部位を腹部の反対側に選択し、残りの投与を行うことができる。 DARZALEX 皮下注射液の投与中は、DARZALEX と同じ部位に他の皮下投与用医薬品を投与しないこと。</p>
禁忌	有効成分又は本剤に含まれる添加剤のいずれかに対する過敏症。

販売名	DARZALEX 1800 mg 注射液
警告及び使用上の注意	<p data-bbox="375 255 603 291"><u>トレーサビリティ</u></p> <p data-bbox="375 315 1394 389">生物学的製剤のトレーサビリティを向上させるために、投与した薬剤の商品名及びロット番号を明確に記録する。</p> <p data-bbox="375 468 673 499"><u>Infusion related reaction</u></p> <p data-bbox="375 508 1394 667">DARZALEX の皮下注射液は、アナフィラキシー反応を含む重度及び/又は重篤な IRR を引き起こす可能性がある。臨床試験において、約 11% (52/490 例) の患者に IRR が認められた。IRR のほとんどは初回投与後に発現し、Grade 1~2 であった。その後の投与で発現した IRR は 1%未満であった。</p> <p data-bbox="375 678 1394 792">DARZALEX 注射後の IRR 発現までの時間の中央値は 3.7 時間 (範囲 0.15~83 時間)。IRR のほとんどは投与日に発現した。1%未満の患者に遅発性の IRR が発現していた。</p> <p data-bbox="375 804 1394 963">IRR の徴候及び症状には、鼻閉、咳嗽、咽喉刺激感、アレルギー性鼻炎、喘鳴のほか、発熱、胸痛、そう痒症、悪寒、嘔吐、悪心及び低血圧などの呼吸器症状がある。気管支痙攣、低酸素症、呼吸困難、高血圧及び頻脈などの重度の反応が認められている。</p> <p data-bbox="375 974 1394 1178">患者には抗ヒスタミン薬、解熱薬及びコルチコステロイドを前投与し、特に初回及び 2 回目の注射中及び注射後の IRR について観察及びカウンセリングを行うこと。アナフィラキシー反応又は生命を脅かす (Grade 4) 反応が発現した場合、適切な処置直ちに救急治療を開始すること。DARZALEX の投与を直ちに中止し、永続的に中止すること。</p> <p data-bbox="375 1245 743 1276"><u>好中球減少症／血小板減少症</u></p> <p data-bbox="375 1285 1394 1359">DARZALEX は、基礎治療により誘発される好中球減少症及び血小板減少症を悪化させる可能性がある。</p> <p data-bbox="375 1370 1394 1664">基礎療法に関する製造業者の処方情報に従って、投与中は全血球数を定期的にモニタリングすること。好中球減少症の患者では、感染の徴候をモニタリングすべきである。血球数が回復するまで DARZALEX の投与を延期する必要がある場合がある。DARZALEX の皮下投与を受けた低体重患者では、好中球減少症の発現率が高かった。しかし、重篤な感染症の発現率が高くなることはなかった。DARZALEX の減量は推奨されない。輸血又は成長因子による支持療法を考慮する。</p> <p data-bbox="375 1686 1054 1718"><u>間接抗グロブリン試験 (間接クームス試験) への干渉</u></p> <p data-bbox="375 1727 1394 1975">ダラツムマブは赤血球 (RBC) 上に低レベルで発現した CD38 に結合し、間接クームス試験で陽性を示す場合がある。ダラツムマブを介在した間接クームス試験結果は、ダラツムマブ最終投与後最長 6 カ月間陽性となる場合がある。RBC に結合したダラツムマブは、患者の血清中の副抗原に対する抗体の検出を遮蔽する場合があることを認識すること。患者の ABO 式及び Rh 式血液型の判定に影響はない。</p> <p data-bbox="375 1986 1394 2056">ダラツムマブの投与開始前に患者の分類及びスクリーニングを実施すること。地域の基準に応じて、ダラツムマブの投与開始前に表現型検査を検討すること。</p>

販売名	DARZALEX 1800 mg 注射液
	<p>赤血球の表現型検査はダラツムマブに影響されることはなく、いつ実施してもよい。</p> <p>予定された輸血の際には、この間接抗グロブリン試験への干渉について輸血センターに通知すること。緊急輸血が必要になった場合は、各地域の血液バンクでの手順に従い、交差適合のない ABO/RhD に合致した RBC を輸血してもよい。</p> <p><u>完全奏効判定への干渉</u></p> <p>ダラツムマブは、内在性 M 蛋白の臨床モニタリングに使用される血清蛋白電気泳動及び免疫固定法の両方で検出可能なヒト IgG κ モノクローナル抗体である。この干渉は IgG κ 型骨髄腫蛋白を有する患者によっては完全奏効及び疾患進行の判定に影響を及ぼす可能性がある。</p> <p><u>B 型肝炎ウイルスの再活性化</u></p> <p>死亡例を含んだ B 型肝炎ウイルスの再活性化が報告されている。DARZALEX の治療前には、スクリーニングを実施すること。</p> <p>検査の結果陽性であった患者には、DARZALEX による治療中及び治療終了から少なくとも 6 カ月は B 型肝炎ウイルスの再活性化の臨床的及び検査的徴候について観察すること。最新のガイドラインに従って、患者を管理すること。また、肝疾患の専門医に相談することを考慮すること。</p> <p>DARZALEX を投与中に B 型肝炎ウイルスの再活性化が見られた患者には、DARZALEX の投与を中断し、適切な治療をおこなうこと。投与再開の際は、B 型肝炎に関する専門知識を有する医師と協議の上、適切に治療を管理すること。</p> <p><u>体重 (>120kg)</u></p> <p>体重が 120 kg を超える患者に対して DARZALEX の皮下注射剤の有効性が低下する可能性がある。</p> <p><u>添加剤</u></p> <p>本剤はソルビトール (E 420) を含有する。まれな遺伝性フルクトース不耐症患者 (HFI) は本剤を服用しないこと。</p> <p>本剤の投与量当たりのナトリウム含有量は 1 mmol (23 mg) 未満であり、本質的にはナトリウムを含まない。</p>

Janssen Research & Development, LLC

COMPANY CORE DATA SHEET

Daratumumab

Subcutaneous formulation

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use DARZALEX FASPRO safely and effectively. See full prescribing information for DARZALEX FASPRO.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection, for subcutaneous use
Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Indications and Usage (1.1, 1.2)	01/2021
Dosage and Administration (2.2, 2.3)	01/2021
Warnings and Precautions (5.1, 5.2)	01/2021

INDICATIONS AND USAGE

DARZALEX FASPRO is a combination of daratumumab, a CD38-directed cytolytic antibody, and hyaluronidase, an endoglycosidase, indicated for the treatment of adult patients with:

- multiple myeloma in combination with bortezomib, melphalan and prednisone in newly diagnosed patients who are ineligible for autologous stem cell transplant
- multiple myeloma 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
- multiple myeloma in combination with bortezomib, thalidomide, and dexamethasone in newly diagnosed patients who are eligible for autologous stem cell transplant
- multiple myeloma in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy
- multiple myeloma as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
- light chain (AL) amyloidosis in combination with bortezomib, cyclophosphamide and dexamethasone in newly diagnosed patients. This indication is approved under accelerated approval based on response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s). (1.2)

Limitations of Use:

- DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials (1.2)

DOSAGE AND ADMINISTRATION

For subcutaneous use only.

- Pre-medicate with a corticosteroid, acetaminophen and a histamine-1 receptor antagonist. (2.5)
- The recommended dosage of DARZALEX FASPRO is (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously into the abdomen over approximately 3 to 5 minutes according to recommended schedule. (2.2, 2.3)
- Administer post-medications as recommended. (2.5)

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection

DOSAGE FORMS AND STRENGTHS

- Injection:** 1,800 mg daratumumab and 30,000 units hyaluronidase per 15 mL (120 mg and 2,000 units/mL) solution in a single-dose vial (3)

CONTRAINDICATIONS

Patients with a history of severe hypersensitivity to daratumumab or any of the components of the formulation. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity and Other Administration Reactions:** Permanently discontinue DARZALEX FASPRO for life-threatening reactions. (5.1)
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis:** Monitor patients with cardiac involvement more frequently for cardiac adverse reactions and administer supportive care as appropriate. (5.2)
- Neutropenia:** Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO to allow recovery of neutrophils. (5.3)
- Thrombocytopenia:** Monitor complete blood cell counts periodically during treatment. Consider withholding DARZALEX FASPRO to allow recovery of platelets. (5.4)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise pregnant women of the potential risk to a fetus and advise females of reproductive potential to use effective contraception (5.5, 8.1, 8.3).
- Interference with cross-matching and red blood cell antibody screening:** Type and screen patients prior to starting treatment. Inform blood banks that a patient has received DARZALEX FASPRO. (5.6, 7.1)

ADVERSE REACTIONS

- The most common adverse reaction ($\geq 20\%$) in patients with multiple myeloma who received DARZALEX FASPRO monotherapy is upper respiratory tracts infection. (6.1)
- The most common adverse reactions ($\geq 20\%$) in patients with multiple myeloma who received D-VMP are upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain. (6.1)
- The most common adverse reactions ($\geq 20\%$) in patients with multiple myeloma who received D-Rd are fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia and dyspnea. (6.1)
- The most common adverse reactions ($\geq 20\%$) in patients with light chain (AL) amyloidosis are upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, insomnia, dyspnea, and cough. (6.1)
- The most common ($\geq 40\%$) hematology laboratory abnormalities with DARZALEX FASPRO are decreased leukocytes, decreased lymphocytes, decreased neutrophils, decreased platelets, and decreased hemoglobin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 3/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Multiple Myeloma

DARZALEX FASPRO is indicated for the treatment of adult patients with multiple myeloma:

- 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.
- in combination with bortezomib and dexamethasone in patients who have received at least one prior therapy.
- as monotherapy, in patients who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

1.2 Light Chain Amyloidosis

DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone is indicated for the treatment of adult patients with newly diagnosed light chain (AL) amyloidosis.

This indication is approved under accelerated approval based on response rate [see *Clinical Studies* (14.1)]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Limitations of Use

DARZALEX FASPRO is not indicated and is not recommended for the treatment of patients with light chain (AL) amyloidosis who have NYHA Class IIIB or Class IV cardiac disease or Mayo Stage IIIB outside of controlled clinical trials [see *Warnings and Precautions* (5.2)].

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing Information

- **DARZALEX FASPRO is for subcutaneous use only.**
- Administer medications before and after administration of DARZALEX FASPRO to minimize administration-related reactions [see *Dosage and Administration* (2.5)].
- Type and screen patients prior to starting DARZALEX FASPRO.

2.2 Recommended Dosage for Multiple Myeloma

The recommended dose of DARZALEX FASPRO is 1,800 mg/30,000 units (1,800 mg daratumumab and 30,000 units hyaluronidase) administered subcutaneously over approximately 3-5 minutes. Tables 1, 2, 3, and 4 provide the recommended dosing schedule when DARZALEX FASPRO is administered as monotherapy or as part of a combination therapy.

Monotherapy and In Combination with Lenalidomide and Dexamethasone (D-Rd)

Use the dosing schedule provided in Table 1 when DARZALEX FASPRO is administered:

- in combination with lenalidomide and dexamethasone (4-week cycle) OR
- as monotherapy.

Table 1: DARZALEX FASPRO dosing schedule in combination with lenalidomide and dexamethasone (4-week cycle) and for monotherapy

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-2-week dosing schedule is given at Week 9
^b First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX FASPRO is administered as part of a combination therapy, see *Clinical Studies* (14.2) and the prescribing information for dosage recommendations for the other drugs.

In Combination with Bortezomib, Melphalan and Prednisone (D-VMP)

Use the dosing schedule provided in Table 2 when DARZALEX FASPRO is administered in combination with bortezomib, melphalan and prednisone (6-week cycle).

Table 2: DARZALEX FASPRO dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54 ^a	every three weeks (total of 16 doses)
Week 55 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 7
^b First dose of the every-4-week dosing schedule is given at Week 55

When DARZALEX FASPRO is administered as part of a combination therapy, see *Clinical Studies* (14.1) and the prescribing information for dosage recommendations for the other drugs.

In Combination with Bortezomib, Thalidomide, and Dexamethasone (D-VTd)
 Use the dosing schedule in Table 3 when DARZALEX FASPRO is administered in combination with bortezomib, thalidomide, and dexamethasone (4-week cycle).

Table 3: DARZALEX FASPRO dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 ^a	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 ^b	every two weeks (total of 4 doses)

^a First dose of the every-2-week dosing schedule is given at Week 9
^b First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

When DARZALEX FASPRO is administered as part of a combination therapy, see the prescribing information for dosage recommendations for the other drugs.

In Combination with Bortezomib and Dexamethasone (D-Vd)

Use the dosing schedule in Table 4 when DARZALEX FASPRO is administered in combination with bortezomib and dexamethasone (3-week cycle).

Table 4: DARZALEX FASPRO dosing schedule in combination with bortezomib and dexamethasone (3-week cycle)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 ^a	every three weeks (total of 5 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 10
^b First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX FASPRO is administered as part of a combination therapy, see the prescribing information for dosage recommendations for the other drugs.

2.3 Recommended Dosage for Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone (D-VCD)

Use the dosing schedule provided in Table 5 when DARZALEX FASPRO is administered in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle).

Table 5: DARZALEX FASPRO dosing schedule in combination with bortezomib, cyclophosphamide and dexamethasone (4-week cycle)

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression or a maximum of 2 years ^b	every four weeks

^a First dose of the every-2-week dosing schedule is given at Week 9
^b First dose of the every-4-week dosing schedule is given at Week 25

When DARZALEX FASPRO is administered as part of a combination therapy, see *Clinical Studies* (14.2) and the prescribing information for dosage recommendations for the other drugs.

2.4 Administration

If a dose of DARZALEX FASPRO is missed, administer the dose as soon as possible and adjust the dosing schedule to maintain the dosing interval.

2.5 Recommended Concomitant Medications

Pre-medication

Administer the following pre-medications 1-3 hours before each dose of DARZALEX FASPRO:

- Acetaminophen 650 to 1,000 mg orally
- Diphenhydramine 25 to 50 mg (or equivalent) orally or intravenously
- Corticosteroid (long- or intermediate-acting)

Monotherapy

Administer methylprednisolone 100 mg (or equivalent) orally or intravenously. Consider reducing the dose of methylprednisolone to 60 mg (or equivalent) following the second dose of DARZALEX FASPRO.

In Combination

Administer dexamethasone 20 mg (or equivalent) orally or intravenously prior to every DARZALEX FASPRO administration.

When dexamethasone is the background regimen-specific corticosteroid, the dexamethasone dose that is part of the background regimen will serve as pre-medication on DARZALEX FASPRO administration days [see *Clinical Studies* (14)].

Do not administer background regimen-specific corticosteroids (e.g. prednisone) on DARZALEX FASPRO administration days when patients have received dexamethasone (or equivalent) as a pre-medication.

Post-medication

Administer the following post-medications:

Monotherapy

Administer methylprednisolone 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) orally for 2 days starting the day after the administration of DARZALEX FASPRO.

In Combination

Consider administering oral methylprednisolone at a dose of less than or equal to 20 mg (or an equivalent dose of an intermediate- or long-acting corticosteroid) beginning the day after administration of DARZALEX FASPRO.

If a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the administration of DARZALEX FASPRO, additional corticosteroids may not be needed [see *Clinical Studies* (14)].

If the patient does not experience a major systemic administration-related reaction after the first 3 doses of DARZALEX FASPRO, consider discontinuing the administration of corticosteroids (excluding any background regimen-specific corticosteroid).

For patients with a history of chronic obstructive pulmonary disease, consider prescribing short and long-acting bronchodilators and inhaled corticosteroids. Following the first 4 doses of DARZALEX FASPRO, consider discontinuing these additional post-medications, if the patient does not experience a major systemic administration-related reaction.

Prophylaxis for Herpes Zoster Reactivation

Initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week after starting DARZALEX FASPRO and continue for 3 months following the end of treatment [see *Adverse Reactions* (6.1)].

2.6 Dosage Modifications for Adverse Reactions

No dose reductions of DARZALEX FASPRO are recommended. Consider withholding DARZALEX FASPRO to allow recovery of blood cell counts in the event of myelosuppression [see *Warnings and Precautions* (5.3, 5.4)].

2.7 Preparation and Administration

DARZALEX FASPRO should be administered by a healthcare provider.

To prevent medication errors, check the vial labels to ensure that the drug being prepared and administered is DARZALEX FASPRO for subcutaneous use. **Do not administer DARZALEX FASPRO intravenously.**

DARZALEX FASPRO is ready to use.

Preparation

- Remove the DARZALEX FASPRO vial from refrigerated storage [2°C to 8°C (36°F to 46°F)] and equilibrate to ambient temperature [15°C to 30°C (59°F to 86°F)]. Store the unopened vial at ambient temperature and ambient light for a maximum of 24 hours. Keep out of direct sunlight. Do not shake.
- Withdraw 15 mL from the vial into a syringe.
- DARZALEX FASPRO is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles. Use the product immediately.
- After the solution of DARZALEX FASPRO is withdrawn into the syringe, replace the transfer needle with a syringe closing cap. Label the syringe appropriately to include the route of administration per institutional standards. Label the syringe with the peel-off label.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration or other foreign particles are present.

Storage

- If the syringe containing DARZALEX FASPRO is not used immediately, store the DARZALEX FASPRO solution for up to 4 hours at ambient temperature and ambient light. Discard after 4 hours, if not used.

Administration

- Inject 15 mL of DARZALEX FASPRO into the subcutaneous tissue of the abdomen approximately 3 inches [7.5 cm] to the right or left of the navel over approximately 3-5 minutes.** No data are available on performing the injection at other sites of the body.
- Rotate injection sites for successive injections.
- Never inject DARZALEX FASPRO into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX FASPRO, do not administer other medications for subcutaneous use at the same site as DARZALEX FASPRO.

3 DOSAGE FORMS AND STRENGTHS

Injection: 1,800 mg daratumumab and 30,000 units hyaluronidase per 15 mL (120 mg and 2,000 units/mL) colorless to yellow and clear to opalescent solution in a single-dose vial.

4 CONTRAINDICATIONS

DARZALEX FASPRO is contraindicated in patients with a history of severe hypersensitivity to daratumumab, hyaluronidase or any of the components of the formulation [see *Warnings and Precautions* (5.1) and *Adverse Reactions* (6.3)].

5 WARNINGS AND PRECAUTIONS**5.1 Hypersensitivity and Other Administration Reactions**

Both systemic administration-related reactions, including severe or life-threatening reactions, and local injection-site reactions can occur with DARZALEX FASPRO.

Systemic Reactions

In a pooled safety population of 683 patients with multiple myeloma (N=490) or light chain (AL) amyloidosis (N=193) who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 10% of patients experienced a systemic administration-related reaction (Grade 2: 3.5%, Grade 3: 1%). Systemic administration-related reactions occurred in 9% of patients with the first injection, 0.4% with the second injection, and cumulatively 1% with subsequent injections. The median time to onset was 3.2 hours (range: 9 minutes to 3.5 days). Of the 117 systemic administration-related reactions that occurred in 66 patients, 100 (85%) occurred on the day of DARZALEX FASPRO administration. Delayed systemic administration-related reactions have occurred in 1% of the patients.

Severe reactions included hypoxia, dyspnea, hypertension and tachycardia. Other signs and symptoms of systemic administration-related reactions may include respiratory symptoms, such as bronchospasm, nasal congestion, cough, throat irritation, allergic rhinitis, and wheezing, as well as anaphylactic reaction, pyrexia, chest pain, pruritus, chills, vomiting, nausea, and hypotension.

Pre-medicate patients with histamine-1 receptor antagonist, acetaminophen and corticosteroids [see *Dosage and Administration* (2.5)]. Monitor patients for systemic administration-related reactions, especially following the first and second injections. For anaphylactic reaction or life-threatening (Grade 4) administration-related reactions, immediately and permanently discontinue DARZALEX FASPRO. Consider administering corticosteroids and other medications after the administration of DARZALEX FASPRO depending on dosing regimen and medical history to minimize the risk of delayed (defined as occurring the day after administration) systemic administration-related reactions [see *Dosage and Administration* (2.5)].

Local Reactions

In this pooled safety population, injection-site reactions occurred in 9% of patients, including Grade 2 reactions in 0.7%. The most frequent (>1%) injection-site reaction was injection site erythema. These local reactions occurred a median of 5 minutes (range: 0 minutes to 4.7 days) after starting administration of DARZALEX FASPRO. Monitor for local reactions and consider symptomatic management.

5.2 Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Serious or fatal cardiac adverse reactions occurred in patients with light chain (AL) amyloidosis who received DARZALEX FASPRO in combination with bortezomib, cyclophosphamide and dexamethasone [see *Adverse Reactions* (6.1)]. Serious cardiac disorders occurred in 16% and fatal cardiac disorders occurred in 10% of patients. Patients with NYHA Class IIIA or Mayo Stage IIIA disease may be at greater risk. Patients with NYHA Class IIIB or IV disease were not studied.

Monitor patients with cardiac involvement of light chain (AL) amyloidosis more frequently for cardiac adverse reactions and administer supportive care as appropriate.

5.3 Neutropenia

Daratumumab may increase neutropenia induced by background therapy [see *Adverse Reactions* (6.1)].

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. Consider withholding DARZALEX FASPRO until recovery of neutrophils. In lower body weight patients receiving DARZALEX FASPRO, higher rates of Grade 3-4 neutropenia were observed.

5.4 Thrombocytopenia

Daratumumab may increase thrombocytopenia induced by background therapy [see *Adverse Reactions* (6.1)].

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Consider withholding DARZALEX FASPRO until recovery of platelets.

5.5 Embryo-Fetal Toxicity

Based on the mechanism of action, DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. DARZALEX FASPRO may cause depletion of fetal immune cells and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

The combination of DARZALEX FASPRO with lenalidomide or thalidomide is contraindicated in pregnant women, because lenalidomide and thalidomide may cause birth defects and death of the unborn child. Refer to the lenalidomide or thalidomide prescribing information on use during pregnancy.

5.6 Interference with Serological Testing

Daratumumab binds to CD38 on red blood cells (RBCs) and results in a positive Indirect Antiglobulin Test (Indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab administration. Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum [see References (15)]. The determination of a patient's ABO and Rh blood type are not impacted [see Drug Interactions (7.1)].

Notify blood transfusion centers of this interference with serological testing and inform blood banks that a patient has received DARZALEX FASPRO. Type and screen patients prior to starting DARZALEX FASPRO [see Dosage and Administration (2.1)].

5.7 Interference with Determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein [see Drug Interactions (7.1)]. This interference can impact the determination of complete response and of disease progression in some DARZALEX FASPRO-treated patients with IgG kappa myeloma protein.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Hypersensitivity and Other Administration Reactions [see Warning and Precautions (5.1)].
- Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis [see Warning and Precautions (5.2)].
- Neutropenia [see Warning and Precautions (5.3)].
- Thrombocytopenia [see Warning and Precautions (5.4)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Multiple Myeloma

In Combination with Bortezomib, Melphalan and Prednisone

The safety of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES [see Clinical Studies (14.1)]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity (N=67) in combination with bortezomib, melphalan and prednisone. Among these patients, 93% were exposed for 6 months or longer and 19% were exposed for greater than one year.

Serious adverse reactions occurred in 39% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia and pyrexia. Fatal adverse reactions occurred in 3% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 4.5% of patients. The adverse reaction resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient was neutropenic sepsis.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 51% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included thrombocytopenia, neutropenia, anemia, and pneumonia.

The most common adverse reactions (≥20%) were upper respiratory tract infection, constipation, nausea, fatigue, pyrexia, peripheral sensory neuropathy, diarrhea, cough, insomnia, vomiting, and back pain.

Table 6 summarizes the adverse reactions in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 6: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (N=67)	
	All Grades (%)	Grades ≥3 (%)
Infections		
Upper respiratory tract infection ^a	39	0
Bronchitis	16	0
Pneumonia ^b	15	7 [#]
Gastrointestinal disorders		
Constipation	37	0
Nausea	36	0
Diarrhea	33	3 [#]
Vomiting	21	0
Abdominal pain ^c	13	0
General disorders and administration site conditions		
Fatigue ^d	36	3
Pyrexia	34	0
Edema peripheral ^e	13	1 [#]
Nervous system disorders		
Peripheral sensory neuropathy	34	1 [#]
Dizziness	10	0
Respiratory, thoracic and mediastinal disorders		
Cough ^f	24	0
Psychiatric disorders		
Insomnia	22	3 [#]
Musculoskeletal and connective tissue disorders		
Back pain	21	3 [#]
Musculoskeletal chest pain	12	0
Metabolism and nutrition disorders		
Decreased appetite	15	1 [#]
Skin and subcutaneous tissue disorders		
Rash	13	0
Pruritus	12	0
Vascular disorders		
Hypertension	13	6 [#]
Hypotension	10	3 [#]

^a Upper respiratory tract infection includes nasopharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, tonsillitis, upper respiratory tract infection, and viral pharyngitis.

^b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, pneumonia, and pneumonia bacterial.

^c Abdominal pain includes abdominal pain, and abdominal pain upper.

^d Fatigue includes asthenia, and fatigue.

^e Edema peripheral includes edema, edema peripheral, and peripheral swelling.

^f Cough includes cough, and productive cough.

[#] Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) included:

- **General disorders and administration site conditions:** infusion reaction, injection site reaction, chills
- **Infections:** herpes zoster, urinary tract infection, influenza, sepsis
- **Musculoskeletal and connective tissue disorders:** arthralgia, muscle spasms
- **Nervous system disorders:** headache, paresthesia
- **Metabolism and nutrition disorders:** hypocalcemia, hyperglycemia
- **Respiratory, thoracic and mediastinal disorders:** dyspnea, pulmonary edema
- **Cardiac disorders:** atrial fibrillation

Table 7 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) in PLEIADES.

Table 7: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone (D-VMP) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Bortezomib, Melphalan and Prednisone ^a	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	96	52
Decreased lymphocytes	93	84
Decreased platelets	93	42
Decreased neutrophils	88	49
Decreased hemoglobin	48	19

^a Denominator is based on the safety population treated with D-VMP (N=67).

Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The safety of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES [see *Clinical Studies* (14.2)]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity (N=65) in combination with lenalidomide and dexamethasone. Among these patients, 92% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Serious adverse reactions occurred in 48% of patients who received DARZALEX FASPRO. Serious adverse reactions in >5% of patients included pneumonia, influenza and diarrhea. Fatal adverse reactions occurred in 3.1% of patients.

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 11% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 1 patient were pneumonia and anemia.

Dosage interruptions due to an adverse reaction occurred in 63% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruptions in >5% of patients included neutropenia, pneumonia, upper respiratory tract infection, influenza, dyspnea, and blood creatinine increased. The most common adverse reactions (≥20%) were fatigue, diarrhea, upper respiratory tract infection, muscle spasms, constipation, pyrexia, pneumonia, and dyspnea.

Table 8 summarizes the adverse reactions in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

Table 8: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

Adverse Reaction	DARZALEX FASPRO with Lenalidomide and Dexamethasone (N=65)	
	All Grades (%)	Grades ≥3 (%)
General disorders and administration site conditions		
Fatigue ^a	52	5 [#]
Pyrexia	23	2 [#]
Edema peripheral	18	3 [#]
Gastrointestinal disorders		
Diarrhea	45	5 [#]
Constipation	26	2 [#]
Nausea	12	0
Vomiting	11	0
Infections		
Upper respiratory tract infection ^b	43	3 [#]
Pneumonia ^c	23	17
Bronchitis ^d	14	2 [#]
Urinary tract infection	11	0
Musculoskeletal and connective tissue disorders		
Muscle spasms	31	2 [#]
Back pain	14	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea ^e	22	3
Cough ^f	14	0
Nervous system disorders		
Peripheral sensory neuropathy	17	2 [#]
Psychiatric disorders		
Insomnia	17	5 [#]
Metabolism and nutrition disorders		
Hyperglycemia	12	9 [#]
Hypocalcemia	11	0

^a Fatigue includes asthenia, and fatigue.

^b Upper respiratory tract infection includes nasopharyngitis, pharyngitis, respiratory tract infection viral, rhinitis, sinusitis, upper respiratory tract infection, and upper respiratory tract infection bacterial.

^c Pneumonia includes lower respiratory tract infection, lung infection, and pneumonia.

^d Bronchitis includes bronchitis, and bronchitis viral.

^e Dyspnea includes dyspnea, and dyspnea exertional.

^f Cough includes cough, and productive cough.

[#] Only grade 3 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) included:

- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain
- **Nervous system disorders:** dizziness, headache, paresthesia
- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Gastrointestinal disorders:** abdominal pain
- **Infections:** influenza, sepsis, herpes zoster
- **Metabolism and nutrition disorders:** decreased appetite
- **Cardiac disorders:** atrial fibrillation
- **General disorders and administration site conditions:** chills, infusion reaction, injection site reaction
- **Vascular disorders:** hypotension, hypertension

Table 9 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) in PLEIADES.

Table 9: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Lenalidomide and Dexamethasone (D-Rd) in PLEIADES

Laboratory Abnormality	DARZALEX FASPRO with Lenalidomide and Dexamethasone ^a	
	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	94	34
Decreased lymphocytes	82	58
Decreased platelets	86	9
Decreased neutrophils	89	52
Decreased hemoglobin	45	8

^a Denominator is based on the safety population treated with D-Rd (N=65).

Monotherapy

The safety of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA [see *Clinical Trials* (14.2)]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity. Among patients receiving DARZALEX FASPRO, 37% were exposed for 6 months or longer and 1% were exposed for greater than one year.

Serious adverse reactions occurred in 26% of patients who received DARZALEX FASPRO. Fatal adverse reactions occurred in 5% of patients. Fatal adverse reactions occurring in more than 1 patient were general physical health deterioration, septic shock, and respiratory failure.

Permanent discontinuation due to an adverse reaction occurred in 10% of patients who received DARZALEX FASPRO. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than 2 patients were thrombocytopenia and hypercalcemia.

Dosage interruptions due to an adverse reaction occurred in 26% of patients who received DARZALEX FASPRO. Adverse reactions requiring dosage interruption in >5% of patients included thrombocytopenia.

The most common adverse reaction (≥20%) was upper respiratory tract infection.

Table 10 summarizes the adverse reactions in COLUMBA.

Table 10: Adverse Reactions (≥10%) in Patients Who Received DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

Adverse Reaction	DARZALEX FASPRO (N=260)		Intravenous Daratumumab (N=258)	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Infections				
Upper respiratory tract infection ^a	24	1 [#]	22	1 [#]
Pneumonia ^b	8	5	10	6 [@]
Gastrointestinal disorders				
Diarrhea	15	1 [#]	11	0.4 [#]
Nausea	8	0.4 [#]	11	0.4 [#]
General disorders and administration site conditions				
Fatigue ^c	15	1 [#]	16	2 [#]
Infusion reactions ^d	13	2 [#]	34	5 [#]
Pyrexia	13	0	13	1 [#]
Chills	6	0.4 [#]	12	1 [#]
Musculoskeletal and connective tissue disorders				
Back pain	10	2 [#]	12	3 [#]
Respiratory, thoracic and mediastinal disorders				
Cough ^e	9	1 [#]	14	0
Dyspnea ^f	6	1 [#]	11	1 [#]

- ^a Upper respiratory tract infection includes acute sinusitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, rhinitis, rhinovirus infection, sinusitis, and upper respiratory tract infection.
- ^b Pneumonia includes lower respiratory tract infection, lung infection, pneumocystis jirovecii pneumonia, and pneumonia.
- ^c Fatigue includes asthenia, and fatigue.
- ^d Infusion reactions includes terms determined by investigators to be related to infusion.
- ^e Cough includes cough, and productive cough.
- ^f Dyspnea includes dyspnea, and dyspnea exertional.
- [#] Only grade 3 adverse reactions occurred.
- [@] Grade 5 adverse reactions occurred.

Clinically relevant adverse reactions in <10% of patients who received DARZALEX FASPRO included:

- **General disorders and administration site conditions:** injection site reaction, peripheral edema
- **Musculoskeletal and connective tissue disorders:** arthralgia, musculoskeletal chest pain, muscle spasms
- **Gastrointestinal disorders:** constipation, vomiting, abdominal pain
- **Metabolism and nutrition disorders:** decreased appetite, hyperglycemia, hypocalcemia, dehydration
- **Psychiatric disorders:** insomnia
- **Vascular disorders:** hypertension, hypotension
- **Nervous system disorders:** dizziness, peripheral sensory neuropathy, paresthesia
- **Infections:** bronchitis, influenza, urinary tract infection, herpes zoster, sepsis, hepatitis B virus reactivation
- **Skin and subcutaneous tissue disorders:** pruritus, rash
- **Cardiac disorders:** atrial fibrillation
- **Respiratory, thoracic and mediastinal disorders:** pulmonary edema

Table 11 summarizes the laboratory abnormalities in COLUMBA.

Table 11: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Receiving DARZALEX FASPRO or Intravenous Daratumumab in COLUMBA

Laboratory Abnormality	DARZALEX FASPRO ^a		Intravenous Daratumumab ^a	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Decreased leukocytes	65	19	57	14
Decreased lymphocytes	59	36	56	36
Decreased neutrophils	55	19	43	11
Decreased platelets	43	16	45	14
Decreased hemoglobin	42	14	39	16

^a Denominator is based on the safety population treated with DARZALEX FASPRO (N=260) and Intravenous Daratumumab (N=258).

Light Chain Amyloidosis

In Combination with Bortezomib, Cyclophosphamide and Dexamethasone

The safety of DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (D-VcD) was evaluated in ANDROMEDA [see *Clinical Studies (14.2)*]. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity or a maximum of 2 years. Among patients who received D-VcD, 74% were exposed for 6 months or longer and 32% were exposed for greater than one year.

Serious adverse reactions occurred in 43% of patients who received DARZALEX FASPRO in combination with VcD. Serious adverse reactions that occurred in at least 5% of patients in the D-VcD arm were pneumonia (9%), cardiac failure (8%), and sepsis (5%). Fatal adverse reactions occurred in 11% of patients. Fatal adverse reactions that occurred in more than one patient included cardiac arrest (4%), sudden death (3%), cardiac failure (3%), and sepsis (1%).

Permanent discontinuation of DARZALEX FASPRO due to an adverse reaction occurred in 5% of patients. Adverse reactions resulting in permanent discontinuation of DARZALEX FASPRO in more than one patient were pneumonia, sepsis, and cardiac failure.

Dosage interruptions (defined as dose delays or skipped doses) due to an adverse reaction occurred in 36% of patients who received DARZALEX FASPRO. Adverse reactions which required a dosage interruption in ≥3% of patients included upper respiratory tract infection (9%), pneumonia (6%), cardiac failure (4%), fatigue (3%), herpes zoster (3%), dyspnea (3%), and neutropenia (3%).

The most common adverse reactions (≥20%) were upper respiratory tract infection, diarrhea, peripheral edema, constipation, fatigue, peripheral sensory neuropathy, nausea, insomnia, dyspnea, and cough.

Table 12 below summarizes the adverse reactions in patients who received DARZALEX FASPRO with VcD in ANDROMEDA.

Table 12: Adverse Reactions (≥10%) in Patients with AL Amyloidosis Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (D-VcD) with a Difference Between Arms of >5% Compared to VcD in ANDROMEDA

Adverse Reaction	D-VcD (N=193)		VcD (N=188)	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Infections				
Upper respiratory tract infection ^a	40	1 [#]	21	1 [#]
Pneumonia ^b	15	10	9	5
Gastrointestinal disorders				
Diarrhea	36	6 [#]	30	4
Constipation	34	2 [#]	29	0
Nervous system disorders				
Peripheral sensory neuropathy	31	3 [#]	20	2 [#]
Respiratory, thoracic and mediastinal disorders				
Dyspnea ^c	26	4	20	4 [#]
Cough ^d	20	1 [#]	11	0
Musculoskeletal and connective tissue disorders				
Back pain	12	2 [#]	6	0
Arthralgia	10	0	5	0
Muscle spasms	10	1 [#]	5	0
Cardiac disorders				
Arrhythmia ^e	11	4	5	2
General disorders and administration site conditions				
Injection site reactions ^f	11	0	0	0

[#] Only grade 3 adverse reactions occurred.

^a Upper respiratory tract infection includes laryngitis, nasopharyngitis, pharyngitis, respiratory syncytial virus infection, respiratory tract infection, respiratory tract infection viral, rhinitis, rhinovirus infection, sinusitis, tonsillitis, tracheitis, upper respiratory tract infection, upper respiratory tract infection bacterial, and viral upper respiratory tract infection.

^b Pneumonia includes lower respiratory tract infection, pneumonia, pneumonia aspiration, and pneumonia pneumococcal.

^c Dyspnea includes dyspnea, and dyspnea exertional.

^d Cough includes cough, and productive cough.

^e Arrhythmia includes atrial flutter, atrial fibrillation, supraventricular tachycardia, bradycardia, arrhythmia, bradyarrhythmia, cardiac flutter, extrasystoles, supraventricular extrasystoles, ventricular arrhythmia, ventricular extrasystoles, atrial tachycardia, ventricular tachycardia

^f Injection site reactions includes terms determined by investigators to be related to daratumumab injection.

Clinically relevant adverse reactions not included in Table 12 and occurred in patients who received DARZALEX FASPRO with bortezomib, cyclophosphamide and dexamethasone (D-VcD) included:

- **Skin and subcutaneous tissue disorders:** rash, pruritus
- **Nervous system disorders:** paresthesia
- **General disorders and administration site conditions:** infusion reaction, chills
- **Cardiac disorders:** cardiac failure^a, cardiac arrest
- **Metabolism and nutrition disorders:** hyperglycemia, hypocalcemia, dehydration
- **Infections:** bronchitis, herpes zoster, sepsis, urinary tract infection, influenza
- **Vascular disorders:** hypertension
- **Musculoskeletal and connective tissue disorders:** musculoskeletal chest pain
- **Gastrointestinal disorders:** pancreatitis
- **Respiratory, thoracic and mediastinal disorders:** pulmonary edema

^a Cardiac failure includes cardiac dysfunction, cardiac failure, cardiac failure congestive, cardiovascular insufficiency, diastolic dysfunction, pulmonary edema, and left ventricular dysfunction occurred in 11% of patients.

Table 13 summarizes the laboratory abnormalities in patients who received DARZALEX FASPRO with VCd in ANDROMEDA.

Table 13: Select Hematology Laboratory Abnormalities Worsening from Baseline in Patients Who Received DARZALEX FASPRO with Bortezomib, Cyclophosphamide and Dexamethasone (D-VCd) in ANDROMEDA

Laboratory Abnormality	D-VCd		VCd	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Decreased lymphocytes	81	54	71	46
Decreased hemoglobin	66	6	70	6
Decreased leukocytes	60	7	46	4
Decreased platelets	46	3	40	4
Decreased neutrophils	30	6	18	4

Denominator is based on the number of patients with a baseline and post-baseline laboratory value for each laboratory test, N=188 for D-VCd and N=186 for VCd.

Cardiac Adverse Reactions in Light Chain (AL) Amyloidosis

Among patients who received DARZALEX FASPRO in combination with VCd, 72% of patients had baseline cardiac involvement with Mayo Cardiac Stage I (3%), Stage II (46%) and Stage III (51%). Serious cardiac disorders occurred in 16% of patients (8% of patients with Mayo Cardiac Stage I and II and 28% of patients with Stage III). Serious cardiac disorders in >2% of patients included cardiac failure (8%), cardiac arrest (4%) and arrhythmia (4%). Fatal cardiac disorders occurred in 10% of patients (5% of patients with Mayo Cardiac Stage I and II and 19% of patients with Stage III) who received DARZALEX FASPRO in combination with VCd. Fatal cardiac disorders that occurred in more than one patient in the D-VCd arm included cardiac arrest (4%), sudden death (3%), and cardiac failure (3%).

6.2 Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other daratumumab products or other hyaluronidase products may be misleading.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, less than 1% of 633 patients developed treatment-emergent anti-daratumumab antibodies.

In patients with multiple myeloma and light chain (AL) amyloidosis who received DARZALEX FASPRO as monotherapy or as part of a combination therapy, 7% of 628 patients developed treatment-emergent anti-rHuPH20 antibodies. The anti-rHuPH20 antibodies did not appear to affect daratumumab exposure. None of the patients who tested positive for anti-rHuPH20 antibodies tested positive for neutralizing antibodies.

6.3 Postmarketing Experience

The following adverse reactions have been identified with post-approval use of daratumumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System: Anaphylactic reaction

Gastrointestinal: Pancreatitis

Infections: Cytomegalovirus, Listeriosis

7 DRUG INTERACTIONS

7.1 Effects of Daratumumab on Laboratory Tests

Interference with Indirect Antiglobulin Tests (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding [see References (15)] or genotyping. Since the Kell blood group system is also sensitive to DTT treatment, supply K-negative units after ruling out or identifying alloantibodies using DTT-treated RBCs.

If an emergency transfusion is required, administer non-cross-matched ABO/RhD-compatible RBCs per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). False positive SPE and IFE assay results may occur for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In DARZALEX FASPRO-treated patients with persistent very good partial response, where daratumumab interference is suspected, consider using a FDA-approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman. The assessment of associated risks with daratumumab products is based on the mechanism of action and data from target antigen CD38 knockout animal models (see Data). There are no available data on the use of DARZALEX FASPRO in pregnant women to evaluate drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Animal reproduction studies have not been conducted.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

The combination of DARZALEX FASPRO and lenalidomide or thalidomide is contraindicated in pregnant women, because lenalidomide and thalidomide may cause birth defects and death of the unborn child. Lenalidomide and thalidomide are only available through a REMS program. Refer to the lenalidomide or thalidomide prescribing information on use during pregnancy.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Immunoglobulin G1 (IgG1) monoclonal antibodies are transferred across the placenta. Based on its mechanism of action, DARZALEX FASPRO may cause depletion of fetal CD38 positive immune cells and decreased bone density. Defer administering live vaccines to neonates and infants exposed to daratumumab *in utero* until a hematology evaluation is completed.

Data

Animal Data

DARZALEX FASPRO for subcutaneous injection contains daratumumab and hyaluronidase. Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density at birth that recovered by 5 months of age. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in the regulation of humoral immune responses (mice), feto-maternal immune tolerance (mice), and early embryonic development (frogs).

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is 45 times higher than the human dose.

There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

8.2 Lactation

Risk Summary

There is no data on the presence of daratumumab and hyaluronidase in human milk, the effects on the breastfed child, or the effects on milk production. Maternal immunoglobulin G is known to be present in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. Because of the potential for serious adverse reactions in the breastfed child when DARZALEX FASPRO is administered with lenalidomide or thalidomide and dexamethasone, advise women not to breastfeed during treatment with DARZALEX FASPRO. Refer to lenalidomide or thalidomide prescribing information for additional information.

Data

Animal Data

No systemic exposure of hyaluronidase was detected in monkeys given 22,000 U/kg subcutaneously (12 times higher than the human dose) and there were no effects on post-natal development through sexual maturity in offspring of mice treated daily during lactation with 990,000 U/kg hyaluronidase subcutaneously, which is 134 times higher than the human doses.

8.3 Females and Males of Reproductive Potential

DARZALEX FASPRO can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Pregnancy Testing

With the combination of DARZALEX FASPRO with lenalidomide or thalidomide, refer to the lenalidomide or thalidomide labeling for pregnancy testing requirements prior to initiating treatment in females of reproductive potential.

Contraception

Advise females of reproductive potential to use effective contraception during treatment with DARZALEX FASPRO and for 3 months after the last dose. Additionally, refer to the lenalidomide or thalidomide labeling for additional recommendations for contraception.

8.4 Pediatric Use

Safety and effectiveness of DARZALEX FASPRO in pediatric patients have not been established.

8.5 Geriatric Use

Of the 291 patients who received DARZALEX FASPRO as monotherapy for relapsed and refractory multiple myeloma, 37% were 65 to <75 years of age, and 19% were 75 years of age or older. No overall differences in effectiveness of DARZALEX FASPRO have been observed between patients ≥65 years of age and younger patients. Adverse reactions that occurred at a higher frequency (≥5% difference) in patients ≥65 years of age included upper respiratory tract infection, urinary tract infection, dizziness, cough, dyspnea, diarrhea, nausea, fatigue, and peripheral edema. Serious adverse reactions that occurred at a higher frequency (≥2% difference) in patients ≥65 years of age included pneumonia.

Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with multiple myeloma did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently from younger patients.

Of the 193 patients who received DARZALEX FASPRO as part of a combination therapy for light chain (AL) amyloidosis, 35% were 65 to <75 years of age, and 10% were 75 years of age or older. Clinical studies of DARZALEX FASPRO as part of a combination therapy for patients with light chain (AL) amyloidosis did not include sufficient numbers of patients aged 65 and older to determine whether effectiveness differs from that of younger patients. Adverse reactions that occurred at a higher frequency in patients ≥65 years of age were peripheral edema, asthenia, pneumonia and hypotension.

No clinically meaningful differences in the pharmacokinetics of daratumumab were observed in geriatric patients compared to younger adult patients [see *Clinical Pharmacology* (12.3)].

11 DESCRIPTION

Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody that binds to the CD38 antigen. Daratumumab is produced in Chinese Hamster Ovary (CHO) cells using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

Hyaluronidase (recombinant human) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is a glycosylated single-chain protein produced by Chinese Hamster Ovary cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). Hyaluronidase (recombinant human) has a molecular weight of approximately 61 kDa.

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration.

Each DARZALEX FASPRO 15 mL single-dose vial contains 1,800 mg of daratumumab and 30,000 units of hyaluronidase, L-histidine (4.9 mg), L-histidine hydrochloride monohydrate (18.4 mg), L-methionine (13.5 mg), polysorbate 20 (6 mg), sorbitol (735.1 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including clonal plasma cells in multiple myeloma and light chain (AL) amyloidosis, as well as other cell types. Surface CD38 has multiple functions, including receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab.

Hyaluronan is a polysaccharide found in the extracellular matrix of the subcutaneous tissue. It is depolymerized by the naturally occurring enzyme hyaluronidase. Unlike the stable structural components of the interstitial matrix, hyaluronan has a half-life of approximately 0.5 days. Hyaluronidase increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase in DARZALEX FASPRO acts locally. The effects of hyaluronidase are reversible and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

12.2 Pharmacodynamics

NK cells express CD38 and are susceptible to daratumumab mediated cell lysis. Decreases in absolute counts and percentages of total NK cells (CD16+CD56+) and activated (CD16+CD56^{dim}) NK cells in peripheral whole blood and bone marrow were observed with DARZALEX FASPRO treatment.

Cardiac Electrophysiology

DARZALEX FASPRO as a large protein has a low likelihood of direct ion channel interactions. There is no evidence from non-clinical or clinical data to suggest that DARZALEX FASPRO has the potential to delay ventricular repolarization.

Exposure-Response Relationship

The exposure-response relationship and time course of pharmacodynamics of DARZALEX FASPRO have not been fully characterized.

12.3 Pharmacokinetics

Following the recommended dose of DARZALEX FASPRO 1,800 mg/30,000 units, C_{max} increased 4.8-fold and AUC_{0-7 days} increased 5.4-fold from the 1st dose to the 8th dose.

Table 14 lists the observed mean (±SD) maximum trough concentrations (C_{trough}) after the 8th dose, simulated median (5th-95th percentiles) maximum C_{trough} after the 8th dose, simulated median (5th-95th percentiles) C_{max} after the 8th dose, and simulated median (5th-95th percentiles) area under the curve (AUC_{0-7day}) after the 8th dose following DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously in patients with multiple myeloma or light chain (AL) amyloidosis.

Table 14: Daratumumab Exposure for Patients with Multiple Myeloma or Light Chain (AL) Amyloidosis

Parameter	Intravenous Daratumumab 16 mg/kg in Patients with Multiple Myeloma	DARZALEX FASPRO 1,800 mg/30,000 units in Patients with Multiple Myeloma	DARZALEX FASPRO 1,800 mg/30,000 units in Patients with Light Chain (AL) Amyloidosis
Observed mean±SD max C _{trough} after 8 th dose (µg/mL)	522±226 ^{a,b}	593±306 ^{a,b}	597±232 ^c
Simulated median (5 th -95 th percentiles) max C _{trough} after 8 th dose (µg/mL)	472 (144-809) ^d	563 (177-1063) ^d	662 (315-1037) ^e
Simulated median (5 th -95 th percentiles) C _{max} after 8 th dose (µg/mL)	688 (369-1061) ^d	592 (234-1114) ^d	729 (390-1105) ^e
Simulated median (5 th -95 th percentiles) AUC _{0-7days} after 8 th dose (µg/mL•day)	4019 (1740-6370) ^d	4017 (1515-7564) ^d	4855 (2562-7522) ^e

^a Geometric mean ratio between 1,800 mg SC and 16 mg/kg was 108% (90% CI: 96, 122) in patients with multiple myeloma

^b Source: MMY3012 Primary Analysis Clinical Study Report

^c Source: AMY3001 Primary Analysis Clinical Study Report

^d Source: Population Pharmacokinetics and Exposure-response Analysis Report for Subcutaneously Administered Daratumumab in Multiple Myeloma Subjects

^e Source: Population Pharmacokinetics and Exposure-response Analysis Report for Daratumumab Subcutaneous Administration for the Treatment of Subjects with AL Amyloidosis

Absorption

At the recommended dose of DARZALEX FASPRO 1,800 mg/30,000 units, the absolute bioavailability is 69%, with peak concentrations occurring around 3 days (T_{max}) in patients with multiple myeloma. Peak concentrations occurred around 4 days in patients with light chain (AL) amyloidosis.

Distribution

The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L in patients with multiple myeloma. The estimated mean volume of distribution was 10.8 L (28%) in patients with light chain (AL) amyloidosis.

Elimination

Daratumumab is cleared by parallel linear and nonlinear saturable target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day (59%) in patients with multiple myeloma and is 210 mL/day (42%) in patients with light chain (AL) amyloidosis. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%) in patients with multiple myeloma and 28 days (74%) in patients with light chain (AL) amyloidosis.

Specific Populations

The following population characteristics have no clinically meaningful effect on the pharmacokinetics of daratumumab in patients administered DARZALEX FASPRO as monotherapy or as combination therapy: sex, age (33 to 92 years), renal impairment [Creatinine clearance (CLCr) 15 to 89 mL/min as determined by the Cockcroft-Gault formula], and mild hepatic impairment (total bilirubin 1 to 1.5 times ULN and AST>ULN). The effect of moderate and severe hepatic impairment on daratumumab pharmacokinetics is unknown.

Racial or Ethnic Groups

Of 190 patients with light chain (AL) amyloidosis who received DARZALEX FASPRO and had a maximum C_{trough} after the 8th dose, African-Americans (4%) had 24% higher daratumumab mean maximum C_{trough} after the 8th dose compared to that of Whites (83%) and Asians (10%) had 16% higher mean maximum C_{trough} after the 8th dose compared to that of Whites. The difference in exposure between that of Asians and Whites could be explained in part by differences in body size. The effect of African-American race on exposure and related safety and efficacy of daratumumab is unknown.

Body Weight

In patients with multiple myeloma who received DARZALEX FASPRO 1,800 mg/30,000 units as monotherapy, the mean maximum C_{trough} after the 8th dose was 12% lower in the higher body weight (BW) group (>85 kg), while the mean maximum C_{trough} after the 8th dose was 81% higher in the lower BW group (≤50 kg) compared to the corresponding BW groups in the intravenous daratumumab arm.

In patients with light chain (AL) amyloidosis who received DARZALEX FASPRO 1,800 mg/30,000 units in combination and had a maximum C_{trough} after the 8th dose, the mean maximum C_{trough} after the 8th dose was 22% lower in the higher BW group (>85 kg), while the mean maximum C_{trough} was 37% higher in the lower BW group (≤50 kg) compared to the patients with body weight of 51-85 kg.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or genotoxicity studies have been conducted with daratumumab. No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development, or to determine potential effects on fertility in males or females.

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. There were no effects on reproductive tissues and function and no systemic exposure of hyaluronidase in monkeys given 22,000 U/kg/week subcutaneously (12 times higher than the human dose) for 39 weeks. As hyaluronidase is a recombinant form of the endogenous human hyaluronidase, no carcinogenicity, mutagenesis, or effects on fertility are expected.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Multiple Myeloma

In Combination with Bortezomib, Melphalan and Prednisone

The efficacy of DARZALEX FASPRO with bortezomib, melphalan and prednisone (D-VMP) was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. Eligible patients were required to have newly diagnosed multiple myeloma who are ineligible for transplant. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 6, once every 3 weeks from weeks 7 to 54 and once every 4 weeks starting with week 55 until disease progression or unacceptable toxicity; bortezomib 1.3 mg/m² subcutaneously twice weekly on Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly on Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle); and melphalan 9 mg/m² and prednisone 60 mg/m² orally on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). The major efficacy outcome measure was overall response rate (ORR).

A total of 67 patients received DARZALEX FASPRO with VMP. The median age was 75 years (range: 66 to 86); 46% were male; 69% were White, 8% Asian, and 2% Black or African American; and 33% had ISS Stage I, 45% had ISS Stage II, and 22% had ISS Stage III disease.

Efficacy results are summarized in Table 15.

Table 15: Efficacy Results from PLEIADES in Patients Who Received D-VMP

	D-VMP (N=67)
Overall response rate (sCR+CR+VGPR+PR), n (%) ^a	59 (88%)
95% CI (%)	(78%, 95%)
Stringent complete response (sCR)	5 (8%)
Complete response (CR)	7 (10%)
Very good partial response (VGPR)	31 (46%)
Partial response (PR)	16 (24%)

CI=confidence interval

^a Based on treated patients

14.2 Relapsed/Refractory Multiple Myeloma

In Combination with Lenalidomide and Dexamethasone

The efficacy of DARZALEX FASPRO with lenalidomide and dexamethasone (D-Rd) was evaluated in a single-arm cohort of PLEIADES (NCT03412565), a multi-cohort, open-label trial. Patients received DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or unacceptable toxicity with lenalidomide 25 mg once daily orally on Days 1-21 of each 28-day cycle; and dexamethasone 40 mg per week (or a reduced dose of 20 mg per week for patients >75 years or BMI <18.5). The major efficacy outcome measure was ORR.

A total of 65 patients received DARZALEX FASPRO with Rd. The median age was 69 years (range: 33 to 82 years); 69% were male; 69% were White, and 3% Black or African American; and 42% had ISS Stage I, 30% had ISS Stage II, and 28% had ISS Stage III disease. Patients had received a median of 1 prior line of therapy. A total of 52% of patients had a prior ASCT; 95% of patients received a prior PI; 59% received a prior immunomodulatory agent, including 22% who received prior lenalidomide; and 54% of patients received both a prior PI and immunomodulatory agent.

Efficacy results are summarized in Table 16.

Table 16: Efficacy Results from PLEIADES in Patients Who Received D-Rd

	D-Rd (N=65)
Overall response rate (sCR+CR+VGPR+PR), n (%) ^a	59 (91%)
95% CI (%)	(81%, 97%)
Stringent complete response (sCR)	4 (6%)
Complete response (CR)	8 (12%)
Very good partial response (VGPR)	30 (46%)
Partial response (PR)	17 (26%)

CI=confidence interval

^a Based on treated patients

Monotherapy

The efficacy of DARZALEX FASPRO as monotherapy was evaluated in COLUMBA (NCT03277105), an open-label, randomized, non-inferiority study. Eligible patients were required to have relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent. Patients were randomized to receive DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously or daratumumab 16 mg/kg administered intravenously; each administered once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until unacceptable toxicity or disease progression. The major efficacy outcome measures were ORR by the IMWG response criteria and maximum C_{trough} at pre-dose Cycle 3 Day 1 [see *Clinical Pharmacology* (12.3)]. Randomization was stratified by body weight, myeloma type, and number of prior lines of therapy.

A total of 522 patients were randomized: 263 to the DARZALEX FASPRO arm and 259 to the intravenous daratumumab arm. The median age was 67 years (range: 33 to 92 years); 55% were male; and 78% were White, 14% Asian, and 3% Black or African American. The median weight was 73 kg (range: 29 to 138). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had a prior ASCT; 100% of patients received both a PI and an immunomodulatory agent. Forty-nine percent of patients were refractory both a PI and an immunomodulatory agent. Eighty-two percent of patients were refractory to their last line of prior systemic therapy.

The results show that DARZALEX FASPRO 1,800 mg/30,000 units administered subcutaneously is non-inferior to daratumumab 16 mg/kg administered intravenously in terms of ORR and maximum trough concentration [see *Clinical Pharmacology* (12.3)]. Median progression-free survival was 5.6 months in the DARZALEX FASPRO arm and 6.1 months in the intravenous daratumumab arm. ORR results are provided in Table 17.

Table 17: Efficacy Results from COLUMBA

	DARZALEX FASPRO (N=263)	Intravenous Daratumumab (N=259)
Overall response (sCR+CR+VGPR+PR), n (%) ^a	108 (41%)	96 (37%)
95% CI (%)	(35%, 47%)	(31%, 43%)
Ratio of response rates (95% CI)		1.11 (0.89, 1.37)
CR or better, n (%)	5 (1.9%)	7 (2.7%)
Very good partial response (VGPR)	45 (17%)	37 (14%)
Partial response (PR)	58 (22%)	52 (20%)

^a Based on intent-to-treat population.

14.3 Light Chain Amyloidosis**In Combination with Bortezomib, Cyclophosphamide and Dexamethasone**

The efficacy of DARZALEX FASPRO with VCd was evaluated in ANDROMEDA (NCT03201965), an open-label, randomized, active-controlled trial. Eligible patients were required to have newly diagnosed light chain (AL) amyloidosis with at least one affected organ, measurable hematologic disease, Cardiac Stage I-IIIa (based on European Modification of Mayo 2004 Cardiac Stage), and NYHA Class I-IIIa. Patients with NYHA Class IIIB and IV were excluded. Patients were randomized to receive bortezomib 1.3 mg/m² administered subcutaneously, cyclophosphamide 300 mg/m² (max dose 500 mg) administered orally or intravenously, and dexamethasone 40 mg (or a reduced dose of 20 mg for patients >70 years or body mass index <18.5 or who have hypervolemia, poorly controlled diabetes mellitus or prior intolerance to steroid therapy) administered orally or intravenously on Days 1, 8, 15, and 22 of each 28-day cycle with or without DARZALEX FASPRO 1,800 mg/30,000 units subcutaneously once weekly from weeks 1 to 8, once every 2 weeks from weeks 9 to 24 and once every 4 weeks starting with week 25 until disease progression or a maximum of two years. When DARZALEX FASPRO and dexamethasone were administered on the same day, dexamethasone 20 mg was administered before DARZALEX FASPRO with the remaining dose of dexamethasone administered after DARZALEX FASPRO if applicable. The major efficacy outcome measure was confirmed hematologic complete response (HemCR) rate based on Consensus Criteria as determined by the Independent Review Committee (negative serum and urine immunofixation, involved free light chain level decrease to less than the upper limit of normal, and normal free light chain ratio). Randomization was stratified by Cardiac Stage (European Modification of Mayo 2004 Cardiac Stage) countries that typically offer autologous stem cell transplant (ASCT) for patients with light chain (AL) amyloidosis, and renal function.

A total of 388 patients were randomized: 195 to D-VCd and 193 to VCd. The median patient age was 64 years (range: 34 to 87 years); 58% were male; 76% White, 17% Asian, and 3% Black or African American; 23% had light chain (AL) amyloidosis Cardiac Stage I, 40% had Stage II, and 37% had Stage IIIa. The median number of organs involved was 2 (range: 1-6) and 66% of patients had 2 or more organs involved. Vital organ involvement was: cardiac 71%, renal 59% and hepatic 8%. The majority (79%) of patients had lambda free light chain disease.

Efficacy results are summarized in Table 18.

Table 18: Efficacy results from ANDROMEDA^a

	D-VCd (n=195)	VCd (n=193)
Hematologic complete response (HemCR), n (%)	82 (42%)	26 (13%)
p-value ^b	<0.0001	
Very good partial response (VGPR), n (%)	71 (36%)	69 (36%)
Partial response (PR), n (%)	26 (13%)	53 (27%)
Hematologic VGPR or better (HemCR + VGPR), n (%)	153 (78%)	95 (49%)
Major organ deterioration progression-free survival ^c ; Hazard ratio with 95% CI	0.58 (0.37, 0.92)	

D-VCd=daratumumab-bortezomib-cyclophosphamide-dexamethasone; VCd=bortezomib-cyclophosphamide-dexamethasone

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Major organ deterioration-PFS defined as hematologic progression, major organ (cardiac or renal) deterioration or death

The median time to HemCR was 59 days (range: 8 to 299 days) in the D-VCd arm and 59 days (range: 16 to 340 days) in the VCd arm. The median time to VGPR or better was 17 days (range: 5 to 336 days) in the D-VCd arm and 25 days (range: 8 to 171 days) in the VCd arm. The median duration of HemCR had not been reached in either arm.

The median follow-up for the study is 11.4 months. Overall survival (OS) data were not mature. A total of 56 deaths were observed [N=27 (13.8%) D-VCd vs. N=29 (15%) VCd group].

15 REFERENCES

- Chapuy, CI, RT Nicholson, MD Aguad, et al., 2015, Resolving the daratumumab interference with blood compatibility testing, *Transfusion*, 55:1545-1554 (accessible at <http://onlinelibrary.wiley.com/doi/10.1111/trf.13069/epdf>).

16 HOW SUPPLIED/STORAGE AND HANDLING

DARZALEX FASPRO® (daratumumab and hyaluronidase-fihj) injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution for subcutaneous use supplied as individually packaged single-dose vials providing 1,800 mg of daratumumab and 30,000 units of hyaluronidase per 15 mL (NDC 57894-503-01).

Store DARZALEX FASPRO vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light.

Do not freeze or shake.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Hypersensitivity and Other Administration Reactions

Advise patients to seek immediate medical attention for any of the following signs and symptoms of systemic administration-related reactions: itchy, runny or blocked nose; chills, nausea, throat irritation, cough, headache, shortness of breath or difficulty breathing [see *Warnings and Precautions* (5.1)].

Cardiac Toxicity in Patients with Light Chain (AL) Amyloidosis

Advise patients to immediately contact their healthcare provider if they have signs or symptoms of cardiac adverse reactions [see *Warnings and Precautions* (5.2)].

Neutropenia

Advise patients to contact their healthcare provider if they have a fever [see *Warnings and Precautions* (5.3)].

Thrombocytopenia

Advise patients to contact their healthcare provider if they have bruising or bleeding [see *Warnings and Precautions* (5.4)].

Embryo-Fetal Toxicity

Advise pregnant women of the potential hazard to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy [see *Warnings and Precautions* (5.5), *Use in Specific Populations* (8.1, 8.3)].

Advise females of reproductive potential to avoid becoming pregnant during treatment with DARZALEX FASPRO and for at least 3 months after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

Advise patients that lenalidomide and thalidomide have the potential to cause fetal harm and have specific requirements regarding contraception, pregnancy testing, blood and sperm donation, and transmission in sperm. Lenalidomide and thalidomide are only available through a REMS program [see *Use in Specific Populations* (8.1, 8.3)].

Interference with Laboratory Tests

Advise patients to inform their healthcare provider, including personnel at blood transfusion centers, that they are taking DARZALEX FASPRO, in the event of a planned transfusion [see *Warnings and Precautions* (5.6)].

Advise patients that DARZALEX FASPRO can affect the results of some tests used to determine complete response in some patients and additional tests may be needed to evaluate response [see *Warnings and Precautions* (5.7)].

Hepatitis B Virus (HBV) Reactivation

Advise patients to inform healthcare providers if they have ever had or might have a hepatitis B infection and that DARZALEX FASPRO could cause hepatitis B virus to become active again [see *Adverse Reactions* (6.1)].

Product of Switzerland

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044
U.S. License Number 1864

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PATIENT INFORMATION
DARZALEX (Dar'-zah-lex) FASPRO® (Fas-pro)
(daratumumab and hyaluronidase-fihj)
injection, for subcutaneous use

DARZALEX FASPRO may be used with other medicines called lenalidomide or thalidomide and dexamethasone. You should also read **the Medication Guide that comes with lenalidomide or thalidomide if you use DARZALEX FASPRO with lenalidomide or thalidomide**. You can ask your healthcare provider or pharmacist for information about dexamethasone.

What is DARZALEX FASPRO?

DARZALEX FASPRO is a prescription medicine used to treat adult patients with multiple myeloma:

- in combination with the medicines bortezomib, melphalan and prednisone, in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant).
- in combination with the medicines lenalidomide and dexamethasone in people with newly diagnosed multiple myeloma who cannot receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant) and in people whose multiple myeloma has come back or did not respond to treatment, who have received at least one prior medicine to treat multiple myeloma.
- in combination with the medicines bortezomib, thalidomide, and dexamethasone in newly diagnosed people who are eligible to receive a type of stem cell transplant that uses their own stem cells (autologous stem cell transplant).
- in combination with the medicines bortezomib and dexamethasone in people who have received at least one prior medicine to treat multiple myeloma.
- alone in people who have received at least three prior medicines, including a proteasome inhibitor and an immunomodulatory agent, **or** did not respond to a proteasome inhibitor and an immunomodulatory agent.

DARZALEX FASPRO is a prescription medicine also used in combination with the medicines bortezomib, cyclophosphamide and dexamethasone in patients with newly diagnosed light chain (AL) amyloidosis.

It is not known if DARZALEX FASPRO is safe and effective in children.

Do not receive DARZALEX FASPRO if you have a history of a severe allergic reaction to daratumumab or any of the ingredients in DARZALEX FASPRO. See the end of this leaflet for a complete list of ingredients in DARZALEX FASPRO.

Before you receive DARZALEX FASPRO, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of breathing problems
- have had shingles (herpes zoster)
- have ever had or might now have a hepatitis B infection as DARZALEX FASPRO could cause hepatitis B virus to become active again. Your healthcare provider will check you for signs of this infection before, during and for some time after treatment with DARZALEX FASPRO. Tell your healthcare provider right away if you get worsening tiredness or yellowing of your skin or white part of your eyes.
- are pregnant or plan to become pregnant. DARZALEX FASPRO may harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you may be pregnant during treatment with DARZALEX FASPRO.
 - Females who are able to become pregnant should use an effective method of birth control (contraception) during treatment and for at least 3 months after your final dose of DARZALEX FASPRO. Talk to your healthcare provider about birth control methods that you can use during this time.
 - Before starting DARZALEX FASPRO in combination with lenalidomide or thalidomide and dexamethasone, females and males must agree to the instructions in the lenalidomide or thalidomide REMS program.
 - The lenalidomide and thalidomide REMS have more information about effective methods of birth control, pregnancy testing, and blood donation for females who can become pregnant.
 - For males who have female partners who can become pregnant, there is information in the lenalidomide and thalidomide REMS about sperm donation and how lenalidomide and thalidomide can pass into human semen.
- are breastfeeding or plan to breastfeed. It is not known if DARZALEX FASPRO passes into your breast milk.

Before you receive DARZALEX FASPRO for light chain (AL) amyloidosis, tell your healthcare provider if you have a history of heart problems. DARZALEX FASPRO should not be used in light chain (AL) amyloidosis patients with highly advanced heart disease outside of clinical trials.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive DARZALEX FASPRO?

- DARZALEX FASPRO may be given alone or together with other medicines used to treat multiple myeloma.
- DARZALEX FASPRO will be given to you by your healthcare provider as an injection under the skin, in the stomach area (abdomen).
- DARZALEX FASPRO is injected over 3 to 5 minutes.
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of DARZALEX FASPRO and after each dose of DARZALEX FASPRO to help reduce the risk of serious allergic reactions and other reactions due to release of certain substances by your body (systemic).

If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What are the possible side effects of DARZALEX FASPRO?

DARZALEX FASPRO may cause serious reactions, including:

- **Serious allergic reactions and other severe injection-related reactions.** Serious allergic reactions and reactions due to release of certain substances by your body (systemic) that can lead to death, can happen with DARZALEX FASPRO. Tell your healthcare provider or get medical help right away if you get any of these symptoms during or after an injection of DARZALEX FASPRO.
 - shortness of breath or trouble breathing
 - dizziness or lightheadedness (hypotension)
 - cough
 - wheezing
 - heart beating faster than usual
 - low oxygen in the blood (hypoxia)
 - throat tightness
 - runny or stuffy nose
 - headache
 - itching
 - high blood pressure
 - nausea
 - vomiting
 - chills
 - fever
 - chest pain
- **Injection site reactions.** Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX FASPRO. Symptoms at the site of injection may include itching, swelling, bruising, pain, rash, bleeding, or redness of the skin. These reactions sometimes happen more than 24 hours after an injection of DARZALEX FASPRO.
- **Decreases in blood cell counts.** DARZALEX FASPRO can decrease white blood cell counts which help fight infections and blood cells called platelets which help to clot blood. Your healthcare provider will check your blood cell counts during treatment with DARZALEX FASPRO. Tell your healthcare provider if you develop fever or have signs of bruising or bleeding.
- **Changes in blood tests.** DARZALEX FASPRO can affect the results of blood tests to match your blood type. These changes can last for up to 6 months after your final dose of DARZALEX FASPRO. Your healthcare provider will do blood tests to match your blood type before you start treatment with DARZALEX FASPRO. **Tell all of your healthcare providers that you are being treated with DARZALEX FASPRO before receiving blood transfusions.**
- **Heart problems in patients with light chain (AL) amyloidosis.** Heart problems, in some cases fatal, have occurred. Your healthcare provider will monitor you closely during treatment with DARZALEX FASPRO. Call your healthcare provider right away if any of the following symptoms occur: chest pain, feeling faint, swollen legs, shortness of breath, or abnormal heart rhythm.

The most common side effects of DARZALEX FASPRO when used alone include cold-like symptoms (upper respiratory infection).

The most common side effects of DARZALEX FASPRO used in combination therapy include:

- tiredness
- nausea
- diarrhea
- shortness of breath
- trouble sleeping
- fever
- cough
- muscle spasms
- back pain
- vomiting
- cold-like symptoms (upper-respiratory infection)
- nerve damage causing tingling, numbness or pain
- constipation
- lung infection (pneumonia)
- swollen hands, ankles, or feet

These are not all the possible side effects of DARZALEX FASPRO.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of DARZALEX FASPRO.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about DARZALEX FASPRO that is written for health professionals.

What are the ingredients in DARZALEX FASPRO?

Active ingredient: daratumumab and hyaluronidase-fihj

Inactive ingredients: L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, and water for injection.

Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044 U.S. License Number 1864
For more information, call 1-800-526-7736 or go to www.DARZALEXFASPRO.com.

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 5 mL vial contains 100 mg of daratumumab (20 mg daratumumab per mL).

Each 20 mL vial contains 400 mg of daratumumab (20 mg daratumumab per mL).

Daratumumab is a human monoclonal IgG1 κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Excipients with known effect

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

The solution is colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

Pre- and post-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below “Recommended concomitant medications”, “Management of infusion-related reactions” and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy:

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-2-week dosing schedule is given at Week 9

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens):

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 2.

Table 2: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone (VMP); 6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54 ^a	every three weeks (total of 16 doses)
Week 55 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 7

^b First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT):

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone (VTd); 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 ^a	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 ^b	every two weeks (total of 4 doses)

^a First dose of the every-2-week dosing schedule is given at Week 9

^b First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen):

The recommended dose is DARZALEX 16 mg/kg body weight administered as an intravenous infusion according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 ^a	every three weeks (total of 5 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 10

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX, see section 5.1 and the corresponding Summary of Product Characteristics.

Infusion rates

Following dilution the DARZALEX infusion should be intravenously administered at the initial infusion rate presented in Table 5 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

To facilitate administration, the first prescribed 16 mg/kg dose at Week 1 may be split over two consecutive days i.e. 8 mg/kg on Day 1 and Day 2 respectively, see Table 5 below.

Table 5: Infusion rates for DARZALEX (16 mg/kg) administration

	Dilution volume	Initial rate (first hour)	Rate Increment ^a	Maximum rate
Week 1 Infusion				
<i>Option 1 (Single dose infusion)</i>				
Week 1 Day 1 (16 mg/kg)	1,000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<i>Option 2 (Split dose infusion)</i>				
Week 1 Day 1 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 1 Day 2 (8 mg/kg)	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Week 2 (16 mg/kg) infusion^b	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent (Week 3 onwards, 16 mg/kg) infusions^c	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

^a Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions.

^b A dilution volume of 500 mL for the 16 mg/kg dose should be used only if there were no IRRs the previous week. Otherwise, use a dilution volume of 1,000 mL.

^c A modified initial rate (100 mL/hour) for subsequent infusions (i.e. Week 3 onwards) should only be used only if there were no IRRs during the previous infusion. Otherwise, continue to use instructions indicated in the table for the Week 2 infusion rate.

Management of infusion-related reactions

Pre-infusion medications should be administered to reduce the risk of infusion-related reactions (IRRs) prior to treatment with DARZALEX.

For IRRs of any grade/severity, immediately interrupt the DARZALEX infusion and manage symptoms.

Management of IRRs may further require reduction in the rate of infusion, or treatment discontinuation of DARZALEX as outlined below (see section 4.4).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, the infusion should be resumed at no more than half the rate at which the IRR occurred. If the patient does not experience any further IRR symptoms, infusion rate escalation may be resumed at increments and intervals as clinically appropriate up to the maximum rate of 200 mL/hour (Table 5).
- Grade 3 (severe): Once reaction symptoms resolve, restarting of the infusion may be considered at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, infusion rate escalation may be resumed at increments and intervals as

appropriate (Table 5). The procedure above should be repeated in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARZALEX upon the third occurrence of a Grade 3 or greater infusion reaction.

- Grade 4 (life-threatening): Permanently discontinue DARZALEX treatment.

Missed dose (s)

If a planned dose of DARZALEX is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

Recommended concomitant medications

Pre-infusion medication

Pre-infusion medications should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every infusion of DARZALEX as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
Methylprednisolone 100 mg, or equivalent, administered intravenously. Following the second infusion, the dose of corticosteroid may be reduced (oral or intravenous methylprednisolone 60 mg).
 - Combination therapy:
Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX infusion. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-medication on DARZALEX infusion days (see section 5.1).
Dexamethasone is given intravenously prior to the first DARZALEX infusion and oral administration may be considered prior to subsequent infusions. Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX infusion days when patients have received dexamethasone as a pre-medication.
- Antipyretics (oral paracetamol 650 to 1,000 mg)
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-infusion medication

Post-infusion medications should be administered to reduce the risk of delayed infusion-related reactions as follows:

Monotherapy:

Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all infusions (beginning the day after the infusion).

Combination therapy:

Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX infusion. However, if a background regimen-specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX infusion, additional post-infusion medications may not be needed (see section 5.1).

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-infusion medications including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four infusions, if the patient experiences no major IRRs, these inhaled post-infusion medications may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustments are necessary for patients with hepatic impairment (see section 5.2).

Elderly

No dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

No data are available (see section 5.1).

Method of administration

DARZALEX is for intravenous use. It is administered as an intravenous infusion following dilution with sodium chloride 9 mg/mL (0.9%) solution for injection. For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Infusion-related reactions

DARZALEX can cause serious infusion-related reactions (IRRs), including anaphylactic reactions (see section 4.8).

All patients should be monitored throughout the infusion for IRRs. For patients that experience any Grade IRRs, continue monitoring post-infusion until symptoms resolve.

In clinical trials IRRs were reported in approximately half of all patients treated with DARZALEX.

The majority of IRRs occurred at the first infusion and were Grade 1-2 (see section 4.8). Four percent of all patients had an IRR at more than one infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension, laryngeal oedema and pulmonary oedema. Symptoms predominantly included nasal congestion, cough, throat irritation, chills, vomiting and nausea. Less common symptoms were wheezing, allergic rhinitis, pyrexia, chest discomfort, pruritus and hypotension (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics and corticosteroids to reduce the risk of IRRs prior to treatment with DARZALEX. DARZALEX infusion should be interrupted for IRRs of any severity and medical management/supportive treatment for IRRs should be instituted as needed. For patients with Grade 1, 2, or 3 IRRs, the infusion rate should be reduced when re-starting the infusion. If an anaphylactic reaction or life-threatening (Grade 4) infusion reaction occurs, appropriate emergency resuscitation should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX infusions. Additionally the use of post-infusion medications (e.g. inhaled corticosteroids, short and long acting bronchodilators) should be considered for patients with a history of chronic obstructive pulmonary disease to manage respiratory complications should they occur (see section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Monitor complete blood cell counts periodically during treatment according to manufacturer's prescribing information for background therapies. Monitor patients with neutropenia for signs of infection. DARZALEX delay may be required to allow recovery of blood cell counts. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Interference with Indirect Antiglobulin Test (Indirect Coombs Test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab infusion. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

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

Interference with determination of Complete Response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B virus (HBV) Reactivation

Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment with DARZALEX.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Excipients

Each 5 mL and 20 mL vial of DARZALEX contains 0.4 mmol and 1.6 mmol (9.3 mg and 37.3 mg) sodium, respectively. This corresponds to 0.46% and 1.86% of the WHO recommended maximum daily intake of 2 g sodium for an adult, respectively.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1 κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

Clinical pharmacokinetic assessments of daratumumab in combination with lenalidomide, pomalidomide, thalidomide, bortezomib and dexamethasone indicated no clinically-relevant drug-drug interaction between daratumumab and these small molecule medicinal products.

Interference with Indirect Antiglobulin Test (Indirect Coombs Test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching (see section 4.4). Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered (see section 4.4).

Interference with Serum Protein Electrophoresis and Immunofixation Tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

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

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk. Maternal IgG is excreted in human milk, but does not enter the neonatal and infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

DARZALEX has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions ($\geq 20\%$) were infusion reactions, fatigue, nausea, diarrhoea, constipation, pyrexia, dyspnoea, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, asthenia, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were sepsis, pneumonia, bronchitis, upper respiratory tract infection, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

Tabulated list of adverse reactions

Table 6 summarises the adverse drug reactions that occurred in patients receiving DARZALEX. The data reflects exposure to DARZALEX (16 mg/kg) in 2066 patients with multiple myeloma including 1910 patients who received DARZALEX in combination with background regimens and 156 patients who received DARZALEX as monotherapy. Post-marketing adverse reactions are also included.

In Study MMY3006, the number of CD34+ cell yield was numerically lower in the D-VTd arm compared with the VTd arm (Median: D-VTd: $6.3 \times 10^6/\text{kg}$; VTd $8.9 \times 10^6/\text{kg}$) and among those who completed mobilisation, more patients in the D-VTd group received plerixafor compared to those in the VTd arm (D-VTd: 21.7%; VTd: 7.9%). The rates of engraftment and haematopoietic reconstitution was similar among the transplanted subjects in the D-VTd and VTd arms (D-VTd: 99.8%; VTd: 99.6%; as measured by the recovery of neutrophils $> 0.5 \times 10^9/\text{L}$, leukocytes $> 1.0 \times 10^9/\text{L}$, and platelets $> 50 \times 10^9/\text{L}$ without transfusion).

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 6: Adverse reactions in multiple myeloma patients treated with DARZALEX 16 mg/kg

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia ^a	Very Common	16	10
	Bronchitis ^a		17	2
	Upper respiratory tract infection ^a		41	3
	Urinary tract infection	Common	8	1
	Influenza		5	1*
	Sepsis ^a		4	4
	Hepatitis B Virus reactivation ^b	Uncommon	-	-
Blood and lymphatic system disorders	Neutropenia ^a	Very Common	44	39
	Thrombocytopenia ^a		31	19
	Anaemia ^a		27	12
	Lymphopenia ^a		14	11
	Leukopenia ^a		12	6
Immune system disorders	Anaphylactic reaction ^b	Rare	-	-
Metabolism and nutrition	Decreased appetite	Very Common	12	1

disorders	Hyperglycemia	Common	7	3
	Hypocalcemia		6	1
	Dehydration		3	1*
Nervous system disorders	Peripheral sensory neuropathy	Very Common	32	3
	Paraesthesia		11	<1
	Headache		12	<1*
Cardiac disorders	Atrial fibrillation	Common	4	1
Vascular disorders	Hypertension ^a	Very Common	10	5
Respiratory, thoracic and mediastinal disorders	Cough ^a	Very Common	25	<1*
	Dyspnoea ^a		21	3
	Pulmonary oedema ^a	Common	1	<1
Gastrointestinal disorders	Diarrhoea	Very Common	32	4
	Constipation		33	1
	Nausea		26	2*
	Vomiting		16	1*
	Pancreatitis ^a	Common	1	1
Musculoskeletal and connective tissue disorders	Back pain	Very Common	18	2
	Muscle spasms		14	<1*
General disorders and administration site conditions	Fatigue	Very Common	26	4
	Oedema peripheral ^a		26	1
	Pyrexia		23	2
	Asthenia		21	2
	Chills	Common	9	<1*
Injury, poisoning and procedural complications	Infusion-related reaction ^c	Very Common	40	4

* No Grade 4

^a Indicates grouping of terms

^b Post-marketing adverse reaction

^c Infusion-related reaction includes terms determined by investigators to be related to infusion, see below

Infusion-related reactions

In clinical trials (monotherapy and combination treatments; N=2066) the incidence of any grade infusion-related reactions was 37% with the first (16 mg/kg, Week 1) infusion of DARZALEX, 2% with the Week 2 infusion, and cumulatively 6% with subsequent infusions. Less than 1% of patients had a Grade 3/4 infusion-related reaction with the Week 2 or subsequent infusions.

The median time to onset of a reaction was 1.5 hours (range: 0 to 72.8 hours). The incidence of infusion modifications due to reactions was 36%. Median durations of 16 mg/kg infusions for the 1st Week, 2nd Week and subsequent infusions were approximately 7, 4 and 3 hours respectively.

Severe infusion-related reactions included bronchospasm, dyspnoea, laryngeal oedema, pulmonary oedema, hypoxia, and hypertension. Other adverse infusion-related reactions included nasal congestion, cough, chills, throat irritation, vomiting and nausea (see section 4.4).

When DARZALEX dosing was interrupted in the setting of ASCT (Study MMY3006) for a median of 3.75 (range: 2.4; 6.9) months, upon re-initiation of DARZALEX the incidence of IRRs was 11% at first infusion following ASCT. Infusion rate/dilution volume used upon re-initiation was that used for the last DARZALEX infusion prior to interruption due to ASCT. IRRs occurring at re-initiation of DARZALEX following ASCT were consistent in terms of symptoms and severity (Grade 3/4: <1%) with those reported in previous studies at Week 2 or subsequent infusions.

In Study MMY1001, patients receiving daratumumab combination treatment (n=97) were administered the first 16 mg/kg daratumumab dose at Week 1 split over two days i.e. 8 mg/kg on Day 1 and Day 2 respectively. The incidence of any grade infusion-related reactions was 42%, with 36% of patients experiencing infusion-related reactions on Day 1 of Week 1, 4% on Day 2 of Week 1, and 8% with subsequent infusions. The median time to onset of a reaction was 1.8 hours (range: 0.1 to 5.4 hours). The incidence of infusion interruptions due to reactions was 30%. Median durations of

infusions were 4.2 h for Week 1-Day 1, 4.2 h for Week 1-Day 2, and 3.4 hours for the subsequent infusions.

Infections

In patients receiving DARZALEX combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients. Fatal infections were primarily due to pneumonia and sepsis.

In patients receiving DARZALEX combination therapy, fatal infections (Grade 5) were reported as follows:

Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other special populations

In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients

Of the 2459 patients who received DARZALEX at the recommended dose, 38% were 65 to 75 years of age, and 15% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1213), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=710), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Symptoms and signs

There has been no experience of overdosage in clinical studies. Doses up to 24 mg/kg have been administered intravenously in a clinical study.

Treatment

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24

Mechanism of action

Daratumumab is an IgG1 κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

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

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

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

Immunogenicity

In patients treated with intravenous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

Clinical efficacy and safety

Newly diagnosed multiple myeloma

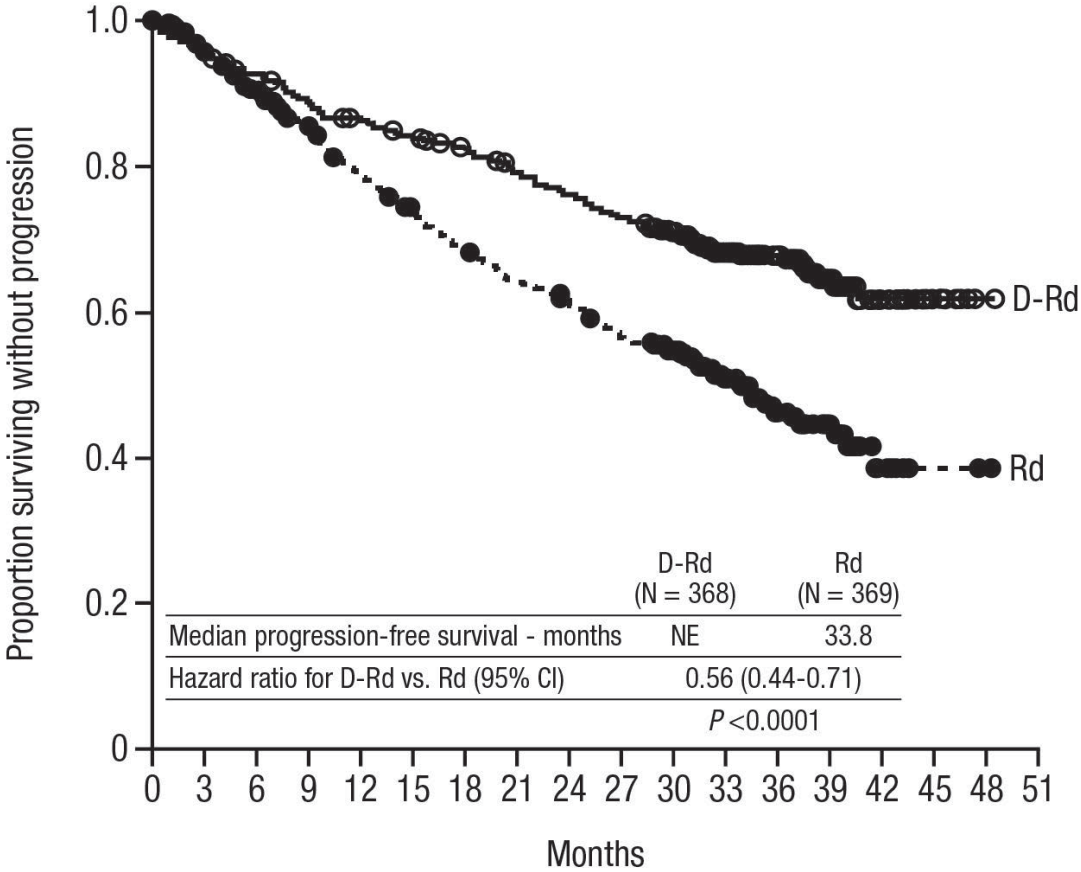
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, the dexamethasone dose was given as a pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥ 75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥ 2 . Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; $p < 0.0001$), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; $p < 0.0001$).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51
Rd	369	333	307	280	254	236	219	204	194	177	161	113	64	33	10	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	233	174	131	70	24	7	1	0

Additional efficacy results from Study MMY3008 are presented in Table 7 below.

Table 7: Additional efficacy results from Study MMY3008^a

	DRd (n=368)	Rd (n=369)
Overall response (sCR+CR+VGPR+PR) n(%) ^a	342 (92.9%)	300 (81.3%)
p-value ^b	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value ^b	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value ^b	<0.0001	
MRD negativity rate ^{a,c} n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
Odds ratio with 95% CI ^d	4.04 (2.55, 6.39)	
p-value ^e	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.

^e p-value from Fisher's exact test.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

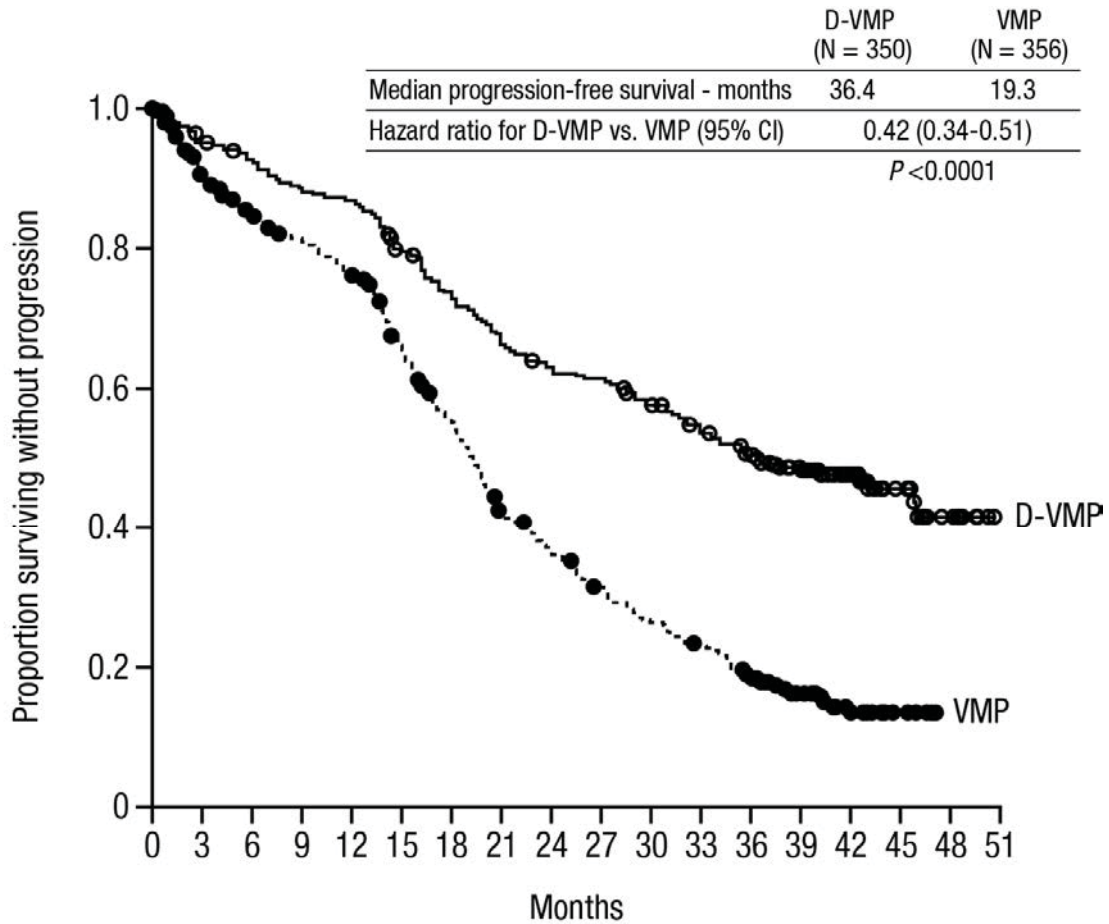
Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous (SC) injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomised: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007

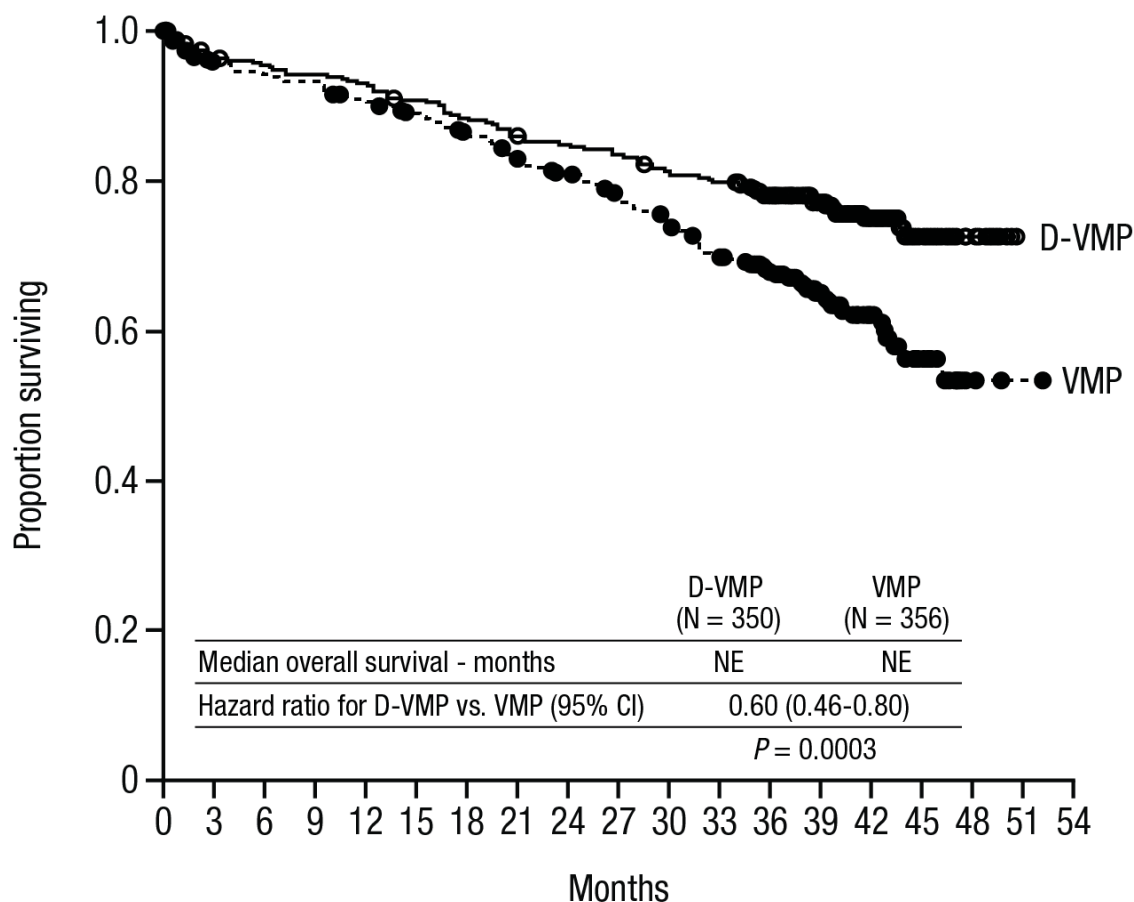


No. at risk

VMP	356	304	278	263	246	207	171	128	110	93	78	67	51	29	15	7	0	0
D-VMP	350	322	312	298	292	265	243	220	207	202	188	173	160	113	63	26	9	0

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



No. at risk

VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

Additional efficacy results from Study MMY3007 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3007^a

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value ^b	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) ^c (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI ^d	4.36 (2.64, 7.21)	
p-value ^e	<0.0001	

D-VMP=daratumumab-bortezomib-melphalan-prednisone; VMP=bortezomib-melphalan-prednisone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.

^e p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration

of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); $p < 0.0001$). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate: 29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):

Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with DARZALEX 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

Bortezomib was administered by SC injection or IV injection at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28 day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of DARZALEX infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65) years. All patients were ≤ 65 years: 43% were in the age group $\geq 60-65$ years, 41% were in the age group $\geq 50-60$ years and 16% below age of 50 years. The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 9: Efficacy results from Study MMY3006^a

	D-VTd (n=543)	VTd (n=542)	P value ^b
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity ^{c, d} n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI ^e	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better ^c n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI ^e	2.06 (1.56, 2.72)		

D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d Regardless of response per IMWG

^e Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma

Monotherapy:

The clinical efficacy and safety of DARZALEX monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 10 below.

Table 10: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	DARZALEX 16 mg/kg N=106
Overall response rate ¹ (ORR: sCR+CR+VGPR+PR) [n (%)]	31 (29.2)
95% CI (%)	(20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)
Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)

Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

¹ Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.

At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg DARZALEX until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

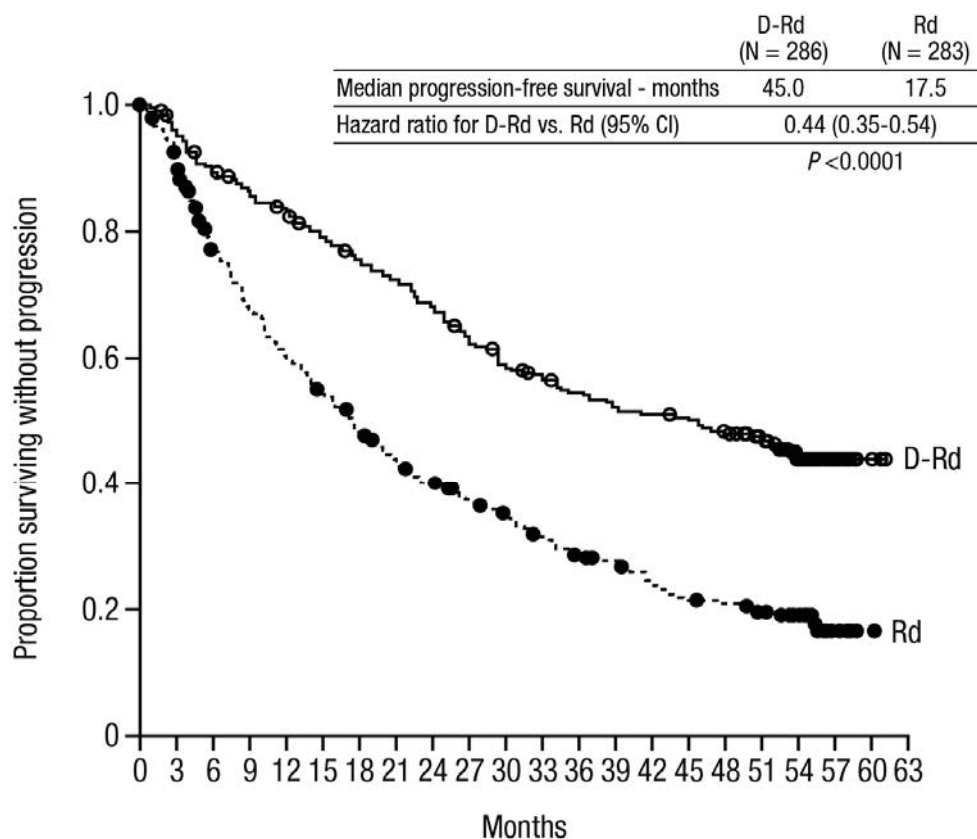
Combination treatment with lenalidomide:

Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 4).

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



No. at risk

Rd	283	249	206	181	160	144	127	112	102	91	83	75	66	63	53	48	45	40	28	5	1	0
D-Rd	286	266	249	238	229	215	204	195	184	168	156	151	143	136	134	131	125	115	76	16	3	0

Additional efficacy results from Study MMY3003 are presented in Table 11 below.

Table 11: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value ^a	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI) ^b (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI ^c	9.31 (4.31, 20.09)	
P-value ^d	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10^{-5}

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.

^d p-value is from a Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; *p*=0.0534).

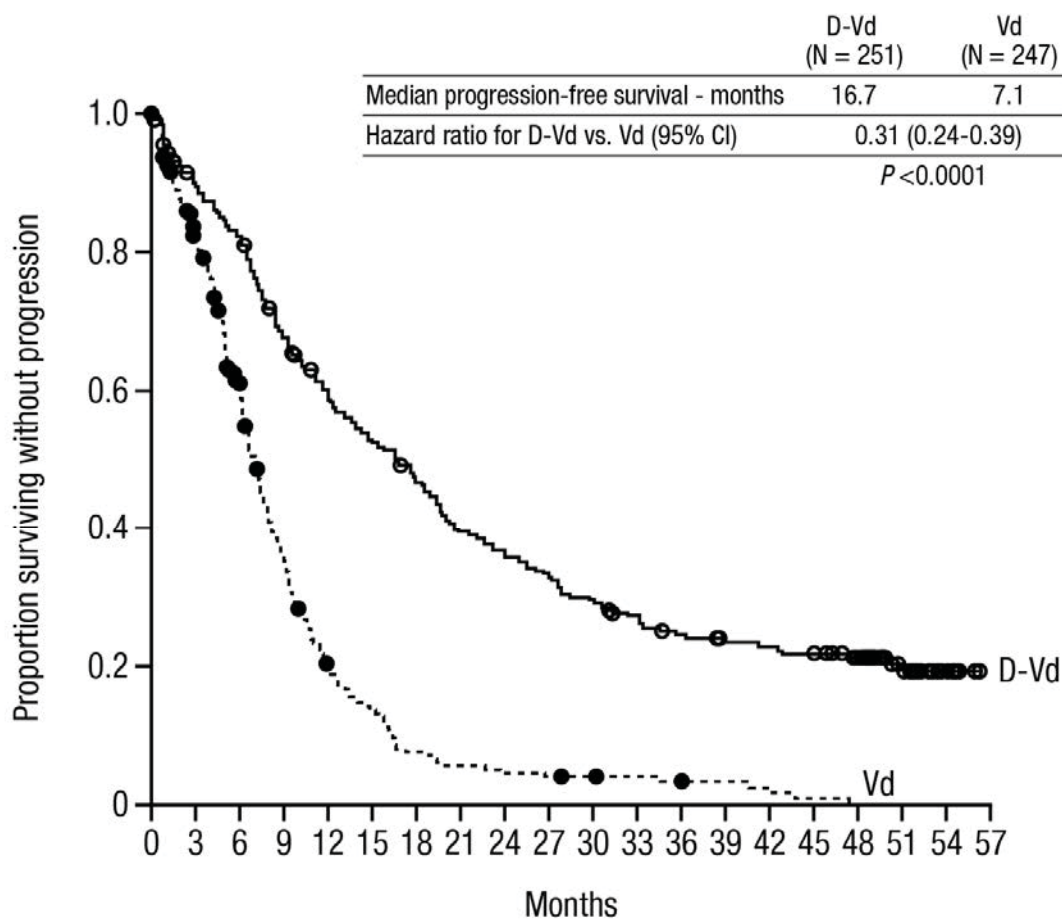
Combination treatment with bortezomib:

Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. DARZALEX treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DVd versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



No. at risk	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57
Vd	247	182	129	74	39	27	15	11	9	8	7	6	5	4	2	1	0	0	0	0
D-Vd	251	215	198	161	138	123	109	92	85	77	68	61	54	50	48	46	38	20	7	0

Additional efficacy results from Study MMY3004 are presented in Table 12 below.

Table 12: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value ^a	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI) ^b	8.8% (5.6%, 13.0%)	1.2% (0.3%, 3.5%)
Odds ratio with 95% CI ^c	9.04 (2.53, 32.21)	
P-value ^d	0.0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10⁻⁵

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DVd.

^d p-value is from Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e. greater than 20 ms) at daratumumab C_{max} .

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with DARZALEX in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of daratumumab following intravenous administration of daratumumab monotherapy were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg.

In the 1 to 24 mg/kg cohorts, peak serum concentrations (C_{max}) after the first dose increased in approximate proportion to dose and volume of distribution was consistent with initial distribution into the plasma compartment. Following the last weekly infusion, C_{max} increased in a greater than dose-proportional manner, consistent with target mediated drug disposition. Increases in AUC were more than dose-proportional and clearance (CL) decreased with increasing dose. These observations suggest CD38 may become saturated at higher doses, after which the impact of target binding clearance is minimised and the clearance of daratumumab approximates the linear clearance of endogenous IgG1. Clearance also decreased with multiple doses, which may be related to tumour burden decreases.

Terminal half-life increases with increasing dose and with repeated dosing. The mean (standard deviation [SD]) estimated terminal half-life of daratumumab following the first 16 mg/kg dose was 9 (4.3) days. The estimated terminal half-life of daratumumab following the last 16 mg/kg dose increased, but there are insufficient data for a reliable estimation. Based on population PK analysis, the mean (SD) half-life associated with non-specific linear elimination was approximately 18 (9) days; this is the terminal half-life that can be expected upon complete saturation of target mediated clearance and repeat dosing of daratumumab.

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

Four population PK analyses were performed to describe the PK characteristics of daratumumab and to evaluate the influence of covariates on the disposition of daratumumab in patients with multiple myeloma; Analysis 1 (n=223) in patients receiving DARZALEX monotherapy while Analysis 2 (n=694), Analysis 3 (n=352) and Analysis 4 (n=355) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Analysis 2 included 694 patients (n=326 for lenalidomide-dexamethasone; n=246 for bortezomib-dexamethasone; n=99 for pomalidomide-dexamethasone; n=11 for bortezomib-melphalan-prednisone; and n=12 for bortezomib-thalidomide-dexamethasone), Analysis 3 included 352 patients (bortezomib-melphalan-prednisone) and Analysis 4 included 355 patients (lenalidomide-dexamethasone).

Based on the population PK analysis of daratumumab monotherapy (Analysis 1), daratumumab steady state is achieved approximately 5 months into the every 4-week dosing period (by the 21st infusion), and the mean (SD) ratio of C_{max} at steady-state to C_{max} after the first dose was 1.6 (0.5). The mean (SD) central volume of distribution is 56.98 (18.07) mL/kg.

Three additional population PK analyses (Analysis 2, Analysis 3 and Analysis 4) were conducted in patients with multiple myeloma that received daratumumab combination therapies. Daratumumab concentration-time profiles were similar following the monotherapy and combination therapies. The mean estimated terminal half-life associated with linear clearance in combination therapy was approximately 15-23 days.

Based on the four population PK analyses (Analyses 1-4) body weight was identified as a statistically significant covariate for daratumumab clearance. Therefore, body weight based dosing is an appropriate dosing strategy for the multiple myeloma patients.

Simulation of daratumumab pharmacokinetics was conducted for all recommended dosing schedules in 1,309 patients with multiple myeloma. The simulation results confirmed that the split and single dosing for the first dose provide similar PK, with the exception of the PK profile in the first day of the treatment.

Special populations

Age and gender

Based on four individual population PK analyses (1-4) in patients receiving daratumumab monotherapy or various combination therapies (Analyses 1-4), age (range: 31-93 years) had no clinically important effect on the PK of daratumumab, and the exposure of daratumumab was similar between younger (aged <65 years, n=518) and older (aged ≥65 to <75 years n=761; aged ≥75 years, n=334) patients.

Gender did not affect exposure of daratumumab to a clinically relevant degree in the population PK analyses.

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Four individual population PK analyses were performed based on pre-existing renal function data in patients receiving daratumumab monotherapy, or various combination therapies (Analyses 1-4), and included a total of 441 patients with normal renal function (creatinine clearance [CRCL] ≥90 mL/min), 621 with mild renal impairment (CRCL <90 and ≥60 mL/min), 523 with moderate renal impairment (CRCL <60 and ≥30 mL/min), and 27 with severe renal impairment or end stage renal disease (CRCL <30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. Changes in hepatic function are unlikely to have any effect on the elimination of daratumumab since IgG1 molecules such as daratumumab are not metabolised through hepatic pathways.

Four individual population PK analyses were performed in patients receiving daratumumab monotherapy or various combination therapies (Analyses 1-4), and included a total of 1404 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] ≤ upper limit of normal [ULN]), 189 with mild hepatic impairment (TB 1.0 x to 1.5 x ULN or AST >ULN) and 8 patients with moderate (TB > 1.5 x to 3.0 x ULN; n=7), or severe (TB > 3.0 x ULN; n=1) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function.

Race

Based on four individual population PK analyses in patients receiving either daratumumab monotherapy or various combination therapies (Analyses 1-4), the exposure to daratumumab was similar between white (n=1371) and non-white subjects (n=242).

5.3 Preclinical safety data

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

Carcinogenicity and mutagenicity

No animal studies have been performed to establish the carcinogenic potential of daratumumab.

Reproductive toxicology

No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development.

Fertility

No animal studies have been performed to determine potential effects on fertility in males or females.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glacial acetic acid
Mannitol (E421)
Polysorbate 20
Sodium acetate trihydrate
Sodium chloride
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials

24 months

After dilution

From a microbiological point of view, unless the method of opening/ dilution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and should be no more than 24 hours at refrigerated conditions (2°C-8°C) protected from light, followed by 15 hours (including infusion time) at room temperature (15°C-25°C) and room light.

6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

5 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 100 mg of daratumumab. Pack size of 1 vial.

20 mL concentrate in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 400 mg of daratumumab. Pack size of 1 vial.

DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

6.6 Special precautions for disposal and other handling

This medicinal product is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride (see section 4.2). Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C-25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C-8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/001
EU/1/16/1101/002
EU/1/16/1101/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016

Date of latest renewal: 24 April 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1,800 mg solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mL vial of solution for injection contains 1,800 mg of daratumumab (120 mg daratumumab per mL).

Daratumumab is a human monoclonal IgG1 κ antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Excipients with known effect

Each 15 mL vial of solution for injection contains 735.1 mg of sorbitol (E420).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

The solution is clear to opalescent, colourless to yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DARZALEX is indicated:

- in combination with lenalidomide and dexamethasone or with bortezomib, melphalan and prednisone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.
- in combination with bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant.
- in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.
- as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified.

DARZALEX should be administered by a healthcare professional, and the first dose should be administered in an environment where resuscitation facilities are available.

It is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed.

For patients currently receiving daratumumab intravenous formulation, DARZALEX solution for subcutaneous injection may be used as an alternative to the intravenous daratumumab formulation starting at the next scheduled dose.

Pre- and post-injection medicinal products should be administered to reduce the risk of infusion-related reactions (IRRs) with daratumumab. See below “Recommended concomitant medicinal products” and section 4.4.

Posology

Dosing schedule in combination with lenalidomide (4-week cycle regimen) and for monotherapy

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 1.

Table 1: DARZALEX dosing schedule in combination with lenalidomide (4-week cycle dosing regimen) and monotherapy

Weeks	Schedule
Weeks 1 to 8	weekly (total of 8 doses)
Weeks 9 to 24 ^a	every two weeks (total of 8 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-2-week dosing schedule is given at Week 9

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib, melphalan and prednisone (6-week cycle regimens)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 2.

Table 2: DARZALEX dosing schedule in combination with bortezomib, melphalan and prednisone (VMP); 6-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 6	weekly (total of 6 doses)
Weeks 7 to 54 ^a	every three weeks (total of 16 doses)
Week 55 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 7

^b First dose of the every-4-week dosing schedule is given at Week 55

Bortezomib is given twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle, followed by **once** weekly at Weeks 1, 2, 4 and 5 for eight more 6-week cycles. For information on the VMP dose and dosing schedule when administered with DARZALEX solution for subcutaneous injection, see section 5.1.

Dosing schedule in combination with bortezomib, thalidomide and dexamethasone (4-week cycle regimens) for treatment of newly diagnosed patients eligible for autologous stem cell transplant (ASCT)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 3.

Table 3: DARZALEX dosing schedule in combination with bortezomib, thalidomide and dexamethasone ([VTd]; 4-week cycle dosing regimen)

Treatment phase	Weeks	Schedule
Induction	Weeks 1 to 8	weekly (total of 8 doses)
	Weeks 9 to 16 ^a	every two weeks (total of 4 doses)
Stop for high dose chemotherapy and ASCT		
Consolidation	Weeks 1 to 8 ^b	every two weeks (total of 4 doses)

^a First dose of the every-2-week dosing schedule is given at Week 9

^b First dose of the every-2-week dosing schedule is given at Week 1 upon re-initiation of treatment following ASCT

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Dosing schedule in combination with bortezomib (3-week cycle regimen)

The recommended dose is 1,800 mg of DARZALEX solution for subcutaneous injection administered over approximately 3-5 minutes according to the following dosing schedule in Table 4.

Table 4: DARZALEX dosing schedule in combination with bortezomib (3-week cycle dosing regimen)

Weeks	Schedule
Weeks 1 to 9	weekly (total of 9 doses)
Weeks 10 to 24 ^a	every three weeks (total of 5 doses)
Week 25 onwards until disease progression ^b	every four weeks

^a First dose of the every-3-week dosing schedule is given at Week 10

^b First dose of the every-4-week dosing schedule is given at Week 25

For dose and schedule of medicinal products administered with DARZALEX solution for subcutaneous injection, see section 5.1 and the corresponding Summary of Product Characteristics.

Missed dose

If a planned dose of DARZALEX is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

No dose reductions of DARZALEX are recommended. Dose delay may be required to allow recovery of blood cell counts in the event of haematological toxicity (see section 4.4). For information concerning medicinal products given in combination with DARZALEX, see corresponding Summary of Product Characteristics.

In clinical studies, no modification to rate or dose of DARZALEX solution for subcutaneous injection was required to manage IRRs.

Recommended concomitant medicinal products

Pre-injection medicinal product

Pre-injection medicinal products (oral or intravenous) should be administered to reduce the risk of IRRs to all patients 1-3 hours prior to every administration of DARZALEX solution for subcutaneous injection as follows:

- Corticosteroid (long-acting or intermediate-acting)
 - Monotherapy:
 - Methylprednisolone 100 mg, or equivalent. Following the second injection, the dose of corticosteroid may be reduced to methylprednisolone 60 mg.
 - Combination therapy:
 - Dexamethasone 20 mg (or equivalent), administered prior to every DARZALEX solution for subcutaneous injection. When dexamethasone is the background-regimen specific corticosteroid, the dexamethasone treatment dose will instead serve as pre-injection

medicinal product on DARZALEX administration days (see section 5.1). Additional background regimen specific corticosteroids (e.g. prednisone) should not be taken on DARZALEX administration days when patients have received dexamethasone (or equivalent) as a pre-injection medicinal product.

- Antipyretics (paracetamol 650 to 1,000 mg).
- Antihistamine (oral or intravenous diphenhydramine 25 to 50 mg or equivalent).

Post-injection medicinal product

Post-injection medicinal products should be administered to reduce the risk of delayed IRRs as follows:

- **Monotherapy:**
Oral corticosteroid (20 mg methylprednisolone or equivalent dose of an intermediate-acting or long-acting corticosteroid in accordance with local standards) should be administered on each of the two days following all injections (beginning the day after the injection).
- **Combination therapy:**
Consider administering low-dose oral methylprednisolone (≤ 20 mg) or equivalent the day after the DARZALEX injection. However, if a background regimen specific corticosteroid (e.g. dexamethasone, prednisone) is administered the day after the DARZALEX injection, additional post-injection medicinal products may not be needed (see section 5.1).

If the patient experiences no major IRRs after the first three injections, post-injection corticosteroids (excluding any background regimen corticosteroids) may be discontinued.

Additionally, for patients with a history of chronic obstructive pulmonary disease, the use of post-injection medicinal products including short and long acting bronchodilators, and inhaled corticosteroids should be considered. Following the first four injections, if the patient experiences no major IRRs, these inhaled post-injection medicinal products may be discontinued at the discretion of the physician.

Prophylaxis for herpes zoster virus reactivation

Anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation.

Special populations

Renal impairment

No formal studies of daratumumab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses no dosage adjustment is necessary for patients with renal impairment (see section 5.2).

Hepatic impairment

No formal studies of daratumumab in patients with hepatic impairment have been conducted. No dosage adjustments are necessary for patients with hepatic impairment (see section 5.2).

Elderly

No dose adjustments are considered necessary (see section 5.2).

Paediatric population

The safety and efficacy of DARZALEX in children aged below 18 years of age have not been established.

No data are available (see section 5.1).

Body weight (>120 kg)

Limited number of patients with body weight >120 kg have been studied using flat-dose (1,800 mg) DARZALEX solution for subcutaneous injection and efficacy in these patients has not been

established. No dose adjustment based on body weight can currently be recommended (see sections 4.4 and 5.2).

Method of administration

DARZALEX subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 6.6 for special precautions prior to administration.

To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Inject 15 mL DARZALEX solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX solution for subcutaneous injection at other sites of the body as no data are available.

Injection sites should be rotated for successive injections.

DARZALEX solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.

Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.

During treatment with DARZALEX solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Infusion-related reactions

DARZALEX solution for subcutaneous injection can cause severe and/or serious IRRs, including anaphylactic reactions. In clinical studies, approximately 11% (52/490) of patients experienced an IRR. Most IRRs occurred following the first injection and were Grade 1-2. IRRs occurring with subsequent injections were seen in less than 1% of patients (see section 4.8).

The median time to onset of IRRs following DARZALEX injection was 3.7 hours (range 0.15-83 hours). The majority of IRRs occurred on the day of treatment. Delayed IRRs have occurred in less than 1% of patients.

Signs and symptoms of IRRs may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.8).

Patients should be pre-medicated with antihistamines, antipyretics, and corticosteroids as well as monitored and counselled regarding IRRs, especially during and following the first and second injections. If an anaphylactic reaction or life-threatening (Grade 4) reactions occur, appropriate

emergency care should be initiated immediately. DARZALEX therapy should be discontinued immediately and permanently (see sections 4.2 and 4.3).

To reduce the risk of delayed IRRs, oral corticosteroids should be administered to all patients following DARZALEX injection (see section 4.2). Patients with a history of chronic obstructive pulmonary disease may require additional post-injection medicinal products to manage respiratory complications. The use of post-injection medicinal products (e.g. short- and long-acting bronchodilators and inhaled corticosteroids) should be considered for patients with chronic obstructive pulmonary disease (see section 4.2).

Neutropenia/Thrombocytopenia

DARZALEX may increase neutropenia and thrombocytopenia induced by background therapy (see section 4.8).

Complete blood cell counts should be monitored periodically during treatment according to manufacturer's prescribing information for background therapies. Patients with neutropenia should be monitored for signs of infection. DARZALEX delay may be required to allow recovery of blood cell counts. In lower body weight patients receiving DARZALEX subcutaneous formulation, higher rates of neutropenia were observed; however, this was not associated with higher rates of serious infections. No dose reduction of DARZALEX is recommended. Consider supportive care with transfusions or growth factors.

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 found at low levels on red blood cells (RBCs) and may result in a positive indirect Coombs test. Daratumumab-mediated positive indirect Coombs test may persist for up to 6 months after the last daratumumab administration. It should be recognised that daratumumab bound to RBCs may mask detection of antibodies to minor antigens in the patient's serum. The determination of a patient's ABO and Rh blood type are not impacted.

Patients should be typed and screened prior to starting daratumumab treatment. Phenotyping may be considered prior to starting daratumumab treatment as per local practice. Red blood cell genotyping is not impacted by daratumumab and may be performed at any time.

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

Interference with determination of complete response

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the determination of complete response and of disease progression in some patients with IgG kappa myeloma protein.

Hepatitis B virus (HBV) reactivation

Hepatitis B virus reactivation, in some cases fatal, has been reported in patients treated with DARZALEX. HBV screening should be performed in all patients before initiation of treatment with DARZALEX.

For patients with evidence of positive HBV serology, monitor for clinical and laboratory signs of HBV reactivation during, and for at least six months following the end of DARZALEX treatment. Manage patients according to current clinical guidelines. Consider consulting a hepatitis disease expert as clinically indicated.

In patients who develop reactivation of HBV while on DARZALEX, suspend treatment with DARZALEX and institute appropriate treatment. Resumption of DARZALEX treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians with expertise in managing HBV.

Body weight (>120 kg)

There is a potential for reduced efficacy with DARZALEX solution for subcutaneous injection in patients with body weight >120 kg (see sections 4.2 and 5.2).

Excipients

This medicinal product contains sorbitol (E420). Patients with rare hereditary fructose intolerance (HFI) should not take this medicinal product (see section 2).

This medicinal product also contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

As an IgG1 κ monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact daratumumab are unlikely to represent major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of daratumumab. Due to the high affinity to a unique epitope on CD38, daratumumab is not anticipated to alter drug-metabolising enzymes.

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

Interference with indirect antiglobulin test (indirect Coombs test)

Daratumumab binds to CD38 on RBCs and interferes with compatibility testing, including antibody screening and cross matching (see section 4.4). Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or other locally validated methods. Since the Kell blood group system is also sensitive to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. Alternatively, phenotyping or genotyping may also be considered (see section 4.4).

Interference with serum protein electrophoresis and immunofixation tests

Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using a validated daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception

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

Pregnancy

There are no human or animal data to assess the risk of daratumumab use during pregnancy. IgG1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. Therefore daratumumab should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh the potential risks to the fetus. If the patient becomes pregnant while taking this medicine, the patient should be informed of the potential risk to the fetus.

Breast-feeding

It is not known whether daratumumab is excreted into human or animal milk.

Maternal IgG is excreted in human milk, but does not enter the neonatal and newborn/infant circulations in substantial amounts as they are degraded in the gastrointestinal tract and not absorbed.

The effect of daratumumab on newborns/infants is unknown. A decision should be made whether to discontinue breast-feeding or to discontinue DARZALEX therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

No data are available to determine potential effects of daratumumab on fertility in males or females (see section 5.3).

4.7 Effects on ability to drive and use machines

DARZALEX has no or negligible influence on the ability to drive and use machines. However, fatigue has been reported in patients taking daratumumab and this should be taken into account when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions of any grade ($\geq 20\%$ patients) with daratumumab (either intravenous or subcutaneous formulations) when administered either as monotherapy or combination treatment were IRRs, fatigue, nausea, diarrhoea, constipation, pyrexia, cough, neutropenia, thrombocytopenia, anaemia, oedema peripheral, peripheral sensory neuropathy and upper respiratory tract infection. Serious adverse reactions were pneumonia, bronchitis, upper respiratory tract infection, sepsis, pulmonary oedema, influenza, pyrexia, dehydration, diarrhoea and atrial fibrillation.

With the exception of IRRs (see Table 5 below), the safety profile of DARZALEX subcutaneous formulation (evaluated in 260 and 258 patients treated with the subcutaneous and intravenous formulations respectively) from the Phase III study MMY3012 was similar to the known safety profile of the intravenous formulation. Neutropenia is the only adverse reaction reported at $\geq 5\%$ higher frequency for DARZALEX subcutaneous formulation compared to intravenous daratumumab (Grade 3 or 4: 13% vs 8%, respectively).

Tabulated list of adverse reactions

Table 5 summarises the adverse reactions that occurred in patients receiving DARZALEX subcutaneous formulation or intravenous formulation of daratumumab.

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

The safety data also reflects exposure to intravenous daratumumab (16 mg/kg) in 2324 patients with multiple myeloma including 1910 patients who received intravenous daratumumab in combination with background regimens and 414 patients who received intravenous daratumumab as monotherapy. Post-marketing adverse reactions are also included.

Frequencies are defined as very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$) and very rare ($< 1/10,000$). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 5: Adverse reactions in multiple myeloma patients treated with intravenous daratumumab or subcutaneous daratumumab

System Organ Class	Adverse reaction	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Upper respiratory tract infection ^a	Very Common	38%	2%
	Bronchitis ^a	Very Common	14%	2%
	Pneumonia ^a	Very Common	14%	9%
	Urinary tract infection	Common	7%	1%
	Influenza	Common	4%	1% [#]
	Sepsis ^a	Common	4%	3%
	Hepatitis B reactivation ^a	Uncommon	<1%	<1%
Blood and lymphatic system disorders	Neutropenia ^a	Very Common	40%	33%
	Thrombocytopenia ^a	Very Common	30%	18%
	Anaemia ^a	Very Common	27%	12%
	Lymphopenia ^a	Very Common	13%	11%
	Leukopenia ^a	Very Common	11%	6%
Immune system disorders	Anaphylactic reaction ^b	Rare	-	-
Metabolism and nutrition disorders	Decreased appetite	Very Common	10%	1%
	Hyperglycaemia	Common	6%	3%
	Hypocalcaemia	Common	5%	1%
	Dehydration	Common	2%	1% [#]
Psychiatric disorders	Insomnia	Very Common	14%	1% [#]
Nervous system disorders	Peripheral sensory neuropathy	Very Common	26%	3%
	Headache	Very Common	11%	<1% [#]
	Dizziness	Common	9%	<1% [#]
	Paraesthesia	Common	9%	<1%
Cardiac disorders	Atrial fibrillation	Common	3%	1%
Vascular disorders	Hypertension ^a	Very Common	10%	5%
Respiratory, thoracic and mediastinal disorders	Cough ^a	Very Common	22%	<1% [#]
	Dyspnoea ^a	Very Common	18%	2%
	Pulmonary oedema ^a	Common	1%	<1%
Gastrointestinal disorders	Diarrhoea	Very Common	29%	3%
	Constipation	Very Common	28%	1%
	Nausea	Very Common	23%	1% [#]
	Vomiting	Very Common	14%	1% [#]
	Pancreatitis ^a	Common	1%	<1%
Skin and subcutaneous tissue disorders	Rash	Common	9%	<1% [#]
	Pruritus	Common	5%	<1% [#]
Musculoskeletal and connective tissue disorders	Back pain	Very Common	17%	2%
	Muscle spasms	Very Common	12%	<1% [#]
	Arthralgia	Very Common	10%	1% [#]
	Musculoskeletal chest pain	Common	6%	<1% [#]
General disorders and administration site conditions	Fatigue	Very Common	23%	3%
	Oedema peripheral ^a	Very Common	22%	1%
	Pyrexia	Very Common	22%	1%
	Asthenia	Very Common	18%	2%
	Chills	Common	9%	<1% [#]
	Injection site erythema ^c	Common	4%	0
	Injection site reactions ^{d,c}	Common	8%	0
Injury, poisoning and procedural complications	Infusion-related reactions ^c			
	Daratumumab intravenous ^f	Very Common	39%	5%
	Daratumumab subcutaneous ^c	Very Common	11%	1% [#]

-
- # No grade 4
 - a Indicates a grouping of terms.
 - b Based on post-marketing adverse reactions.
 - c Infusion-related reactions includes terms determined by investigators as related to infusion/injection of daratumumab.
 - d Injection site reactions includes terms determined by investigators as related to injection of daratumumab.
 - e Frequency based on daratumumab subcutaneous studies only (N=490).
 - f Frequency based on daratumumab intravenous studies only (N=2324).

Note: Based on 2814 multiple myeloma patients treated with daratumumab intravenous or daratumumab subcutaneous.

Description of selected adverse reactions

Infusion-related reactions (IRRs)

In clinical studies (monotherapy and combination treatments; N=490) with DARZALEX subcutaneous formulation, the incidence of any grade IRRs was 10.2% with the first injection of DARZALEX (1,800 mg, Week 1), 0.2% with the Week 2 injection, and 0.8% with subsequent injections. Grade 3 IRRs were seen in 1.4% of patients. No patients had Grade 4 IRRs.

Signs and symptoms of IRR may include respiratory symptoms, such as nasal congestion, cough, throat irritation, allergic rhinitis, wheezing as well as pyrexia, chest pain, pruritis, chills, vomiting, nausea, and hypotension. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnoea, hypertension and tachycardia (see section 4.4).

Injection site reactions (ISRs)

In clinical studies (N=490) with DARZALEX subcutaneous formulation, the incidence of any grade injection site reaction was 8.2%. There were no Grade 3 or 4 ISRs. The most common ($\geq 1\%$) ISRs were erythema, injection site induration, pruritis.

Infections

In patients receiving DARZALEX subcutaneous formulation as monotherapy, incidence of infections was similar between DARZALEX subcutaneous formulation (52.9%) versus intravenous daratumumab groups (50.0%). Additionally, Grade 3 or 4 infections also occurred at similar frequencies between DARZALEX subcutaneous formulation (11.7%) and intravenous daratumumab (14.3%). Most infections were manageable and rarely led to treatment discontinuation. Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies.

In patients receiving intravenous daratumumab combination therapy, Grade 3 or 4 infections were reported as follows:

Relapsed/refractory patient studies: DVd: 21%, Vd: 19%; DRd: 27%, Rd: 23%; DPd: 28%

Newly diagnosed patient studies: D-VMP: 23%, VMP: 15%; DRd: 32%, Rd: 23%; D-VTd: 22%, VTd: 20%.

Pneumonia was the most commonly reported severe (Grade 3 or 4) infection across studies. In active controlled studies, discontinuations from treatment due to infections occurred in 1-4% of patients.

Fatal infections were primarily due to pneumonia and sepsis.

In patients receiving intravenous daratumumab combination therapy, fatal infections (Grade 5) were reported as follows:

Relapsed/refractory patient studies: DVd: 1%, Vd: 2%; DRd: 2%, Rd: 1%; DPd: 2%

Newly diagnosed patient studies: D-VMP: 1%, VMP: 1%; DRd: 2%, Rd: 2%; DVTd: 0%, VTd: 0%.

Key: D=daratumumab; Vd=bortezomib-dexamethasone; Rd=lenalidomide-dexamethasone; Pd=pomalidomide-dexamethasone; VMP=bortezomib-melphalan-prednisone; VTd=bortezomib-thalidomide-dexamethasone.

Haemolysis

There is a theoretical risk of haemolysis. Continuous monitoring for this safety signal will be performed in clinical studies and post-marketing safety data.

Other special populations

In the Phase III study MMY3007, which compared treatment with D-VMP to treatment with VMP in patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was consistent with the overall population (see section 5.1).

Elderly patients

Of the 3207 patients who received daratumumab (n=490 subcutaneous; n=2717 intravenous) at the recommended dose, 38% were 65 to 75 years of age, and 17% were 75 years of age or older. No overall differences in effectiveness were observed based on age. The incidence of serious adverse reactions was higher in older than in younger patients. Among patients with relapsed and refractory multiple myeloma (n=1827), the most common serious adverse reactions that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis. Among patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant (n=777), the most common serious adverse reaction that occurred more frequently in elderly (≥ 75 years of age) was pneumonia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via [the national reporting system listed in Appendix V](#).

4.9 Overdose

Symptoms and signs

There has been no experience of overdose in clinical studies.

Treatment

There is no known specific antidote for daratumumab overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC24

DARZALEX solution for subcutaneous injection contains recombinant human hyaluronidase (rHuPH20). rHuPH20 works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid) which comprise HA. rHuPH20 has a half-life in skin of less than 30 minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

Mechanism of action

Daratumumab is an IgG1 κ human monoclonal antibody (mAb) that binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells, as well as other cell types and tissues at various levels. CD38 protein has multiple functions such as receptor mediated adhesion, signalling and enzymatic activity.

Daratumumab has been shown to potently inhibit the *in vivo* growth of CD38-expressing tumour cells. Based on *in vitro* studies, daratumumab may utilise multiple effector functions, resulting in immune mediated tumour cell death. These studies suggest that daratumumab can induce tumour cell lysis

through complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis in malignancies expressing CD38. A subset of myeloid derived suppressor cells (CD38+MDSCs), regulatory T cells (CD38+T_{regs}) and B cells (CD38+B_{regs}) are decreased by daratumumab mediated cell lysis. T cells (CD3+, CD4+, and CD8+) are also known to express CD38 depending on the stage of development and the level of activation. Significant increases in CD4+ and CD8+ T cell absolute counts, and percentages of lymphocytes, were observed with daratumumab treatment in peripheral whole blood and bone marrow. In addition, T-cell receptor DNA sequencing verified that T-cell clonality was increased with daratumumab treatment, indicating immune modulatory effects that may contribute to clinical response.

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

Pharmacodynamic effects

Natural killer (NK) cell and T-cell count

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

Immunogenicity

In patients treated with subcutaneous daratumumab in clinical trials, less than 1% of patients developed treatment-emergent anti-daratumumab antibodies.

The incidence of treatment-emergent non-neutralizing anti-rHuPH20 antibodies was 7.8% (35/447); with 7.5% (19/255) in the monotherapy DARZALEX subcutaneous formulation groups, and 8.3% (16/192) in the pooled combination DARZALEX subcutaneous formulation groups. The anti-rHuPH20 antibodies did not appear to impact daratumumab exposures. The clinical relevance of the development of anti-daratumumab or anti-rHuPH20 antibodies after treatment with DARZALEX subcutaneous formulation is not known.

Clinical experience of DARZALEX solution for subcutaneous injection (subcutaneous formulation)

Monotherapy – relapsed/refractory multiple myeloma

MMY3012, an open-label, randomised, Phase III non-inferiority study, compared efficacy and safety of treatment with DARZALEX solution for subcutaneous injection (1,800 mg) vs. intravenous (16 mg/kg) daratumumab in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD). Treatment continued until unacceptable toxicity or disease progression.

A total of 522 patients were randomised: 263 to the DARZALEX subcutaneous formulation arm and 259 to the intravenous daratumumab arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median patient age was 67 years (range: 33-92 years), 55% were male and 78% were Caucasian. The median patient weight was 73 kg (range: 29 – 138 kg). Patients had received a median of 4 prior lines of therapy. A total of 51% of patients had prior autologous stem cell transplant (ASCT), 100% of patients were previously treated with both PI(s) and IMiD(s) and most patients were refractory to a prior systemic therapy, including both PI and IMiD (49%).

The study met its co-primary endpoints of overall response rate (ORR) by the IMWG response criteria (Table 6) and maximum C_{trough} at pre-dose Cycle 3 Day 1, (see section 5.2).

Table 6: Key results from Study MMY3012

	Subcutaneous Daratumumab (N=263)	Intravenous Daratumumab (N=259)
Primary Endpoint		
Overall response (sCR+CR+VGPR+PR), n (%) ^a	108 (41.1%)	96 (37.1%)
95% CI (%)	(35.1%, 47.3%)	(31.2%, 43.3%)
Ratio of response rates (95% CI) ^b		1.11 (0.89, 1.37)
CR or better, n (%)	5 (1.9%)	7 (2.7%)
Very good partial response (VGPR)	45 (17.1%)	37 (14.3%)
Partial response (PR)	58 (22.1%)	52 (20.1%)
Secondary Endpoint		
Rate of Infusion-related Reaction, n (%) ^c	33 (12.7%)	89 (34.5%)
Progression-free Survival, months		
Median (95% CI)	5.59 (4.67, 7.56)	6.08 (4.67, 8.31)
Hazard ratio (95% CI)		0.99 (0.78, 1.26)

^a Based on intent-to-treat population.

^b p-value <0.0001 from Farrington-Manning test for non-inferiority hypothesis.

^c Based on safety population. P-value<0.0001 from Cochran-Mantel-Haenszel Chi-Squared test.

Safety and tolerability results, including in lower weight patients, were consistent with the known safety profile for DARZALEX subcutaneous formulation and intravenous daratumumab.

Results from the modified-CTSQ, a patient reported outcome questionnaire that assesses patient satisfaction with their therapy, demonstrated that patients receiving DARZALEX subcutaneous formulation had greater satisfaction with their therapy compared with patients receiving intravenous daratumumab. However, open-label studies are subject to bias.

Combination therapies in multiple myeloma

MMY2040 was an open-label trial evaluating the efficacy and safety of DARZALEX subcutaneous formulation 1,800 mg:

- in combination with bortezomib, melphalan, and prednisone (D-VMP) in patients with newly diagnosed multiple myeloma (MM) who are ineligible for transplant. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). DARZALEX subcutaneous formulation was continued until disease progression or unacceptable toxicity.
- in combination with lenalidomide and dexamethasone (D-Rd) in patients with relapsed or refractory MM. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI<18.5). DARZALEX subcutaneous formulation was continued until disease progression or unacceptable toxicity.
- in combination with bortezomib, lenalidomide, and dexamethasone (D-VRd) in patients with newly diagnosed MM who are transplant eligible. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1 and 2. Lenalidomide was administered orally at 25 mg once daily on Days 1-14; low dose dexamethasone was administered 40 mg/week in 3-week cycles. Total treatment duration was 4 cycles.

A total of 199 patients (D-VMP: 67; D-Rd: 65; D-VRd: 67) were enrolled. Efficacy results were determined by computer algorithm using IMWG criteria. The study met its primary endpoint ORR for D-VMP and D-Rd and the primary endpoint VGPR or better for D-VRd (see Table 7).

Table 7: Efficacy results from Study MMY2040

	D-VMP (n=67)	D-Rd (n=65)	D-VRd (n=67)
Overall response (sCR+CR+VGPR+PR), n (%) ^a	60 (89.6%)	61 (93.8%)	65 (97.0%)
90% CI(%)	(81.3%, 95.0%)	(86.5%, 97.9%)	(90.9%, 99.5%)
Stringent complete response (sCR)	13 (19.4%)	12 (18.5%)	6 (9.0%)
Complete response (CR)	19 (28.4%)	13 (20.0%)	5 (7.5%)
Very good partial response (VGPR)	20 (29.9%)	26 (40.0%)	37 (55.2%)
Partial response (PR)	8 (11.9%)	10 (15.4%)	17 (25.4%)
VGPR or better (sCR + CR + VGPR)	52 (77.6%)	51 (78.5%)	48 (71.6%)
90% CI(%)	(67.6%, 85.7%)	(68.4%, 86.5%)	(61.2%, 80.6%)

D-VMP = Daratumumab-bortezomib-melphalan-prednisone; D-Rd = Daratumumab-lenalidomide-dexamethasone; D-VRd = Daratumumab-bortezomib-lenalidomide-dexamethasone; Daratumumab = DARAZALEX subcutaneous formulation; CI=confidence interval.

^a Based on treated subjects

Clinical experience with daratumumab concentrate for solution for infusion (intravenous formulation)

Newly diagnosed multiple myeloma

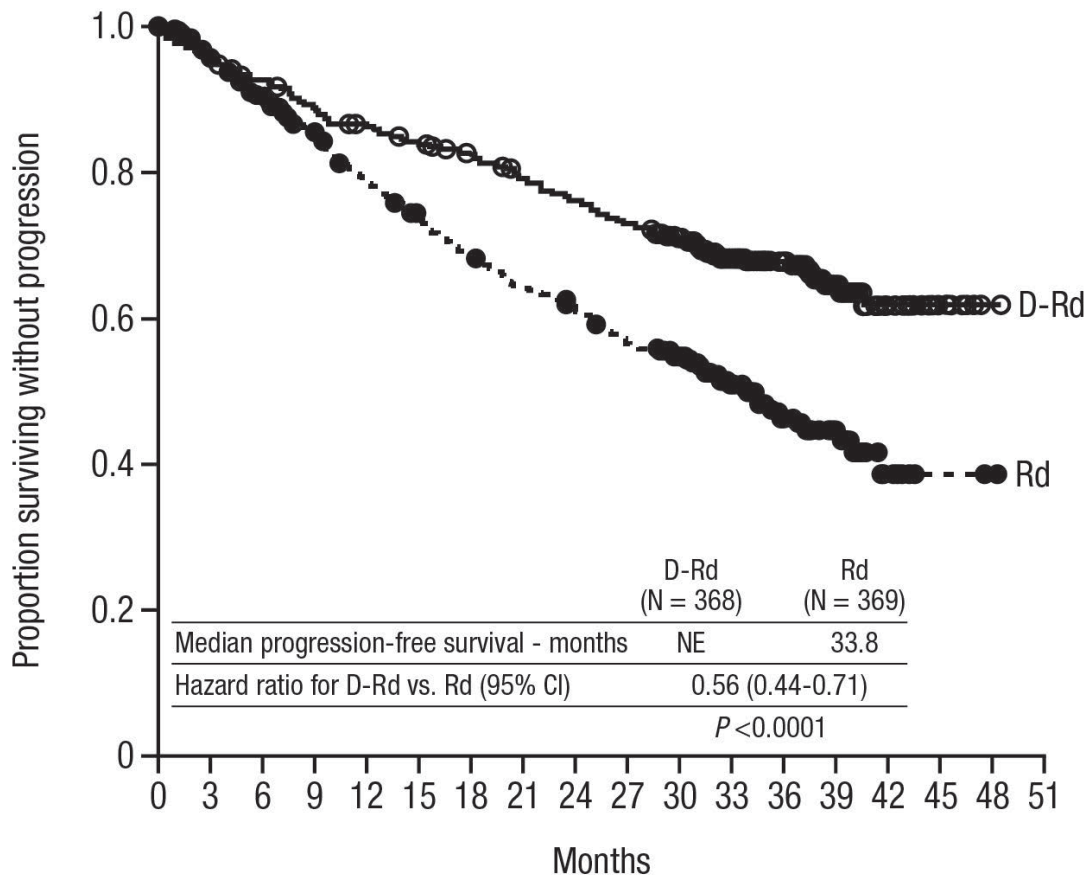
Combination treatment with lenalidomide and dexamethasone in patients ineligible for autologous stem cell transplant:

Study MMY3008, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with newly diagnosed multiple myeloma. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On intravenous daratumumab infusion days, the dexamethasone dose was given as a pre-infusion medicinal product. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 737 patients were randomised: 368 to the DRd arm and 369 to the Rd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 73 (range: 45-90) years, with 44% of the patients ≥75 years of age. The majority were white (92%), male (52%), 34% had an Eastern Cooperative Oncology Group (ECOG) performance score of 0, 49.5% had an ECOG performance score of 1 and 17% had an ECOG performance score of ≥2. Twenty-seven percent had International Staging System (ISS) Stage I, 43% had ISS Stage II and 29% had ISS Stage III disease. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

Study MMY3008 showed an improvement in Progression Free Survival (PFS) in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 31.9 months in the Rd arm (hazard ratio [HR]=0.56; 95% CI: 0.43, 0.73; p<0.0001), representing 44% reduction in the risk of disease progression or death in patients treated with DRd. Results of an updated PFS analysis approximately 9 months after the original clinical cutoff, continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was not reached in the DRd arm and was 33.8 months in the Rd arm (HR=0.56; 95% CI: 0.44, 0.71; p<0.0001).

Figure 1: Kaplan-Meier Curve of PFS in Study MMY3008



No. at risk

Rd	369	333	307	280	254	236	219	204	194	177	161	113	64	33	10	2	1	0
D-Rd	368	347	335	320	309	300	290	276	266	256	233	174	131	70	24	7	1	0

Additional efficacy results from Study MMY3008 are presented in Table 8 below.

Table 8: Additional efficacy results from Study MMY3008^a

	DRd (n=368)	Rd (n=369)
Overall response (sCR+CR+VGPR+PR) n(%) ^a	342 (92.9%)	300 (81.3%)
p-value ^b	<0.0001	
Stringent complete response (sCR)	112 (30.4%)	46 (12.5%)
Complete response (CR)	63 (17.1%)	46 (12.5%)
Very good partial response (VGPR)	117 (31.8%)	104 (28.2%)
Partial response (PR)	50 (13.6%)	104 (28.2%)
CR or better (sCR + CR)	175 (47.6%)	92 (24.9%)
p-value ^b	<0.0001	
VGPR or better (sCR + CR + VGPR)	292 (79.3%)	196 (53.1%)
p-value ^b	<0.0001	
MRD negativity rate ^{a,c} n(%)	89 (24.2%)	27 (7.3%)
95% CI (%)	(19.9%, 28.9%)	(4.9%, 10.5%)
Odds ratio with 95% CI ^d	4.04 (2.55, 6.39)	
p-value ^e	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d Mantel-Haenszel estimate of the odds ratio for un-stratified tables is used. An odds ratio >1 indicates an advantage for DRd.

^e p-value from Fisher's exact test.

In responders, the median time to response was 1.05 months (range: 0.2 to 12.1 months) in the DRd group and 1.05 months (range: 0.3 to 15.3 months) in the Rd group. The median duration of response had not been reached in the DRd group and was 34.7 months (95% CI: 30.8, not estimable) in the Rd group.

Combination treatment with bortezomib, melphalan and prednisone (VMP) in patients ineligible for autologous stem cell transplant:

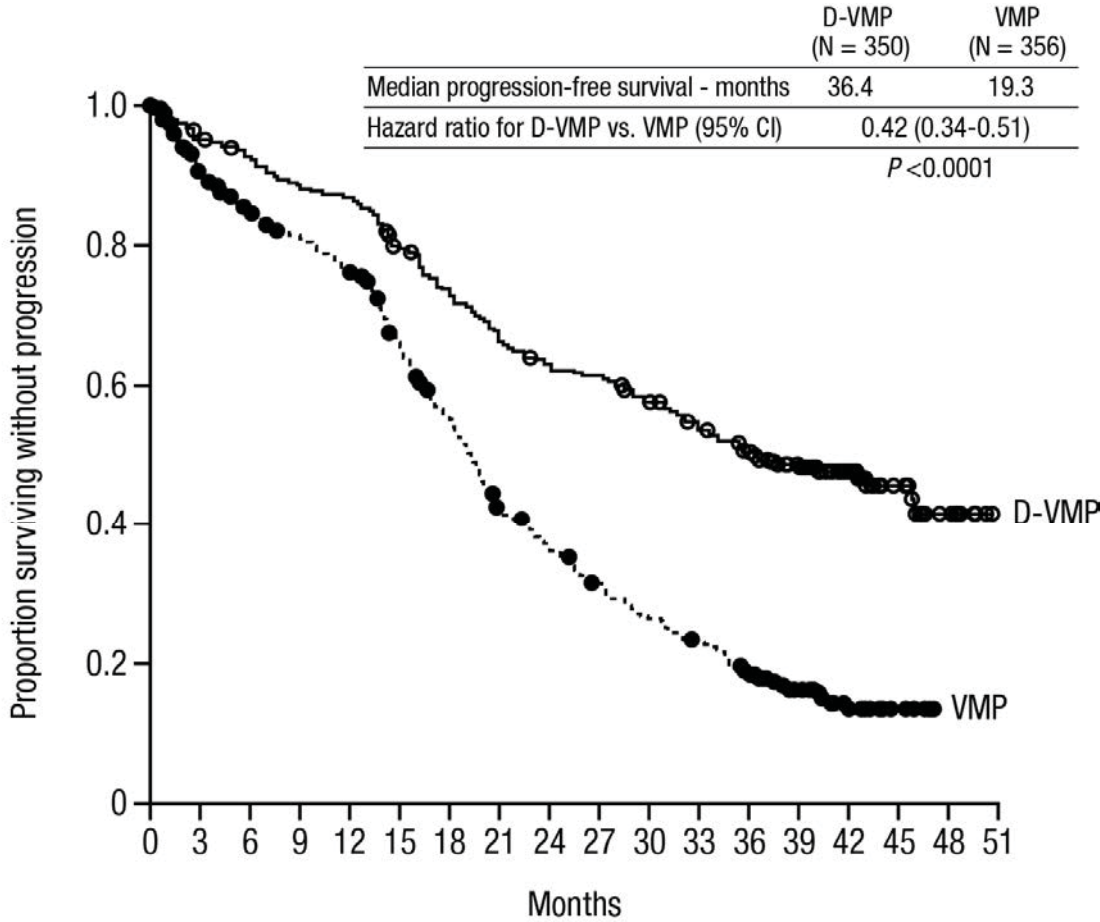
Study MMY3007, an open-label, randomised, active-controlled Phase III study, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, melphalan and prednisone (D-VMP), to treatment with VMP in patients with newly diagnosed multiple myeloma. Bortezomib was administered by subcutaneous injection at a dose of 1.3 mg/m² body surface area twice weekly at Weeks 1, 2, 4 and 5 for the first 6-week cycle (Cycle 1; 8 doses), followed by once weekly administrations at Weeks 1, 2, 4 and 5 for eight more 6-week cycles (Cycles 2-9; 4 doses per cycle). Melphalan at 9 mg/m², and prednisone at 60 mg/m² were orally administered on Days 1 to 4 of the nine 6-week cycles (Cycles 1-9). Intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 706 patients were randomised: 350 to the D-VMP arm and 356 to the VMP arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 71 (range: 40-93) years, with 30% of the patients ≥75 years of age. The majority were white (85%), female (54%), 25% had an ECOG performance score of 0, 50% had an ECOG performance score of 1 and 25% had an ECOG performance score of 2. Patients had IgG/IgA/Light chain myeloma in 64%/22%/10% of instances, 19% had ISS Stage I, 42% had ISS Stage II, 38% had ISS Stage III disease and 84% had standard risk cytogenetics. Efficacy was evaluated by PFS based on IMWG criteria and overall survival (OS).

With a median follow-up of 16.5 months, the primary analysis of PFS in Study MMY3007 showed an improvement in the D-VMP arm as compared to the VMP arm; the median PFS had not been reached in the D-VMP arm and was 18.1 months in the VMP arm (HR=0.5; 95% CI: 0.38, 0.65; p<0.0001). Results of an updated PFS analysis after a median follow-up of 40 months continued to show an

improvement in PFS for patients in the D-VMP arm compared with the VMP arm. Median PFS was 36.4 months in the D-VMP arm and 19.3 months in the VMP arm (HR=0.42; 95% CI: 0.34, 0.51; p<0.0001), representing a 58% reduction in the risk of disease progression or death in patients treated with D-VMP.

Figure 2: Kaplan-Meier Curve of PFS in Study MMY3007

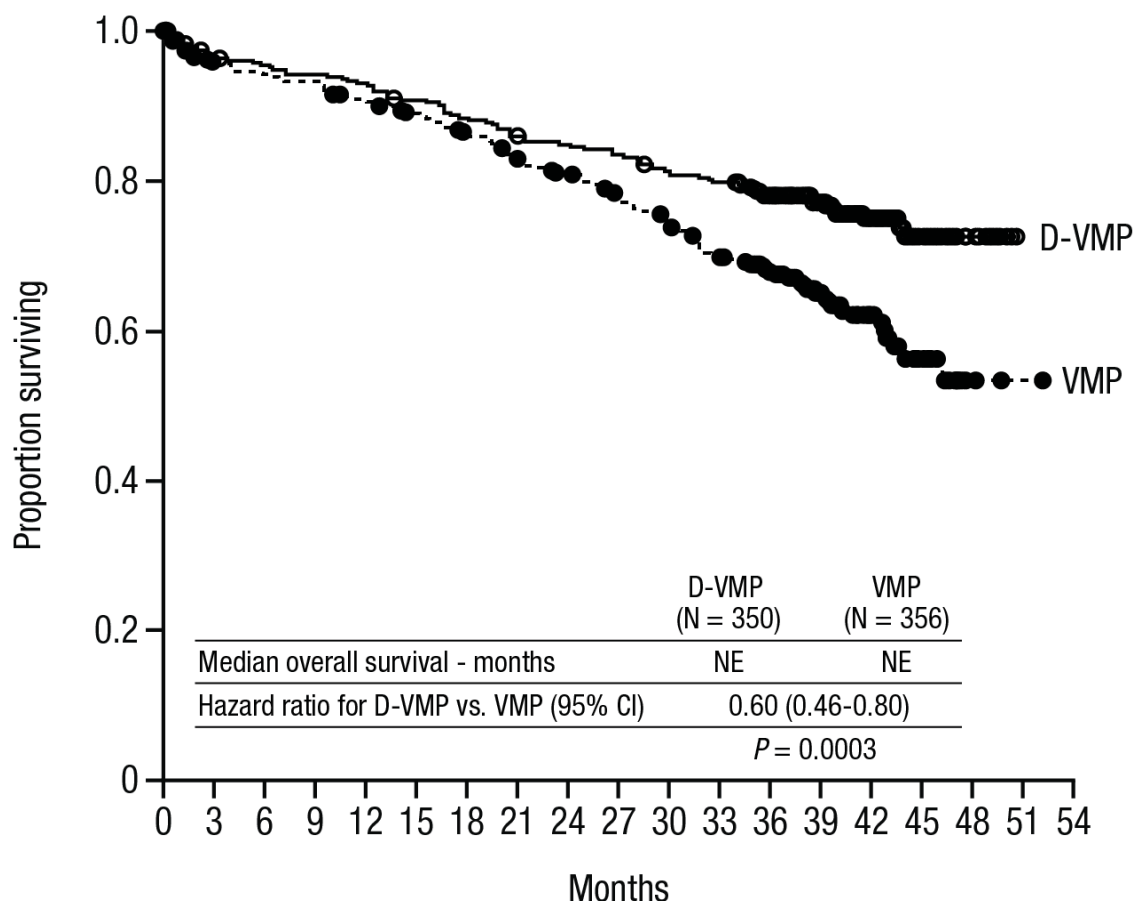


No. at risk

VMP	356	304	278	263	246	207	171	128	110	93	78	67	51	29	15	7	0	0
D-VMP	350	322	312	298	292	265	243	220	207	202	188	173	160	113	63	26	9	0

After a median follow-up of 40 months, D-VMP has shown an overall survival (OS) advantage over the VMP arm (HR=0.60; 95% CI: 0.46, 0.80; p=0.0003), representing a 40% reduction in the risk of death in patients treated in the D-VMP arm. Median OS was not reached for either arm.

Figure 3: Kaplan-Meier Curve of OS in Study MMY3007



No. at risk

VMP	356	331	325	322	312	302	292	278	269	257	242	226	198	132	73	27	3	1	0
D-VMP	350	330	327	322	318	309	301	292	288	283	275	270	248	171	97	40	12	0	0

Additional efficacy results from Study MMY3007 are presented in Table 9 below.

Table 9: Additional efficacy results from Study MMY3007^a

	D-VMP (n=350)	VMP (n=356)
Overall response (sCR+CR+VGPR+PR) [n(%)]	318 (90.9)	263 (73.9)
p-value ^b	<0.0001	
Stringent complete response (sCR) [n(%)]	63 (18.0)	25 (7.0)
Complete response (CR) [n(%)]	86 (24.6)	62 (17.4)
Very good partial response (VGPR) [n(%)]	100 (28.6)	90 (25.3)
Partial response (PR) [n(%)]	69 (19.7)	86 (24.2)
MRD negativity rate (95% CI) ^c (%)	22.3 (18.0, 27.0)	6.2 (3.9, 9.2)
Odds ratio with 95% CI ^d	4.36 (2.64, 7.21)	
p-value ^e	<0.0001	

D-VMP=daratumumab-bortezomib-melphalan-prednisone; VMP=bortezomib-melphalan-prednisone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d A Mantel-Haenszel estimate of the common odds ratio for stratified tables is used. An odds ratio >1 indicates an advantage for D-VMP.

^e p-value from Fisher's exact test.

In responders, the median time to response was 0.79 months (range: 0.4 to 15.5 months) in the D-VMP group and 0.82 months (range: 0.7 to 12.6 months) in the VMP group. The median duration of response had not been reached in the D-VMP group and was 21.3 months (range: 18.4, not estimable) in the VMP group.

A subgroup analysis was performed on patients at least 70 years old, or those 65-69 years old with ECOG performance score of 2, or aged less than 65 years of age with significant comorbidity or ECOG performance score of 2 (D-VMP: n=273, VMP: n=270). The efficacy results in this subgroup were consistent with the overall population. In this subgroup, median PFS was not reached in the D-VMP group and was 17.9 months in the VMP group (HR=0.56; 95% CI: 0.42, 0.75); p<0.0001). The overall response rate was 90% in the D-VMP group and 74% in the VMP group (VGPR rate: 29% in D-VMP group and 26% in VMP group; CR: 22% in D-VMP group and 18% in VMP group; sCR rate: 20% in D-VMP group and 7% in VMP group). The safety results of this subgroup were consistent with the overall population. Furthermore, safety analysis of the subgroup of patients with an ECOG performance score of 2 (D-VMP: n=89, VMP: n=84), was also consistent with the overall population.

Combination treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients eligible for autologous stem cell transplant (ASCT):

Study MMY3006 is a 2 Part, open-label, randomised, active-controlled Phase III study. Part 1 compared induction and consolidation treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib, thalidomide and dexamethasone (D-VTd) to treatment with bortezomib, thalidomide and dexamethasone (VTd) in patients with newly diagnosed multiple myeloma eligible for ASCT. The consolidation phase of treatment began a minimum of 30 days post-ASCT, when the patient had recovered sufficiently, and engraftment was complete. In Part 2, subjects with at least a partial response (PR) by Day 100 post-transplant were re-randomised in a 1:1 ratio to daratumumab maintenance or observation only. Only results from Part 1 are described henceforth.

Bortezomib was administered by subcutaneous injection or intravenous injection at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 28 day (4-week) induction treatment cycles (Cycles 1-4) and two consolidation cycles (Cycles 5 and 6) following ASCT after Cycle 4. Thalidomide was administered orally at 100 mg daily during the six bortezomib cycles. Dexamethasone (oral or intravenous) was administered at 40 mg on Days 1, 2, 8, 9, 15, 16, 22 and 23 of Cycles 1 and 2, and at 40 mg on Days 1-2 and 20 mg on subsequent dosing days (Days 8, 9, 15, 16) of Cycles 3-4. Dexamethasone 20 mg was administered on Days 1, 2, 8, 9, 15, 16 in Cycles 5 and 6. On the days of intravenous daratumumab infusion, the dexamethasone dose was administered intravenously as a pre-infusion medication. Dose adjustments for bortezomib, thalidomide and dexamethasone were applied according to manufacturer's prescribing information.

A total of 1085 patients were randomised: 543 to the D-VTd arm and 542 to the VTd arm. The baseline demographic and disease characteristics were similar between the two treatment groups. The median age was 58 (range: 22 to 65) years. All patients were ≤65 years: 43% were in the age group ≥60-65 years, 41% were in the age group ≥50-60 years and 16% below age of 50 years. The majority were male (59%), 48% had an ECOG performance score of 0, 42% had an ECOG performance score of 1 and 10% had an ECOG performance score of 2. Forty percent had International Staging System (ISS) Stage I, 45% had ISS Stage II and 15% had ISS Stage III disease.

Efficacy was evaluated by the stringent Complete Response (sCR) rate at Day 100 post-transplant and Progression free survival (PFS).

Table 10: Efficacy results from Study MMY3006^a

	D-VTd (n=543)	VTd (n=542)	P value^b
Response assessment Day 100 post-transplant			
Stringent Complete Response (sCR)	157 (28.9%)	110 (20.3%)	0.0010
CR or better (sCR+CR)	211 (38.9%)	141 (26.0%)	<0.0001
Very Good Partial Response or better (sCR+CR+VGPR)	453 (83.4%)	423 (78.0%)	
MRD negativity ^{c, d} n(%)	346 (63.7%)	236 (43.5%)	<0.0001
95% CI (%)	(59.5%, 67.8%)	(39.3%, 47.8%)	
Odds ratio with 95% CI ^e	2.27 (1.78, 2.90)		
MRD negativity in combination with CR or better ^c n(%)	183 (33.7%)	108 (19.9%)	<0.0001
95% CI (%)	(29.7%, 37.9%)	(16.6%, 23.5%)	
Odds ratio with 95% CI ^e	2.06 (1.56, 2.72)		

D-VTd=daratumumab-bortezomib-thalidomide-dexamethasone; VTd=bortezomib-thalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval

^a Based on intent-to-treat population

^b p-value from Cochran Mantel-Haenszel Chi-Squared test.

^c Based on threshold of 10⁻⁵

^d Regardless of response per IMWG

^e Mantel-Haenszel estimate of the common odds ratio for stratified tables is used.

Results of a PFS analysis by censoring patients who were randomised to daratumumab maintenance in the second randomisation, at the date of the second randomisation showed HR=0.50; 95% CI: 0.34, 0.75; p=0.0005.

Relapsed/Refractory multiple myeloma

Monotherapy:

The clinical efficacy and safety of intravenous daratumumab monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who had demonstrated disease progression on the last therapy, was demonstrated in two open-label studies.

In Study MMY2002, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 11% of patients were ≥75 years of age, 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation (ASCT). Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). At baseline, 97% of patients were refractory to the last line of treatment, 95% were refractory to both, a proteasome inhibitor (PI) and immunomodulatory agent (IMiD), 77% were refractory to alkylating agents, 63% were refractory to pomalidomide and 48% of patients were refractory to carfilzomib.

Efficacy results of the pre-planned interim analysis based on Independent Review Committee (IRC) assessment are presented in Table 11 below.

Table 11: IRC assessed efficacy results for study MMY2002

Efficacy endpoint	Intravenous daratumumab 16 mg/kg N=106
Overall response rate ¹ (ORR: sCR+CR+VGPR+PR) [n (%)] 95% CI (%)	31 (29.2) (20.8, 38.9)
Stringent complete response (sCR) [n (%)]	3 (2.8)
Complete response (CR) [n]	0
Very good partial response (VGPR) [n (%)]	10 (9.4)
Partial response (PR) [n (%)]	18 (17.0)

Clinical Benefit Rate (ORR+MR) [n (%)]	36 (34.0)
Median Duration of Response [months (95% CI)]	7.4 (5.5, NE)
Median Time to Response [months (range)]	1 (0.9; 5.6)

¹ Primary efficacy endpoint (International Myeloma Working Group criteria)
CI=confidence interval; NE=not estimable; MR=minimal response

Overall response rate (ORR) in MMY2002 was similar regardless of type of prior anti-myeloma therapy.

At a survival update with a median duration of follow-up of 14.7 months, median Overall Survival (OS) was 17.5 months (95% CI:13.7, not estimable).

In Study GEN501, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg intravenous daratumumab until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior ASCT. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). At baseline, 76% of patients were refractory to the last line of treatment, 64% were refractory to both a PI and IMiD, 60% were refractory to alkylating agents, 36% were refractory to pomalidomide and 17% were refractory to carfilzomib.

Pre-planned interim analysis showed that treatment with daratumumab at 16 mg/kg led to a 36% ORR with 5% CR and 5% VGPR. The median time to response was 1 (range: 0.5 to 3.2) month. The median duration of response was not reached (95% CI: 5.6 months, not estimable).

At a survival update with a median duration of follow-up of 15.2 months, median OS was not reached (95% CI: 19.9 months, not estimable), with 74% of subjects still alive.

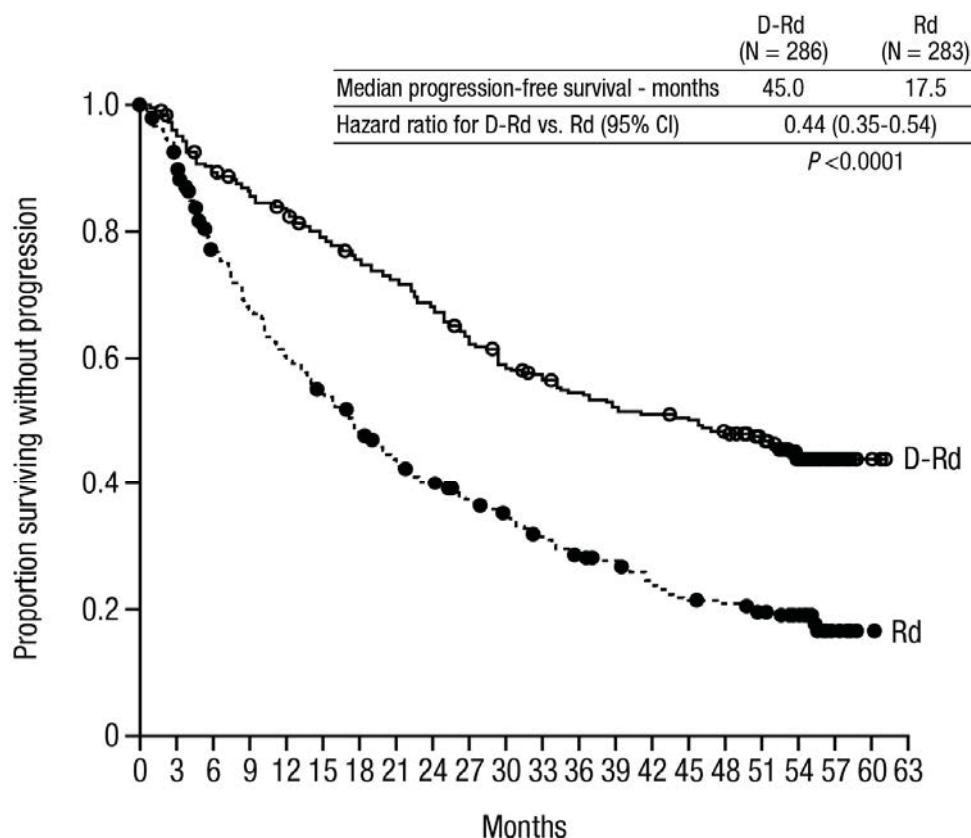
Combination treatment with lenalidomide:

Study MMY3003, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose dexamethasone at 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or BMI <18.5). On intravenous daratumumab infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomised; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 65 years (range 34 to 89 years) and 11% were ≥75 years. The majority of patients (86%) received a prior PI, 55% of patients had received a prior IMiD, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and IMiD. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Patients refractory to lenalidomide were excluded from the study.

With a median follow-up of 13.5 months, the primary analysis of PFS in study MMY3003 demonstrated an improvement in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (HR=0.37; 95% CI: 0.27, 0.52; p<0.0001). Results of an updated PFS analysis after a median follow-up of 55 months continued to show an improvement in PFS for patients in the DRd arm compared with the Rd arm. Median PFS was 45.0 months in the DRd arm and 17.5 months in the Rd arm (HR=0.44; 95% CI: 0.35, 0.54; p<0.0001), representing a 56% reduction in the risk of disease progression or death in patients treated with DRd (see Figure 4).

Figure 4: Kaplan-Meier Curve of PFS in Study MMY3003



No. at risk

Rd	283	249	206	181	160	144	127	112	102	91	83	75	66	63	53	48	45	40	28	5	1	0
D-Rd	286	266	249	238	229	215	204	195	184	168	156	151	143	136	134	131	125	115	76	16	3	0

Additional efficacy results from Study MMY3003 are presented in Table 12 below.

Table 12: Additional efficacy results from Study MMY3003

Response evaluable patient number	DRd (n=281)	Rd (n=276)
Overall response (sCR+CR+VGPR+PR) n(%)	261 (92.9)	211 (76.4)
p-value ^a	<0.0001	
Stringent complete response (sCR)	51 (18.1)	20 (7.2)
Complete response (CR)	70 (24.9)	33 (12.0)
Very good partial response (VGPR)	92 (32.7)	69 (25.0)
Partial response (PR)	48 (17.1)	89 (32.2)
Median Time to Response [months (95% CI)]	1.0 (1.0, 1.1)	1.3 (1.1, 1.9)
Median Duration of Response [months (95% CI)]	NE (NE, NE)	17.4 (17.4, NE)
MRD negative rate (95% CI) ^b (%)	21.0 (16.4, 26.2)	2.8 (1.2, 5.5)
Odds ratio with 95% CI ^c	9.31 (4.31, 20.09)	
P-value ^d	<0.0001	

DRd=daratumumab-lenalidomide-dexamethasone; Rd=lenalidomide-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10^{-5}

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DRd.

^d p-value is from a Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 13.5 months, the hazard ratio for OS was 0.64 (95% CI: 0.40, 1.01; *p*=0.0534).

Combination treatment with bortezomib:

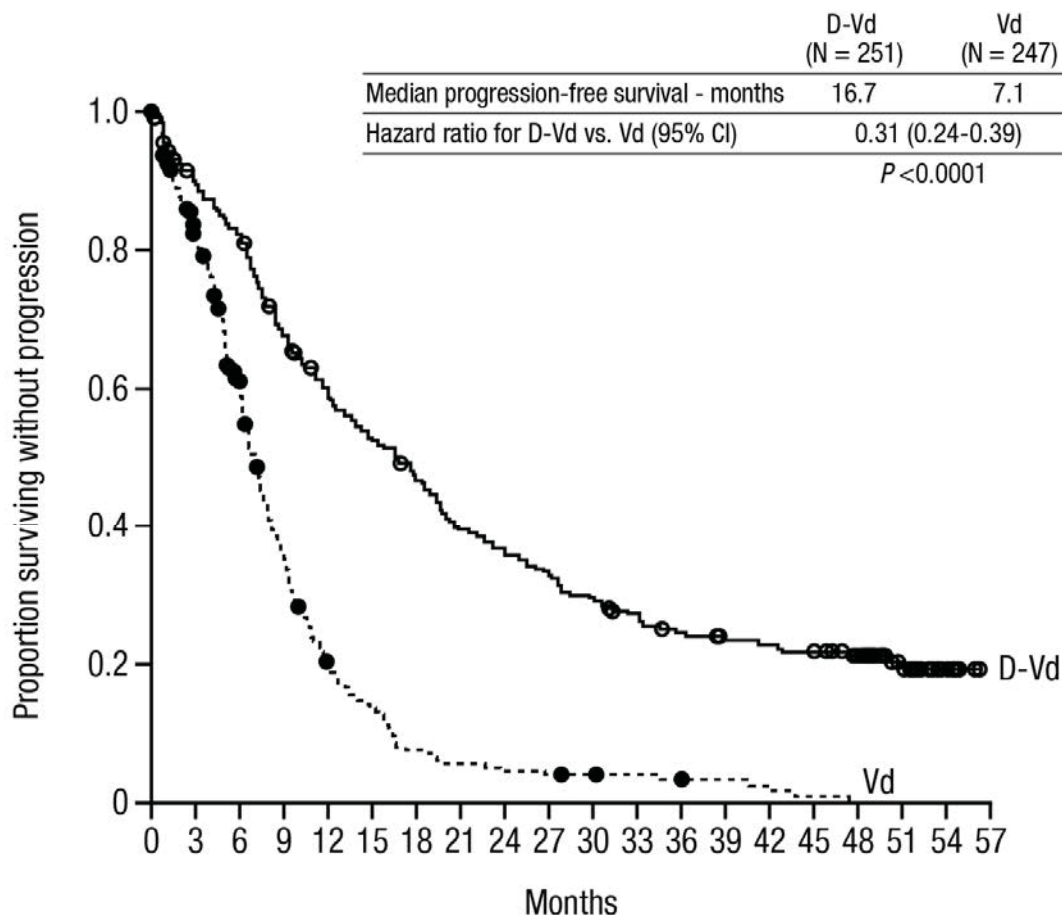
Study MMY3004, an open-label, randomised, active-controlled Phase III trial, compared treatment with intravenous daratumumab 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with relapsed or refractory multiple myeloma who had received at least one prior therapy. Bortezomib was administered by subcutaneous injection or intravenous infusion at a dose of 1.3 mg/m² body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles.

Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of intravenous daratumumab infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. intravenous daratumumab treatment was continued until disease progression or unacceptable toxicity.

A total of 498 patients were randomised; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the intravenous daratumumab and the control arm. The median patient age was 64 years (range 30 to 88 years) and 12% were ≥75 years. Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an IMiD (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment. Thirty-three percent (33%) of patients were refractory to an IMiD only, and 28% were refractory to lenalidomide. Patients refractory to bortezomib were excluded from the study.

With a median follow-up of 7.4 months, the primary analysis of PFS in study MMY3004 demonstrated an improvement in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value<0.0001). Results of an updated PFS analysis after a median follow-up of 50 months continued to show an improvement in PFS for patients in the DVd arm compared with the Vd arm. Median PFS was 16.7 months in the DVd arm and 7.1 months in the Vd arm (HR [95% CI]: 0.31 [0.24, 0.39]; p-value<0.0001), representing a 69% reduction in the risk of disease progression or death in patients treated with DVd versus Vd (see Figure 5).

Figure 5: Kaplan-Meier Curve of PFS in Study MMY3004



No. at risk

Vd	247	182	129	74	39	27	15	11	9	8	7	6	5	4	2	1	0	0	0	0
D-Vd	251	215	198	161	138	123	109	92	85	77	68	61	54	50	48	46	38	20	7	0

Additional efficacy results from Study MMY3004 are presented in Table 13 below.

Table 13: Additional efficacy results from Study MMY3004

Response evaluable patient number	DVd (n=240)	Vd (n=234)
Overall response (sCR+CR+VGPR+PR) n(%)	199 (82.9)	148 (63.2)
P-value ^a	<0.0001	
Stringent complete response (sCR)	11 (4.6)	5 (2.1)
Complete response (CR)	35 (14.6)	16 (6.8)
Very good partial response (VGPR)	96 (40.0)	47 (20.1)
Partial response (PR)	57 (23.8)	80 (34.2)
Median Time to Response [months (range)]	0.9 (0.8, 1.4)	1.6 (1.5, 2.1)
Median Duration of Response [months (95% CI)]	NE (11.5, NE)	7.9 (6.7, 11.3)
MRD negative rate (95% CI) ^b	8.8% (5.6%, 13.0%)	1.2% (0.3%, 3.5%)
Odds ratio with 95% CI ^c	9.04 (2.53, 32.21)	
P-value ^d	0.0001	

DVd=daratumumab- bortezomib-dexamethasone; Vd=bortezomib-dexamethasone; MRD=minimal residual disease; CI=confidence interval; NE=not estimable.

^a p-value from Cochran Mantel-Haenszel Chi-Squared test.

^b Based on Intent-to-treat population and threshold of 10⁻⁵

^c Mantel-Haenszel estimate of the common odds ratio is used. An odds ratio >1 indicates an advantage for DVd.

^d p-value is from Fisher's exact test.

Median OS was not reached for either treatment group. With an overall median follow-up of 7.4 months (95% CI: 0.0, 14.9), the hazard ratio for OS was 0.77 (95% CI: 0.47, 1.26; p=0.2975).

Cardiac electrophysiology

Daratumumab as a large protein has a low likelihood of direct ion channel interactions. The effect of daratumumab on the QTc interval was evaluated in an open-label study for 83 patients (Study GEN501) with relapsed and refractory multiple myeloma following daratumumab infusions (4 to 24 mg/kg). Linear mixed PK-PD analyses indicated no large increase in mean QTcF interval (i.e. greater than 20 ms) at daratumumab C_{max} .

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with DARZALEX in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Daratumumab exposure in a monotherapy study following the recommended 1,800 mg administration of DARZALEX subcutaneous formulation (weekly for 8 weeks, biweekly for 16 weeks, monthly thereafter) as compared to 16 mg/kg intravenous daratumumab for the same dosing schedule, showed non-inferiority for the co-primary endpoint of maximum C_{trough} (Cycle 3 Day 1 pre-dose), with mean \pm SD of 593 ± 306 $\mu\text{g/mL}$ compared to 522 ± 226 $\mu\text{g/mL}$ for intravenous daratumumab, with a geometric mean ratio of 107.93% (90% CI: 95.74-121.67).

Following the recommended dose of 1,800 mg DARZALEX solution for subcutaneous injection, peak concentrations (C_{max}) increased 4.8-fold and total exposure ($AUC_{0-7 \text{ days}}$) increased 5.4-fold from first dose to last weekly dose (8th dose). Highest trough concentrations for DARZALEX solution for subcutaneous injection are typically observed at the end of the weekly dosing regimens for both monotherapy and combination therapy.

The simulated trough concentrations following 6 weekly doses of 1,800 mg DARZALEX solution for subcutaneous injection for combination therapy were similar to 1,800 mg DARZALEX solution for subcutaneous injection monotherapy.

Absorption and distribution

At the recommended dose of 1,800 mg, the absolute bioavailability of DARZALEX solution for subcutaneous injection is 69%, with an absorption rate of 0.012 hour^{-1} , with peak concentrations occurring at 70 to 72 h (T_{max}).

The model predicted mean estimate of the volume of distribution for the central compartment was 5.25 L (36.9% CV) and peripheral compartment was 3.78 L, suggesting that daratumumab is primarily localised to the vascular system with limited extravascular tissue distribution.

Metabolism and elimination

Daratumumab exhibits both concentration and time-dependent pharmacokinetics with parallel linear and nonlinear (saturable) elimination that is characteristic of target-mediated clearance. The population PK model estimated mean clearance value of daratumumab is 4.96 mL/h (58.7% CV). The model-based geometric mean for half-life associated with linear elimination is 20.4 days (22.4% CV). For the monotherapy regimen, the steady state is achieved at approximately 5 months into every 4 weeks dosage at the recommended dose and schedule (1,800 mg; once weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter).

A population PK analysis was conducted using data from DARZALEX solution for subcutaneous injection monotherapy and combination therapy, and the predicted PK exposures are summarised in Table 14.

Table 14: Daratumumab exposure following administration of DARZALEX subcutaneous formulation (1,800 mg) or intravenous daratumumab (16 mg/kg) monotherapy

PK parameters	Cycles	subcutaneous daratumumab Median (5 th ; 95 th percentile)	intravenous daratumumab Median (5 th ; 95 th percentile)
C _{trough} (µg/mL)	Cycle 1, 1 st weekly dose	123 (36; 220)	112 (43; 168)
	Cycle 2, last weekly dose (Cycle 3 Day 1 C _{trough})	563 (177; 1063)	472 (144; 809)
C _{max} (µg/mL)	Cycle 1, 1 st weekly dose	132 (54; 228)	256 (173; 327)
	Cycle 2, last weekly dose	592 (234; 1114)	688 (369; 1061)
AUC _{0-7 days} (µg/mL•day)	Cycle 1, 1 st weekly dose	720 (293; 1274)	1187 (773; 1619)
	Cycle 2, last weekly dose	4017 (1515; 7564)	4019 (1740; 6370)

Special populations

Age and gender

Based on population PK analyses in patients (33-92 years) receiving monotherapy or various combination therapies, age had no statistically significant effect on the PK of daratumumab. No individualisation is necessary for patients on the basis of age.

Gender had a statistically significant effect on PK, with slightly higher exposure in females than males, but the difference in exposure is not considered clinically meaningful. No individualisation is necessary for patients on the basis of gender.

Renal impairment

No formal studies of DARZALEX subcutaneous formulation in patients with renal impairment have been conducted. Population PK analyses were performed based on pre-existing renal function data in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 220 patients with normal renal function (creatinine clearance [CRCL] ≥ 90 mL/min), 273 with mild renal impairment (CRCL < 90 and ≥ 60 mL/min), 215 with moderate renal impairment (CRCL < 60 and ≥ 30 mL/min), and 33 with severe renal impairment or end stage renal disease (CRCL < 30 mL/min). No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function.

Hepatic impairment

No formal studies of DARZALEX subcutaneous formulation in patients with hepatic impairment have been conducted.

Population PK analyses were performed in patients receiving DARZALEX subcutaneous formulation monotherapy or various combination therapies, including 655 patients with normal hepatic function (total bilirubin [TB] and aspartate aminotransferase [AST] \leq upper limit of normal [ULN]), 82 with mild hepatic impairment [(total bilirubin \leq ULN and AST $>$ ULN) or (ULN $<$ total bilirubin $\leq 1.5 \times$ ULN)] and 5 patients with moderate ($1.5 \times$ ULN $<$ total bilirubin $\leq 3 \times$ ULN) hepatic impairment. No clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment. There were very few patients with moderate hepatic impairment and no patients with severe hepatic impairment to make meaningful conclusions for these populations.

Race

Based on the population PK analyses in patients receiving either DARZALEX subcutaneous formulation monotherapy or various combination therapies, the daratumumab exposure was similar across races.

Body weight

The flat-dose administration of DARZALEX subcutaneous formulation 1,800 mg as monotherapy achieved adequate exposure for all body-weight subgroups. The mean Cycle 3 Day 1 C_{trough} in the lower body-weight subgroup (≤ 65 kg) was 60% higher and in the higher body weight (> 85 kg)

subgroup, 12% lower than the intravenous daratumumab subgroup. In some patients with body weight >120 kg, lower exposure was observed which may result in reduced efficacy. However, this observation is based on limited number of patients.

5.3 Preclinical safety data

Toxicology data have been derived from studies with daratumumab in chimpanzees and with a surrogate anti-CD38 antibody in cynomolgus monkeys. No chronic toxicity testing has been conducted.

No animal studies have been performed to establish the carcinogenic potential of daratumumab.

No animal studies have been performed to evaluate the potential effects of daratumumab on reproduction or development or to determine potential effects on fertility in males or females.

No carcinogenicity, genotoxicity, or fertility studies were conducted for recombinant human hyaluronidase. There were no effects on reproductive tissues and function and no systemic exposure of hyaluronidase in monkeys given 22,000 U/kg/week subcutaneously (12 times higher than the human dose) for 39 weeks. As hyaluronidase is a recombinant form of the endogenous human hyaluronidase, no carcinogenicity, mutagenesis, or effects on fertility are expected.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
L-histidine
L-histidine hydrochloride monohydrate
L-methionine
Polysorbate 20
Sorbitol (E420)
Water for injections

6.2 Incompatibilities

This medicinal product must not be used with other materials except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

1 year

During the shelf-life, the product in unpunctured vials may be stored at room temperature ($\leq 30^{\circ}\text{C}$) for a single period of up to 24 hours. Once the product has been taken out of the refrigerator, it must not be returned to the refrigerator (see section 6.6).

Prepared syringe

Chemical and physical in-use stability in syringe has been demonstrated for 4 hours at ambient temperature up to 30°C (86°F) and ambient light. From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the original package in order to protect from light.

For storage conditions of the opened medicinal product (see section 6.3).

6.5 Nature and contents of container

15 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off button containing 1,800 mg of daratumumab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

DARZALEX solution for subcutaneous injection is for single use only and is ready to use.

DARZALEX solution for subcutaneous injection should be a clear to opalescent and colourless to yellow solution. Do not use if opaque particles, discoloration or other foreign particles are present.

DARZALEX solution for subcutaneous injection is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles.

Remove the DARZALEX solution for subcutaneous injection vial from refrigerated storage (2°C-8°C) and equilibrate to ambient temperature (15°C-30°C). The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours in the original carton to protect from light. Keep out of direct sunlight. Do not shake.

Prepare the dosing syringe in controlled and validated aseptic conditions. Once transferred from the vial into the syringe, store DARZALEX solution for subcutaneous injection for up to 4 hours at ambient temperature and ambient light (see section 6.3).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 May 2016

Date of latest renewal: 24 April 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>.

ANNEX II

- A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURE RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen Inc.
5000 Davis Drive
Research Triangle Park
North Carolina
27709
United States

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy, Co. Cork
Ireland

Samsung Biologics Co, LTD
300, Songdo bio-daero,
Yeonsu-gu, Incheon, 21987,
Republic of Korea

Biogen (Denmark) Manufacturing ApS
Biogen Alle 1
Hillerod, 3400
Denmark (DNK)

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
NL-2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

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

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

• **Periodic safety update reports (PSURs)**

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

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

• Risk management plan (RMP)

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

• Additional risk minimisation measures

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

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

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

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

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

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

The Patient Alert Card, shall contain the following key elements:

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

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR INITIATION PACK COMPRISING 11 PACKS (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
Initiation pack: 11 vials (6 x 5 mL vials + 5 x 20 mL vials)

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) FOR 1 VIAL COMPONENT AS INTERMEDIATE PACK/COMPONENT OF AN INITIATION PACK (WITHOUT BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL
Component of an initiation pack, cannot be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY**15. INSTRUCTIONS ON USE****16. INFORMATION IN BRAILLE**

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (100 mg/400 mg) (WITH BLUE BOX)

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial of 5 mL concentrate contains 100 mg of daratumumab (20 mg/mL).
Each vial of 20 mL concentrate contains 400 mg of daratumumab (20 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial, 100 mg/5 mL
1 vial, 400 mg/20 mL

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/001
EU/1/16/1101/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 20 mg/mL concentrate for solution for infusion
daratumumab
For intravenous use after dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg/5 mL
400 mg/20 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

DARZALEX 1,800 mg solution for injection
daratumumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One 15 mL vial contains 1,800 mg of daratumumab (120 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For subcutaneous use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.

Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1101/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

DARZALEX 1,800 mg solution for injection
daratumumab
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

15 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

DARZALEX 20 mg/mL concentrate for solution for infusion daratumumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is

DARZALEX is a cancer medicine that contains the active substance daratumumab. It belongs to a group of medicines called “monoclonal antibodies”. Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific cancer cells in your body, so that your immune system can destroy the cancer cells.

What DARZALEX is used for

DARZALEX is used in adults 18 years or older, who have a type of cancer called “multiple myeloma”. This is a cancer of your bone marrow.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX

- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions

Talk to your doctor or nurse before you are given DARZALEX:

Infusion-related reactions

DARZALEX is given as an infusion (drip) into a vein. Before and after each infusion of DARZALEX, you will be given medicines which help to lower the chance of infusion-related reactions (see “Medicines given during treatment with DARZALEX” in section 3). These reactions can happen during the infusion or in the 3 days after the infusion.

In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives).

Tell your doctor or nurse straight away if you get any of the infusion-related reactions listed at the top of section 4.

If you get infusion-related reactions, you may need other medicines, or the infusion may need to be slowed down or stopped. When these reactions go away, or get better, the infusion can be started again.

These reactions are most likely to happen with the first infusion. If you have had an infusion-related reaction once it is less likely to happen again. Your doctor may decide not to use DARZALEX if you have a strong infusion reaction.

Decreased blood cell counts

DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop fever or if you have signs of bruising or bleeding.

Blood transfusions

If you need a blood transfusion, you will have a blood test first to match your blood type. DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

Hepatitis B

Tell your doctor if you have ever had or might now have a hepatitis B infection. This is because DARZALEX could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with DARZALEX. Tell your doctor right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes.

Children and adolescents

Do not give DARZALEX to children or young people below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy

Talk to your doctor or nurse before you are given DARZALEX if you are pregnant, think you might be pregnant or are planning to have a baby.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception

Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding

You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines

You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX contains sodium

This medicine contains 9.3 mg sodium (main component of cooking/table salt) in each 5 mL vial. This is equivalent to 0.46% of the recommended maximum daily dietary intake of sodium for an adult.

This medicine contains 37.3 mg sodium (main component of cooking/table salt) in each 20 mL vial. This is equivalent to 1.86% of the recommended maximum daily dietary intake of sodium for an adult.

3. How DARZALEX is given

How much is given

Your doctor will work out your dose and schedule of DARZALEX. The dose of DARZALEX will depend on your body weight.

The usual starting dose of DARZALEX is 16 mg per kg of body weight. DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.

When given alone, DARZALEX is given as follows:

- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

In the first week your doctor may give you the DARZALEX dose split over two consecutive days.

How the medicine is given

DARZALEX will be given to you by a doctor or nurse. It is given as a drip into a vein (“intravenous infusion”) over several hours.

Medicines given during treatment with DARZALEX

You may be given medicines to lower the chance of getting shingles.

Before each infusion of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each infusion of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

If you are given more DARZALEX than you should

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you forget your appointment to have DARZALEX

It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions

Tell your doctor or nurse straight away if you get any of the following signs of an infusion-related reaction during or in the 3 days after the infusion. You may need other medicines, or the infusion may need to be slowed down or stopped.

These reactions are very common (may affect more than 1 in 10 people):

- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Other common symptoms (affecting up to 1 in 10 people) are:

- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1,000 people):

- Severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives).

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Other side effects

Very common (may affect more than 1 in 10 people):

- fever
- feeling very tired
- diarrhoea
- constipation
- decreased appetite
- headache
- nerve damage that may cause tingling, numbness, or pain
- high blood pressure
- muscle spasms
- swollen hands, ankles or feet
- feeling weak
- back pain
- chills
- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)
- unusual feeling in the skin (such as a tingling or crawling feeling).

Common (may affect up to 1 in 10 people):

- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath

- flu
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- high level of sugar in the blood
- low level of calcium in the blood
- inflamed pancreas

Uncommon (may affect up to 1 in 100 people)

- inflamed liver (hepatitis)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

DARZALEX will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains

- The active substance is daratumumab. One mL of concentrate contains 20 mg daratumumab. Each vial of 5 mL concentrate contains 100 mg of daratumumab. Each vial of 20 mL concentrate contains 400 mg of daratumumab.
- The other ingredients are glacial acetic acid, mannitol (E421), polysorbate 20, sodium acetate trihydrate, sodium chloride and water for injections (see “DARZALEX contains sodium” in section 2).

What DARZALEX looks like and contents of the pack

DARZALEX is a concentrate for solution for infusion and is a colourless to yellow liquid.

DARZALEX is supplied as a carton pack containing 1 glass vial.

DARZALEX is also supplied as an initiation pack containing 11 vials: (6 x 5 mL vials + 5 x 20 mL vials).

Marketing Authorisation Holder

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Manufacturer

Janssen Biologics B.V.
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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

This medicinal product is for single-use only.

Prepare the solution for infusion using aseptic technique as follows:

- Calculate the dose (mg), total volume (mL) of DARZALEX solution required and the number of DARZALEX vials needed based on patient weight.
- Check that the DARZALEX solution is colourless to yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Using aseptic technique, remove a volume of 0.9% Sodium Chloride from the infusion bag/container that is equal to the required volume of DARZALEX solution.
- Withdraw the necessary amount of DARZALEX solution and dilute to the appropriate volume by adding to an infusion bag/container containing 0.9% Sodium Chloride. Infusion bags/containers must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend (PP+PE). Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.

- Visually inspect parenteral medicinal products for particulate matter and discolouration prior to administration. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visibly opaque particles, discolouration or foreign particles are observed.
- Since DARZALEX does not contain a preservative, diluted solutions should be administered within 15 hours (including infusion time) at room temperature (15°C-25°C) and in room light.
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions (2°C-8°C) and protected from light. Do not freeze.
- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used.
- Do not infuse DARZALEX concomitantly in the same intravenous line with other agents.
- Do not store any unused portion of the infusion solution for reuse. Any unused product or waste material should be disposed of in accordance with local requirements.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

Package leaflet: Information for the patient

DARZALEX 1,800 mg solution for injection daratumumab

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What DARZALEX is and what it is used for
2. What you need to know before you are given DARZALEX
3. How DARZALEX is given
4. Possible side effects
5. How to store DARZALEX
6. Contents of the pack and other information

1. What DARZALEX is and what it is used for

What DARZALEX is

DARZALEX is a cancer medicine that contains the active substance daratumumab. It belongs to a group of medicines called “monoclonal antibodies”. Monoclonal antibodies are proteins that have been designed to recognise and attach to specific targets in the body. Daratumumab has been designed to attach to specific cancer cells in your body, so that your immune system can destroy the cancer cells.

What DARZALEX is used for

DARZALEX is used in adults 18 years or older, who have a type of cancer called “multiple myeloma”. This is a cancer of your bone marrow.

2. What you need to know before you are given DARZALEX

You must not be given DARZALEX

- if you are allergic to daratumumab or any of the other ingredients of this medicine (listed in section 6).

Do not use DARZALEX if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given DARZALEX.

Warnings and precautions

Talk to your doctor or nurse before you are given DARZALEX:

Infusion-related reactions

DARZALEX is given as a subcutaneous injection using a small needle to inject the medicine under your skin. Before and after each injection, you will be given medicines which help to lower the chance of infusion-related reactions (see “Medicines given during treatment with DARZALEX” in section 3). These reactions are most likely to happen with the first injection and most reactions occur on the day of injection. If you have had an infusion-related reaction once it is less likely to happen again.

However, delayed reactions can happen up to 3-4 days after the injection. Your doctor may decide not to use DARZALEX if you have a strong reaction after the injection.

In some cases you may have a severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 4.

Tell your doctor or nurse straight away if you get any of the infusion-related reactions listed at the top of section 4. If you get infusion-related reactions, you may need other medicines to treat your symptoms, or the injections may need to be stopped. When these reactions go away, or get better, the injection can be started again.

Decreased blood cell counts

DARZALEX can decrease white blood cell counts which help fight infections, and blood cells called platelets which help to clot blood. Tell your healthcare provider if you develop any symptoms of infection such as fever or any symptoms of decreased platelet counts such as bruising or bleeding.

Blood transfusions

If you need a blood transfusion, you will have a blood test first to match your blood type. DARZALEX can affect the results of this blood test. Tell the person doing the test that you are using DARZALEX.

Hepatitis B

Tell your doctor if you have ever had or might now have a hepatitis B infection. This is because DARZALEX could cause hepatitis B virus to become active again. Your doctor will check you for signs of this infection before, during and for some time after treatment with DARZALEX. Tell your doctor right away if you get worsening tiredness, or yellowing of your skin or white part of your eyes.

Children and adolescents

Do not give DARZALEX to children or adolescents below 18 years of age. This is because it is not known how the medicine will affect them.

Other medicines and DARZALEX

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines. This includes medicines you can get without a prescription, and herbal medicines.

Pregnancy

Talk to your doctor or nurse before you are given DARZALEX if you are pregnant, think you might be pregnant or are planning to have a baby.

If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Contraception

Women who are being given DARZALEX should use effective contraception during treatment and for 3 months after treatment.

Breast-feeding

You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby. This is because the medicine may pass into the mother's milk and it is not known how it will affect the baby.

Driving and using machines

You may feel tired after taking DARZALEX which may affect your ability to drive or use machines.

DARZALEX solution for subcutaneous injection contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per 15 mL, that is to say essentially 'sodium-free'.

DARZALEX solution for subcutaneous injection contains sorbitol

Sorbitol is a source of fructose. If your doctor has told you that you have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you take this medicine.

3. How DARZALEX is given

How much is given

The dose of DARZALEX solution for subcutaneous injection is 1,800 mg.

DARZALEX may be given alone or together with other medicines used to treat multiple myeloma.

When given alone, DARZALEX is given as follows:

- once a week for the first 8 weeks
- then once every 2 weeks for 16 weeks
- then once every 4 weeks after that as long as your condition does not worsen.

When DARZALEX is given together with other medicines your doctor may change the time between doses as well as how many treatments you will receive.

How the medicine is given

DARZALEX will be given to you by a doctor or nurse as an injection under your skin (subcutaneous injection) over approximately 3 to 5 minutes. It is given in the stomach area (abdomen), not in other sites of the body, and not into areas of the abdomen where the skin is red, bruised, tender, hard or where there are scars.

If you experience pain during the injection, the doctor or nurse may interrupt the injection and give you the remaining injection in another area of your abdomen.

Medicines given during treatment with DARZALEX

You may be given medicines to lower the chance of getting shingles.

Before each injection of DARZALEX you will be given medicines which help to lower the chance of infusion-related reactions. These may include:

- medicines for an allergic reaction (anti-histamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

After each injection of DARZALEX you will be given medicines (such as corticosteroids) to lower the chance of infusion-related reactions.

People with breathing problems

If you have breathing problems, such as asthma or Chronic Obstructive Pulmonary Disease (COPD), you will be given medicines to inhale which help your breathing problems:

- medicines to help the airways in your lungs stay open (bronchodilators)
- medicines to lower swelling and irritation in your lungs (corticosteroids)

If you are given more DARZALEX than you should

This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects.

If you forget your appointment to have DARZALEX

It is very important to go to all your appointments to make sure your treatment works. If you miss an appointment, make another one as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Infusion-related reactions

Tell your doctor or nurse straight away if you get any of the following symptoms within 3-4 days after the injection. You may need other medicines, or the injection may need to be interrupted or stopped.

These reactions include the following symptoms:

Very common (may affect more than 1 in 10 people):

- chills
- sore throat, cough
- feeling sick (nausea)
- vomiting
- itchy, runny or blocked nose
- feeling short of breath or other breathing problems.

Common (may affect up to 1 in 10 people):

- chest discomfort
- dizziness or lightheadedness (hypotension)
- itching
- wheezing.

Rare (may affect up to 1 in 1,000 people):

- Severe allergic reaction which may include a swollen face, lips, mouth, tongue or throat, difficulty swallowing or breathing or an itchy rash (hives). See section 2.

If you get any of the infusion-related reactions above, tell your doctor or nurse straight away.

Injection site reactions

Skin reactions at or near the injection site (local), including injection site reactions, can happen with DARZALEX solution for subcutaneous injection. These reactions are common (may affect up to 1 in 10 people) and symptoms may include:

- redness of the skin
- itching
- swelling

Other side effects

Very common (may affect more than 1 in 10 people):

- fever
- feeling very tired
- diarrhoea
- constipation
- decreased appetite
- difficulty sleeping
- headache
- nerve damage that may cause tingling, numbness, or pain
- muscle spasms
- joint pain
- high blood pressure
- swollen hands, ankles or feet
- feeling weak
- back pain

- lung infection (pneumonia)
- bronchitis
- infections of the airways – such as nose, sinuses or throat
- low number of red blood cells which carry oxygen in the blood (anaemia)
- low number of white blood cells which help fight infections (neutropenia, lymphopenia, leukopenia)
- low number of a type of blood cell called platelets which help to clot blood (thrombocytopenia)

Common (may affect up to 1 in 10 people):

- irregular heart beat (atrial fibrillation)
- build up of fluid in the lungs making you short of breath
- urinary tract infection
- severe infection throughout the body (sepsis)
- dehydration
- high level of sugar in the blood
- low level of calcium in the blood
- feeling dizzy
- chest muscle pain
- flu
- chills
- rash
- itching
- unusual feeling in the skin (such as a tingling or crawling feeling)
- inflamed pancreas

Uncommon (may affect up to 1 in 100 people)

- inflamed liver (hepatitis)

Reporting of side effects

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store DARZALEX

DARZALEX solution for subcutaneous injection will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after “EXP”. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C-8°C). Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What DARZALEX contains

- The active substance is daratumumab. One mL of solution contains 120 mg daratumumab. One vial of 15 mL solution for injection contains 1,800 mg of daratumumab.
- The other ingredients are recombinant human hyaluronidase (rHuPH20), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol (E420), and water for injections (see “DARZALEX contains sodium and sorbitol” in section 2).

What DARZALEX looks like and contents of the pack

DARZALEX solution for subcutaneous injection is a colourless to yellow liquid.

DARZALEX solution for subcutaneous injection is supplied as a carton pack containing 1 single-dose glass vial.

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
<http://www.ema.europa.eu>.

The following information is intended for healthcare professionals only:

DARZALEX solution for subcutaneous injection should be administered by a healthcare professional.

To prevent medication errors, it is important to check the vial labels to ensure that the appropriate formulation (intravenous or subcutaneous formulation) and dose is being given to the patient as prescribed. DARZALEX solution for injection should be given by subcutaneous injection only, using the dose specified. DARZALEX subcutaneous formulation is not intended for intravenous administration.

DARZALEX solution for subcutaneous injection is for single use only and is ready to use.

- DARZALEX solution for subcutaneous injection is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless steel transfer and injection needles.
- DARZALEX solution for subcutaneous injection should be a clear to opalescent and colourless to yellow solution. Do not use if opaque particles, discoloration or other foreign particles are present.
- Remove the DARZALEX solution for subcutaneous injection vial from refrigerated storage (2°C – 8°C) and equilibrate to ambient temperature (15°C–30°C). The unpunctured vial may be stored at ambient temperature and ambient light for a maximum of 24 hours in the original carton to protect from light. Keep out of direct sunlight. Do not shake.
- Prepare the dosing syringe in controlled and validated aseptic conditions.
- To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection.

Storage of prepared syringe

- If the syringe containing DARZALEX is not used immediately, store the solution of DARZALEX for up to 4 hours at ambient temperature and ambient light.

Administration

- Inject 15 mL DARZALEX solution for subcutaneous injection into the subcutaneous tissue of the abdomen approximately 7.5 cm to the right or left of the navel over approximately 3-5 minutes. Do not inject DARZALEX solution for subcutaneous injection at other sites of the body as no data are available.
- Injection sites should be rotated for successive injections.
- DARZALEX solution for subcutaneous injection should never be injected into areas where the skin is red, bruised, tender, hard or areas where there are scars.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by slowing down the injection, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- During treatment with DARZALEX solution for subcutaneous injection, do not administer other medicinal products for subcutaneous use at the same site as DARZALEX.
- Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Traceability

In order to improve the traceability of biological medicinal products, the tradename and the batch number of the administered product should be clearly recorded.

1.7 同種同効品一覧表

該当なし

ヒト型抗 CD38 モノクローナル抗体／ヒアルロン酸分解酵素配合剤

ダラツムマブ（遺伝子組換え）・ボルヒアルロニダーゼ アルファ（遺伝子組換え）製剤

ダラキューロ[®]配合皮下注生物由来製品
劇薬
処方箋医薬品*

承認番号	30300AMX00250000
販売開始	2021年5月

DARZQURO[®] Combination Subcutaneous Injection

※ 注意—医師等の処方箋により使用すること

1. 警告

本剤の投与は、緊急時に十分対応できる医療施設において、**造血器悪性腫瘍又は全身性ALアミロイドーシスの治療に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例のみに行うこと。また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。**

2. 禁忌（次の患者には投与しないこと）

本剤の成分に対し過敏症の既往歴のある患者

3. 組成・性状

3.1 組成

販売名	ダラキューロ配合皮下注
有効成分	(1バイアル15mL中) ダラツムマブ（遺伝子組換え）1800mg、 ボルヒアルロニダーゼ アルファ（遺伝子組換え）30000単位
添加剤	L-ヒスチジン 4.9mg、L-ヒスチジン塩酸塩水和物 18.4mg、D-ソルビトール 735.1mg、L-メチオニン 13.5mg、ポリソルベート 20 6.0mg

本剤はチャイニーズハムスター卵巣細胞を用いて製造される。

3.2 製剤の性状

性状	無色～黄色の液
pH	5.1～6.1
浸透圧比	約1（生理食塩液に対する比）

4. 効能又は効果

○多発性骨髄腫

○全身性ALアミロイドーシス

5. 効能又は効果に関連する注意

<多発性骨髄腫>

5.1 「17.臨床成績」の項及びダラツムマブ（遺伝子組換え）点滴静注製剤の添付文書の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。
[17.1.1-17.1.7参照]

<全身性ALアミロイドーシス>

5.2 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。
[17.1.8参照]

6. 用法及び用量

<多発性骨髄腫>

他の抗悪性腫瘍剤との併用において、通常、成人には本剤1回15mL（ダラツムマブ（遺伝子組換え）として1,800mg及びボルヒアルロニダーゼ アルファ（遺伝子組換え）として30,000単位（2,000単位/mL）を、併用する抗悪性腫瘍剤の投与サイクルを考慮して、以下のA法又はB法の投与間隔で皮下

投与する。

A法：1週間間隔、2週間間隔及び4週間間隔の順で投与する。

B法：1週間間隔、3週間間隔及び4週間間隔の順で投与する。

<全身性ALアミロイドーシス>

他の薬剤との併用において、通常、成人には本剤1回15mL（ダラツムマブ（遺伝子組換え）として1,800mg及びボルヒアルロニダーゼ アルファ（遺伝子組換え）として30,000単位（2,000単位/mL）を皮下投与する。

投与間隔は、1週間間隔、2週間間隔及び4週間間隔の順で投与とする。

7. 用法及び用量に関連する注意

<効能共通>

7.1 本剤を単独投与した場合の有効性及び安全性は確立していない。

7.2 本剤投与によるinfusion reactionを軽減させるために、本剤投与開始1～3時間前に副腎皮質ホルモン、解熱鎮痛剤及び抗ヒスタミン剤を投与すること。また、遅発性のinfusion reactionを軽減させるために、必要に応じて本剤投与後に副腎皮質ホルモン等を投与すること。[11.1.1参照]

7.3 Infusion reactionが発現した場合、以下のように、本剤の投与中止、投与速度の変更等、適切な処置を行うこと。なお、GradeはNCI-CTCAE v4.0に準じる。[11.1.1参照]

・Grade 3のinfusion reactionが3回発現した場合は本剤の投与を中止すること。

・Grade 4のinfusion reactionが発現した場合は本剤の投与を中止すること。

<多発性骨髄腫>

7.4 本剤の投与間隔、投与間隔の変更時期、本剤と併用する抗悪性腫瘍剤等について、「17.臨床成績」の項及びダラツムマブ（遺伝子組換え）点滴静注製剤の添付文書の内容を熟知した上で選択すること。[17.1.1-17.1.7参照]

7.5 ボルテゾミブ及びデキサメタゾン併用、又はボルテゾミブ、メルファラン及びブレドニゾロン併用の場合、併用投与終了後も本剤単独投与を継続すること。

<全身性ALアミロイドーシス>

7.6 本剤の投与間隔、投与間隔の変更時期、本剤と併用する薬剤等について、「17.臨床成績」の項の内容を熟知した上で選択すること。[17.1.8参照]

8. 重要な基本的注意

8.1 骨髄抑制があらわれることがあるので、本剤の投与前及び投与中は、定期的に血液検査等を行い、患者の状態を十分に観察すること。[9.1.3、11.1.2参照]

8.2 本剤は、赤血球上に発現しているCD38と結合し、間接クームス試験結果が偽陽性となる可能性がある。当該干渉は本剤最終投与より6ヵ月後まで持続する可能性がある。このため、本剤投与前に不規則抗体のスクリーニングを含めた一般的な輸血前検査の実施をすること。輸血が予定されている場合は、本剤を介した間接クームス試験への干渉について関係者に周知すること。¹⁾ [12.1参照]

8.3 腫瘍崩壊症候群があらわれることがあるので、血清中電解

最新の添付文書を参照すること

質濃度及び腎機能検査を行う等、患者の状態を十分に観察すること。[11.1.4 参照]

- 8.4 本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがあるので、本剤投与に先立って肝炎ウイルス感染の有無を確認し、本剤投与前に適切な処置を行うこと。[9.1.2、11.1.3 参照]
- 8.5 本剤の使用にあたっては、ダラツムマブ（遺伝子組換え）点滴静注製剤との取り違えに注意すること。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 慢性閉塞性肺疾患若しくは気管支喘息のある患者又はそれらの既往歴のある患者

本剤の投与後処置として気管支拡張剤及び吸入ステロイド剤の投与を考慮すること。本剤投与後に遅発性を含む気管支痙攣の発現リスクが高くなるおそれがある。

9.1.2 B 型肝炎ウイルスキャリアの患者又は HBs 抗原陰性で HBc 抗体陽性若しくは HBs 抗体陽性の患者

本剤の投与開始後は継続して肝機能検査や肝炎ウイルスマーカーのモニタリングを行うなど、B 型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがある。[8.4、11.1.3 参照]

9.1.3 体重 65kg 以下の患者

好中球減少等の骨髄抑制の発現が増加することがある。[8.1、11.1.2 参照]

9.4 生殖能を有する者

妊娠可能な女性及びパートナーが妊娠する可能性のある男性に対しては、本剤投与中及び本剤投与終了後一定期間は適切な避妊を行うよう指導すること。男性の受胎能に対する影響は検討されておらず不明である。[9.5 参照]

9.5 妊婦

妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を用いた生殖発生毒性試験は実施されていないが、IgG1 モノクローナル抗体に胎盤通過性があることが知られている。[9.4 参照]

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行は検討されていないが、ヒト IgG は乳汁中に移行するので、本剤も移行する可能性がある。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。高齢者では一般に生理機能が低下している。ダラツムマブ（遺伝子組換え）点滴静注製剤の臨床試験において、再発又は難治性の多発性骨髄腫患者のうち 65 歳未満と比較して 65 歳以上で重篤な有害事象の発現頻度は高く、主な重篤な有害事象は肺炎、敗血症であった。造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者において、75 歳未満と比較して 75 歳以上で重篤な有害事象の発現頻度は高く、主な重篤な有害事象は肺炎であった。未治療の全身性 AL アミロイドーシス患者において、65 歳以上における主な重篤な有害事象は肺炎であった。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 Infusion reaction

アナフィラキシー、鼻閉、咳嗽、悪寒、気管支痙攣、低酸素症、呼吸困難等の infusion reaction (25.8%) があらわれることがあり、多くの場合は、初回投与時に発現が認められたが、2 回目以降の投与時にも認められている。異常が認められた場合は、本剤の投与を中断又は中止し適切な

処置を行うとともに、症状が回復するまで患者の状態を十分に観察すること。重度の infusion reaction が認められた場合、本剤の投与中止等の適切な処置を行うこと。[7.2、7.3 参照]

11.1.2 骨髄抑制

好中球減少 (12.3%)、血小板減少 (12.3%)、リンパ球減少 (9.7%) 及び発熱性好中球減少症 (0.9%) 等の骨髄抑制があらわれることがある。[8.1、9.1.3 参照]

11.1.3 感染症

肺炎 (4.8%) や敗血症 (0.7%) 等の重篤な感染症や、B 型肝炎ウイルスの再活性化があらわれることがある。[8.4、9.1.2 参照]

11.1.4 腫瘍崩壊症候群 (頻度不明)

異常が認められた場合には適切な処置 (生理食塩液、高尿酸血症治療剤等の投与、透析等) を行うとともに、症状が回復するまで患者の状態を十分に観察すること。[8.3 参照]

11.1.5 間質性肺疾患 (0.3%)

異常が認められた場合には、本剤の投与を中止し、必要に応じて、胸部 CT、血清マーカー等の検査を実施するとともに、適切な処置を行うこと。

11.2 その他の副作用

	10%未満5%以上	5%未満	頻度不明
感染症及び寄生虫症	上気道感染	気管支炎、尿路感染、インフルエンザ、サイトメガロウイルス感染	
血液及びリンパ系障害	貧血	白血球減少	
代謝及び栄養障害		食欲減退、低カルシウム血症、高血糖	脱水
精神障害			不眠症
神経系障害		浮動性めまい、頭痛、末梢性感覚ニューロパチー、錯感覚	
心臓障害		心房細動	
血管障害		高血圧	
呼吸器、胸部及び縦隔障害		呼吸困難、咳嗽	肺水腫
胃腸障害	下痢	便秘、悪心、嘔吐	
皮膚および皮下組織障害		そう痒症、発疹	
筋骨格系及び結合組織障害		筋痙攣、関節痛、背部痛、筋骨格系胸痛	
一般・全身障害及び投与部位の状態	疲労、発熱、注射部位反応	悪寒、無力症、注射部位紅斑、末梢性浮腫	

12. 臨床検査結果に及ぼす影響

12.1 本剤は赤血球上の CD38 と結合し、抗体スクリーニングや交差試験等の適合性試験に干渉する。本剤による間接クームス試験への干渉を回避するために、ジチオスレイトール (DTT) 処理 (本剤と赤血球上の CD38 との結合を阻害する) を考慮すること。Kell 血液型抗原は DTT 処理で変性するので、不規則抗体スクリーニングにおいて Kell 血液型抗原に対する抗体の評価が不能となることに注意すること。¹⁾ [8.2 参照]

12.2 本剤はヒト IgG κ 型モノクローナル抗体であり、血清中 M タンパクの血清蛋白電気泳動法及び血清免疫固定法の結果に干渉する可能性がある。IgG κ 型多発性骨髄腫細胞を有する患者における完全奏効 (CR) の評価及び CR からの再発の評価に影響を及ぼす可能性があるため注意すること。

最新の添付文書を参照すること

14. 適用上の注意

14.1 薬剤調製時の注意

- 14.1.1 本剤の投与には、ポリプロピレン、ポリエチレン又はポリ塩化ビニル (PVC) の皮下投与セットとステンレス鋼製の注射針を用いること。
 - 14.1.2 本剤は、無菌環境下において、調製すること。
 - 14.1.3 本剤を冷蔵庫から取り出し、15～30℃に戻しておくこと。未穿刺バイアルは、室温及び室内光下で最長 24 時間保管ができる。
 - 14.1.4 注射針の詰まりを避けるために、投与直前に皮下注射針又は皮下投与セットをシリンジに取り付ける。
 - 14.1.5 薬液入りシリンジを直ちに使用しない場合は、本剤調製後、室温及び室内光下で 4 時間まで保存することができる。
- ### 14.2 薬剤投与時の注意
- 14.2.1 本剤投与前に粒子や変色の有無を目視で確認すること。不透明粒子や変色又は異物が認められた場合は使用しないこと。
 - 14.2.2 臍から左又は右に約 7.5cm の腹部皮下に、本剤 15mL を約 3～5 分かけて投与する。他の部位への投与はデータが得られていないため行わないこと。
 - 14.2.3 同一部位への反復注射は行わないこと。
 - 14.2.4 皮膚の発赤、挫傷、圧痛、硬結又は瘢痕がある部位には注射しないこと。
 - 14.2.5 患者が痛みを感じた場合は、注射速度を減速又は注射を中断する。減速しても痛みが軽減しない場合は、残りを左右逆側の腹部に投与することができる。
 - 14.2.6 本剤投与中は、同一部位に他剤を皮下投与しないこと。
 - 14.2.7 本剤は 1 回使い切りである。未使用残液については適切に廃棄すること。

15. その他の注意

15.1 臨床使用に基づく情報

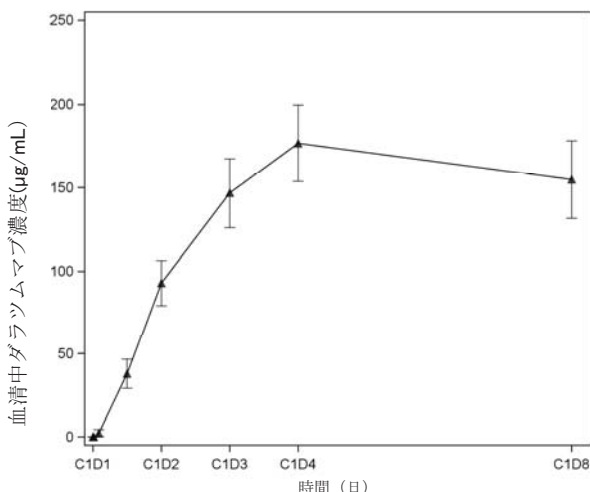
本剤の投与によりダラツムマブ (遺伝子組換え) に対する抗体産生が認められた患者の割合は、0.2% (1 例) であり、この 1 例においては、ダラツムマブ (遺伝子組換え) に対する中和抗体を認めた。また、ボルヒアルロニダージェ アルファ (遺伝子組換え) に対する抗体産生が認められた患者の割合は、6.6% (41 例) であった。

16. 薬物動態

16.1 血中濃度

16.1.1 MMY1008 試験 (国内試験、単剤療法)

日本人の再発又は難治性の多発性骨髄腫患者 6 例に、本剤 15mL を 1 週間隔で 8 週、続いて 2 週間隔で 16 週、それ以降は 4 週間隔で反復皮下投与した。初回投与後の血清中ダラツムマブ濃度推移を図 1 に示す。また、初回投与及び 1 週間隔での最終 (8 回目) 投与後の薬物動態パラメータを表 1 に示す。²⁾



C: サイクル, D: 日

図 1 日本人の再発又は難治性の多発性骨髄腫患者 6 例に本剤を初回投与したときの血清中ダラツムマブ濃度推移

(平均値±標準偏差)

表 1 日本人の再発又は難治性の多発性骨髄腫患者 6 例における本剤初回投与時及び 1 週間隔での最終 (8 回目、第 50 日) 投与時のダラツムマブの薬物動態パラメータ

	初回投与後	8 回目投与後
C_{max} (µg/mL)	177 (27.8)	1092 (318)
AUC_{0-7day} (µg · day/mL)	990 (145)	7015 (1895)
T_{max} (day)	3.0 (2.9-7.0)	0.9 (0.9-3.1)

平均値 (標準偏差)、ただし T_{max} は中央値 (範囲)

16.1.2 MMY3012 試験 (国際共同試験、単剤療法)

再発又は難治性の多発性骨髄腫患者 259 例に、本剤 15mL を 1 週間隔で 8 週、続いて 2 週間隔で 16 週、それ以降は 4 週間隔で反復皮下投与した。平均血清中ダラツムマブ濃度は、初回投与から 3 日後に 124µg/mL、1 週間隔での最終 (8 回目) 投与から 1 週間後 (2 週間隔投与への移行日) の投与前に 582µg/mL、2 週間隔での初回投与から 3 日目に 738µg/mL、2 週間隔での最終投与から 2 週間後 (4 週間隔投与への移行日) の投与前に 555µg/mL、4 週間隔投与への移行日から約 5 ヶ月後の投与前に 297µg/mL であった。³⁾

16.1.3 MMY2040 試験 (国際共同試験、ボルテゾミブ、メルファラン及びプレドニゾン又は prednisone*との併用療法)

未治療の多発性骨髄腫患者 67 例に、本剤 15mL をボルテゾミブ、メルファラン及びプレドニゾン又は prednisone*との併用療法にて 1 週間隔で 6 週、続いて 3 週間隔で 48 週、それ以降は 4 週間隔で反復皮下投与した。平均血清中ダラツムマブ濃度は、初回投与から 3 日後に 99µg/mL、1 週間隔での最終 (6 回目) 投与から 1 週間後 (3 週間隔投与への移行日) の投与前に 482µg/mL、3 週間隔での初回投与から 3 日目に 612µg/mL、3 週間隔での 3 回目投与の投与前に 392µg/mL であった。⁴⁾

*: 国内未承認

16.1.4 AMY3001 試験 (国際共同第Ⅲ相試験)

未治療の全身性 AL アミロイドーシス患者 381 例を対象に、本剤をボルテゾミブ、シクロホスファミド水和物及びデキサメタゾンとの併用療法にて 1 週間隔で 8 週、続いて 2 週間隔で 16 週、それ以降は 4 週間隔で反復皮下投与した。平均血清中ダラツムマブ濃度は、初回投与から 4 日後に 149µg/mL、2 週間隔での初回投与 (9 週目) の投与前及び投与 4 日後に 597µg/mL 及び 708µg/mL、4 週間隔での初回投与 (25 週目) の投与前に 478µg/mL、4 週間隔投与への移行後から約 5 ヶ月後の投与前に 273µg/mL であった。⁵⁾

17. 臨床成績

17.1 有効性及び安全性に関する試験

<多発性骨髄腫>

17.1.1 MMY3012 試験 (国際共同第Ⅲ相臨床試験)

プロテアソーム阻害剤及び免疫調節薬を含む 3 レジメン以上の前治療歴を有する、又はプロテアソーム阻害剤及び免疫調節薬に治療抵抗性の再発又は難治性の多発性骨髄腫患者 522 例を対象に、ダラツムマブ (遺伝子組換え) 点滴静注製剤単独療法に対する本剤単独療法の非劣性を確認するランダム化非盲検群間比較試験を実施した。主要評価項目の一つである中央判定による奏効率は、本剤群では 41.1% (95%信頼区間: 35.1～47.3%) (108/263 例)、ダラツムマブ (遺伝子組換え) 点滴静注製剤群では 37.1% (95%信頼区間: 31.2～43.3%) (96/259 例) であり、奏効率の比は 1.11 (95%信頼区間: 0.89～1.37) であった。また、もう一つの主要評価項目である最高血清中トラフ濃度 (第 3 サイクルの第 1 日目投与前) (平均値±標準偏差) は、本剤群では 593±306µg/mL、ダラツムマブ (遺伝子組換え) 点滴静注製剤群では 522±226µg/mL であり、最高血清中トラフ濃度の幾何平均比は 107.93% (90%信頼区間: 95.74～121.67%) であった。以上より、ダラツムマブ (遺伝子組換え) 点滴静注製剤群に対する本剤群の非劣

最新の添付文書を参照すること

性が検証された (2019年1月8日クリニカルカットオフ)。³⁾

- 注1) 本剤の用法及び用量: 28日間を1サイクルとし、ダラツムマブとして1回1,800mg (ボルヒアルロニダーゼ アルファ 30,000単位を含む)を、1週間間隔(1~8週目)、2週間間隔(9~24週目)及び4週間間隔(25週日以降)で皮下投与した。
- 注2) ダラツムマブ(遺伝子組換え)点滴静注製剤の用法及び用量: 28日間を1サイクルとし、1回16mg/kgを、1週間間隔(1~8週目)、2週間間隔(9~24週目)及び4週間間隔(25週日以降)で点滴静注した。
- 注3) 非劣性の判定基準: ①奏効率について、ダラツムマブ(遺伝子組換え)点滴静注製剤群に対する本剤群の奏効率の比の95%信頼区間の下限値が60%以上であり、かつ②最高血清中トラフ濃度について、ダラツムマブ(遺伝子組換え)点滴静注製剤群に対する本剤群の幾何平均比の90%信頼区間の下限値が80%以上の場合に、ダラツムマブ(遺伝子組換え)点滴静注製剤群に対する本剤群の非劣性が検証されたとすることとされた。

本剤群260例中134例(51.5%)に副作用が認められた。主な副作用は、infusion reaction 68例(26.2%)、好中球減少症32例(12.3%)、血小板減少症24例(9.2%)、上気道感染21例(8.1%)、貧血21例(8.1%)等であった(2019年7月8日クリニカルカットオフ)。^[5.1、7.4参照]

17.1.2 MMY2040 試験 (国際共同第II相臨床試験)

多発性骨髄腫患者132例(日本人患者4例を含む)を対象に、ボルテゾミブ、メルファラン及びブレドニゾン又はprednisone[※]との併用療法(MPB療法)に本剤を上乗せした本剤/MPB療法、並びにレナリドミド及びデキサメタゾンの併用療法(Ld療法)に本剤を上乗せした本剤/Ld療法の有効性及び安全性を検討する非盲検非対照試験を実施した。中央判定による奏効率は、本剤/MPB群では88.1%(90%信頼区間:79.5~93.9%)(59/67例)、本剤/Ld群では90.8%(90%信頼区間:82.6~95.9%)(59/65例)であった。⁴⁾

- 注1) 本剤の用法及び用量: 本剤/MPB群では、1~9サイクルまでは42日間を1サイクル、10サイクル以降は28日間を1サイクルとし、ダラツムマブとして1回1,800mg (ボルヒアルロニダーゼ アルファ 30,000単位を含む)を、1週間間隔(1~6週目)、3週間間隔(7~54週目)及び4週間間隔(55週日以降)で皮下投与した。本剤/Ld療法では、28日間を1サイクルとし、ダラツムマブとして1回1,800mg (ボルヒアルロニダーゼ アルファ 30,000単位を含む)を、1週間間隔(1~8週目)、2週間間隔(9~24週目)及び4週間間隔(25週日以降)で皮下投与した。
- 注2) ボルテゾミブの用法及び用量: 21日間を1サイクルとし、1.3mg/m²を第1~2サイクルでは週2回(1,4,8及び11日目)、第3~18サイクルでは週1回(1及び8日目)皮下投与又は静脈内投与した。なお、症状に応じ適宜減量した。
- 注3) メルファランの用法及び用量: 42日間を1サイクルとし、9サイクルまで9mg/m²を1,2,3及び4日目に経口投与した。なお、症状に応じ適宜減量した。
- 注4) ブレドニゾン又はprednisone[※]の用法及び用量: 42日間を1サイクルとし、9サイクルまで60mg/m²を1,2,3及び4日目に経口投与した。なお、症状に応じ適宜減量した。
- 注5) レナリドミドの用法及び用量: 28日間を1サイクルとし、CrCL>60 mL/minの被験者には25mgを、CrCL 30~60 mL/minの被験者には10mgを1日1回、21日間経口投与した。なお、症状に応じ適宜減量した。
- 注6) デキサメタゾンの用法及び用量: 28日間を1サイクルとし、40mgを1,8,15及び22日目に静脈内又は経口投与した。なお、症状に応じ適宜減量した。

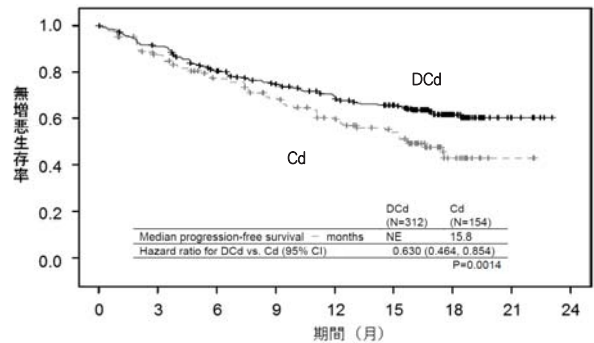
[※]: 国内未承認

本剤が投与された安全性評価対象例132例中93例(70.5%)に副作用が認められた。主な副作用は、Infusion reaction 33例(25.0%)、好中球減少33例(25.0%)、血小板減少32例(24.2%)、発熱23例(17.4%)、リンパ球減少19例(14.4%)等であった。^[5.1、7.4参照]

17.1.3 (参考) 20160275 (CANDOR) 試験 (国際共同第III相臨床試験): 点滴静注製剤

1~3 レジメンの前治療歴を有する再発又は難治性の多発性

骨髄腫患者466例(日本人患者31例を含む)を対象に、カルフィルゾミブ(週2回投与)及びデキサメタゾンの併用療法(Cd療法)とCd療法にダラツムマブ(遺伝子組換え)点滴静注製剤を上乗せしたDCd療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である無増悪生存期間の中央値は、DCd群では未到達、Cd群で15.8ヵ月(95%信頼区間:12.1~推定不能)であり、DCd群で統計学的に有意な延長を示した[ハザード比0.630、95%信頼区間:0.464~0.854、p=0.0014(層別log-rank検定)、2019年7月14日クリニカルカットオフ]。副次評価項目である全生存期間の中央値は、いずれの群も未到達であり、統計学的に有意な延長は認められていない[ハザード比0.745、95%信頼区間:0.491~1.131、p=0.0836(層別log-rank検定)、2019年7月14日クリニカルカットオフ]。⁶⁾



at risk数

	0	3	6	9	12	15	18	21	24
Cd	154	122	100	85	70	55	13	2	0
DCd	312	279	236	211	189	165	57	14	0

無増悪生存期間のKaplan-Meier 曲線 [20160275 (CANDOR) 試験]

DCd群: ダラツムマブ(遺伝子組換え)点滴静注製剤+カルフィルゾミブ+デキサメタゾン、Cd群: カルフィルゾミブ+デキサメタゾン

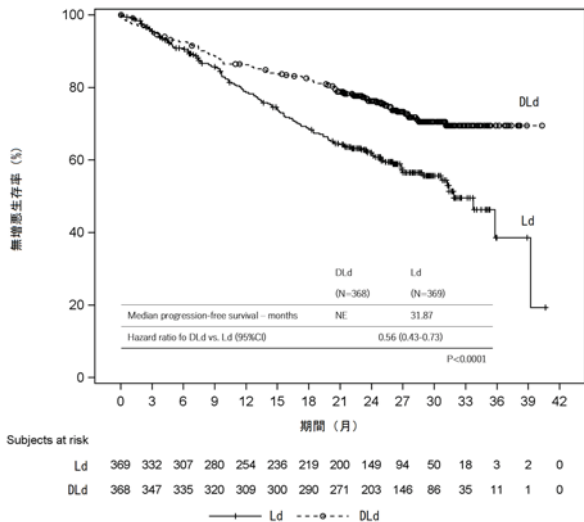
- 注1) ダラツムマブ(遺伝子組換え)点滴静注製剤の用法及び用量: 28日間を1サイクルとし、1回16mg/kgを、1週間間隔(1~8週目、初回のみ2日間に分割して8mg/kgずつ投与)、2週間間隔(9~24週目)及び4週間間隔(25週日以降)で点滴静注した。
- 注2) カルフィルゾミブの用法及び用量(週2回投与): 28日間を1サイクルとし、1日1回、1,2,8,9,15,16日目に点滴静注した。投与量は、1サイクル目の1,2日目のみ20mg/m²(体表面積)、それ以降は56mg/m²(体表面積)で点滴静注した。
- 注3) デキサメタゾンの用法及び用量: 28日間を1サイクルとし、20mgを1,2,8,9,15,16日目に、40mgを22日目に静脈内又は経口投与した。デキサメタゾンの投与日がカルフィルゾミブと同日の場合、カルフィルゾミブ投与の4時間~30分前、ダラツムマブ(遺伝子組換え)点滴静注製剤投与の1~3時間前に投与した。

DCd群308例中198例(64.3%)に副作用が認められた。主な副作用は、infusion reaction 127例(41.2%)、血小板減少症65例(21.1%)、貧血41例(13.3%)、上気道感染27例(8.8%)、肺炎26例(8.4%)、疲労23例(7.5%)であった。^[5.1、7.4参照]

17.1.4 (参考) MMY3008 試験 (海外第III相臨床試験): 点滴静注製剤

造血幹細胞移植が適応とならない未治療の多発性骨髄腫患者737例を対象に、レナリドミド及びデキサメタゾンの併用療法(Ld療法)とLd療法にダラツムマブ(遺伝子組換え)点滴静注製剤を上乗せしたDLd療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である無増悪生存期間の中央値は、DLd群では未到達、Ld群で31.9ヵ月(95%信頼区間:28.9~推定不能)であり、DLd群で統計学的に有意な延長を示した[ハザード比:0.56、95%信頼区間:0.43~0.73、p<0.0001(層別Log-rank検定)、2018年9月24日クリニカルカットオフ]。⁷⁾

最新の添付文書を参照すること



無増悪生存期間のKaplan-Meier 曲線 [MMY3008 試験]

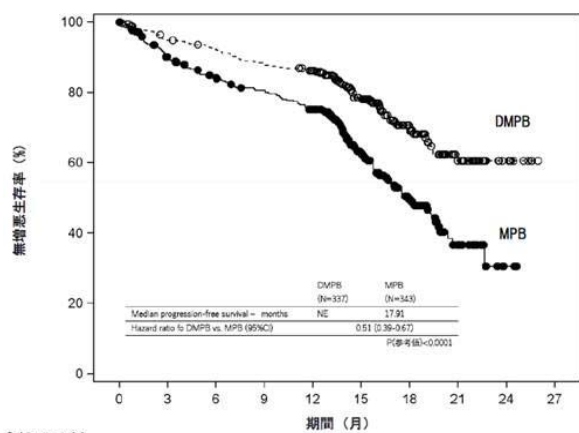
DLd 群：ダラツムマブ（遺伝子組換え）点滴静注製剤＋レナリドミド＋デキサメタゾン、Ld 群：レナリドミド＋デキサメタゾン

- 注1) ダラツムマブ（遺伝子組換え）点滴静注製剤の用法及び用量：28 日間を 1 サイクルとし、1 回 16mg/kg を、1 週間間隔（1～8 週目）、2 週間間隔（9～24 週目）及び 4 週間間隔（25 週目以降）で点滴静注した。
- 注2) レナリドミドの用法及び用量：28 日間を 1 サイクルとし、CrCL>50mL/min の被験者には 25mg を、CrCL 30～50mL/min の被験者には 10mg を 1 日 1 回、21 日間経口投与した。なお、症状に応じ適宜減量した。
- 注3) デキサメタゾンの用法及び用量：28 日間を 1 サイクルとし、40mg を 1、8、15 及び 22 日目に静脈内又は経口投与した。なお、症状に応じ適宜減量した。

DLd 群 364 例中 308 例（84.6%）に副作用が認められた。主な副作用は、infusion reaction 203 例（55.8%）、好中球減少 96 例（26.4%）、疲労 70 例（19.2%）、呼吸困難 50 例（13.7%）、貧血 49 例（13.5%）等であった。[5. 1、7. 4 参照]

17. 1. 5 (参考) MMY3007 試験 (国際共同第Ⅲ相臨床試験)：点滴静注製剤

造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者 680 例（日本人患者 24 例を含む）を対象に、ボルテゾミブ、メルファラン及びプレドニゾン又は prednisone[※]の併用療法（MPB 療法）と MPB 療法にダラツムマブ（遺伝子組換え）点滴静注製剤を上乗せした DMPB 療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である無増悪生存期間の中央値は、DMPB 群では未到達、MPB 群で 17.9 ヶ月（95%信頼区間：16.1～19.8）であり、DMPB 群で統計学的に有意な延長を示した [ハザード比：0.51、95%信頼区間：0.39～0.67、p<0.0001（層別 Log-rank 検定）、2017 年 6 月 12 日クリニカルカットオフ]。⁸⁾



無増悪生存期間のKaplan-Meier 曲線 [MMY3007 試験]

DMPB 群：ダラツムマブ（遺伝子組換え）点滴静注製剤＋ボルテゾミブ＋メルファラン＋プレドニゾン又は prednisone[※]、MPB 群：ボルテゾミブ＋メルファラン＋プレドニゾン又は prednisone[※]

- 注1) ダラツムマブ（遺伝子組換え）点滴静注製剤の用法及び用量：1～9 サイクルまでは 42 日間を 1 サイクル、10 サイクル以降は 28 日間を 1 サイクルとし、1 回 16mg/kg を、1 週間間隔（1～6 週目）、3 週間間隔（7～54 週目）及び 4 週間間隔（55 週目以降）で点滴静注した。
- 注2) ボルテゾミブの用法及び用量：21 日間を 1 サイクルとし、1.3mg/m² を第 1～2 サイクルでは週 2 回（1、4、8 及び 11 日目）、第 3～18 サイクルでは週 1 回（1 及び 8 日目）皮下投与又は静脈内投与した。なお、症状に応じ適宜減量した。
- 注3) メルファランの用法及び用量：42 日間を 1 サイクルとし、9 サイクルまで 9mg/m² を 1、2、3 及び 4 日目に経口投与した。なお、症状に応じ適宜減量した。
- 注4) プレドニゾン又は prednisone[※]の用法及び用量：42 日間を 1 サイクルとし、9 サイクルまで 60mg/m² を 1、2、3 及び 4 日目に経口投与した。なお、症状に応じ適宜減量した。

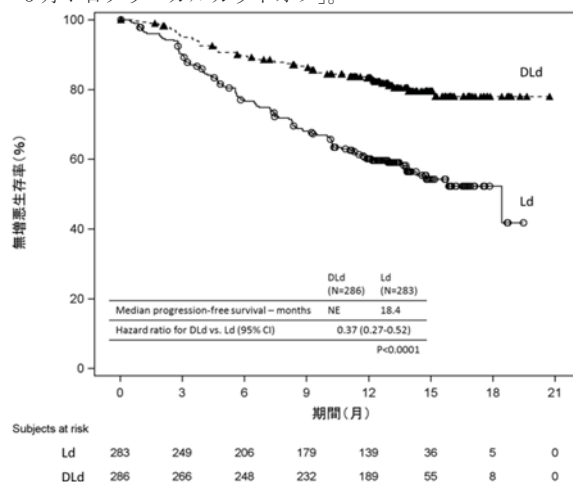
- 注2) ボルテゾミブの用法及び用量：21 日間を 1 サイクルとし、1.3mg/m² を第 1～2 サイクルでは週 2 回（1、4、8 及び 11 日目）、第 3～18 サイクルでは週 1 回（1 及び 8 日目）皮下投与又は静脈内投与した。なお、症状に応じ適宜減量した。
- 注3) メルファランの用法及び用量：42 日間を 1 サイクルとし、9 サイクルまで 9mg/m² を 1、2、3 及び 4 日目に経口投与した。なお、症状に応じ適宜減量した。
- 注4) プレドニゾン又は prednisone[※]の用法及び用量：42 日間を 1 サイクルとし、9 サイクルまで 60mg/m² を 1、2、3 及び 4 日目に経口投与した。なお、症状に応じ適宜減量した。

[※]：国内未承認

DMPB 群 333 例中 193 例（58.0%）に副作用（が認められた。主な副作用は、infusion reaction 103 例（30.9%）、好中球減少 71 例（21.3%）、血小板減少 63 例（18.9%）、貧血 28 例（8.4%）、呼吸困難 24 例（7.2%）等であった。[5. 1、7. 4 参照]

17. 1. 6 (参考) MMY3003 試験 (国際共同第Ⅲ相臨床試験)：点滴静注製剤

1 レジメン以上の前治療歴を有する再発又は難治性の多発性骨髄腫患者 569 例（日本人患者 36 例を含む）を対象に、レナリドミド及びデキサメタゾンの併用療法（Ld 療法）と Ld 療法にダラツムマブ（遺伝子組換え）点滴静注製剤を上乗せした DLd 療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である無増悪生存期間の中央値は、DLd 群では未到達、Ld 群で 18.4 ヶ月（95%信頼区間：13.9～推定不能）であり、DLd 群で統計学的に有意な延長を示した [ハザード比：0.37、95%信頼区間：0.27～0.52、p<0.0001（層別 Log-rank 検定）]。副次評価項目である全生存期間の中央値は、DLd 群では未到達、Ld 群で 20.3 ヶ月であり、統計学的に有意な延長は認められていない [ハザード比：0.64、95%信頼区間：0.40～1.01、p=0.0534（非層別 Log-rank 検定）、2016 年 3 月 7 日クリニカルカットオフ]。⁹⁾



無増悪生存期間のKaplan-Meier 曲線 [MMY3003 試験]

DLd 群：ダラツムマブ（遺伝子組換え）点滴静注製剤＋レナリドミド＋デキサメタゾン、Ld 群：レナリドミド＋デキサメタゾン

- 注1) ダラツムマブ（遺伝子組換え）点滴静注製剤の用法及び用量：28 日間を 1 サイクルとし、1 回 16mg/kg を、1 週間間隔（1～8 週目）、2 週間間隔（9～24 週目）及び 4 週間間隔（25 週目以降）で点滴静注した。
- 注2) レナリドミドの用法及び用量：28 日間を 1 サイクルとし、CrCL>60mL/min の被験者には 25mg を、CrCL 30～60mL/min の被験者には 10mg を 1 日 1 回、21 日間経口投与した。なお、症状に応じ適宜減量した。
- 注3) デキサメタゾンの用法及び用量：28 日間を 1 サイクルとし、40mg を 1、8、15 及び 22 日目に静脈内又は経口投与した。なお、症状に応じ適宜減量した。
- 注4) レナリドミドに対して治療抵抗性を示す又は忍容性が不良の患者は除外した。

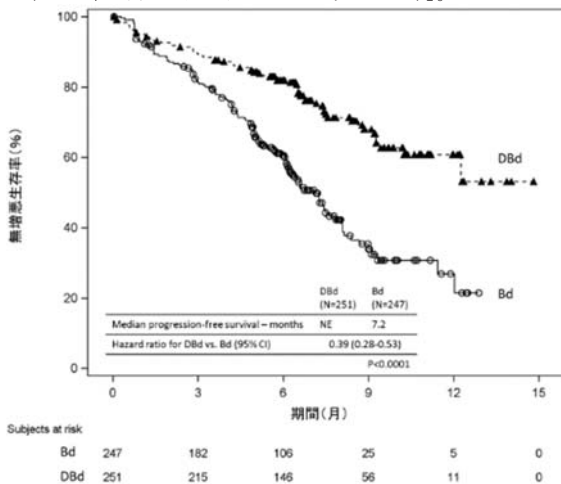
DLd 群 283 例中 215 例（76.0%）に副作用が認められた。主な副作用は、infusion reaction 158 例（55.8%）、好中球減少 43 例（15.2%）、上気道感染 43 例（15.2%）、疲労 35 例（12.4%）、咳嗽 34 例（12.0%）等であった。[5. 1、7. 4 参照]

17. 1. 7 (参考) MMY3004 試験 (海外第Ⅲ相臨床試験)：点滴静

最新の添付文書を参照すること

注製剤

1 レジメン以上の前治療歴を有する再発又は難治性の多発性骨髄腫患者 498 例を対象に、ボルテゾミブ及びデキサメタゾンの併用療法 (Bd 療法) と Bd 療法にダラツムマブ (遺伝子組換え) 点滴静注製剤を上乗せした DCyBorD 療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である無増悪生存期間の中央値は、DBd 群では未到達、Bd 群で 7.2 ヶ月 (95%信頼区間: 6.2~7.9) であり、DBd 群で統計学的に有意な延長を示した [ハザード比: 0.39, 95%信頼区間: 0.28~0.53, $p < 0.0001$ (層別 Log-rank 検定)]。副次評価項目である全生存期間の中央値は、いずれの群も未到達であり、統計学的に有意な延長は認められていない [ハザード比: 0.77, 95%信頼区間: 0.47~1.26, $p = 0.2975$ (非層別 Log-rank 検定)、(2016 年 1 月 11 日クリニカルカットオフ)]。¹⁰⁾



無増悪生存期間の Kaplan-Meier 曲線 [MMY3004 試験]

DBd 群: ダラツムマブ (遺伝子組換え) 点滴静注製剤+ボルテゾミブ+デキサメタゾン、Bd 群: ボルテゾミブ+デキサメタゾン

- 注1) ダラツムマブ (遺伝子組換え) 点滴静注製剤の用法及び用量: 1~8 サイクルまでは 21 日間を 1 サイクル、9 サイクル以降は 28 日間を 1 サイクルとし、1 回 16mg/kg を、1 週間間隔 (1~9 週目)、3 週間間隔 (10~24 週目) 及び 4 週間間隔 (25 週目以降) で点滴静注した。
- 注2) ボルテゾミブの用法及び用量: 21 日間を 1 サイクルとし、1.3mg/m² を週 2 回 (1、4、8 及び 11 日) 8 サイクルまで静脈内投与又は皮下投与した。なお、症状に応じ適宜減量した。
- 注3) デキサメタゾンの用法及び用量: 21 日間を 1 サイクルとし、8 サイクルまで 20mg を 1、2、4、5、8、9、11 及び 12 日目に静脈内又は経口投与した。なお、症状に応じ適宜減量した。
- 注4) ボルテゾミブ、イキサゾミブ若しくはカルフィルゾミブに対して治療抵抗性を示す又はボルテゾミブに対し忍容性が不良の患者は除外した。

DBd 群 243 例中 182 例 (74.9%) に副作用が認められた。主な副作用は、infusion reaction 120 例 (49.4%)、血小板減少 73 例 (30.0%)、呼吸困難 34 例 (14.0%)、咳嗽 30 例 (12.3%)、疲労 27 例 (11.1%) 等であった。[5.1、7.4 参照]

<全身性 AL アミロイドーシス>

17.1.8 AMY3001 試験 (国際共同第 III 相臨床試験)

未治療の全身性 AL アミロイドーシス患者 388 例を対象に、シクロホスファミド水和物、ボルテゾミブ及びデキサメタゾンの併用療法 (CyBorD 療法) と本剤を上乗せした DCyBorD 療法を比較するランダム化非盲検群間比較試験を実施した。主要評価項目である血液学的完全奏効 (CR) 率は、DCyBorD 群では 53.3% (95%信頼区間: 46.1~60.5) (104/195 例)、CyBorD 群では 18.1% (95%信頼区間: 13.0~24.3) (35/193 例) であり、DCyBorD 群で統計学的に有意な改善を示した [オッズ比: 5.13, 95%信頼区間: 3.22~8.16, $p < 0.0001$ (層別 Cochran-Mantel-Haenszel 検定)、有意水準: 0.04999、2020 年 2 月 14 日クリニカルカットオフ]。⁵⁾

注1) 本剤の用法及び用量: 28 日間を 1 サイクルとし、ダラツムマブとして 1 回 1,800mg (ボルヒアルロニダーゼ アルファ 30,000 単位を含む) を、1 週間間隔 (1~8 週目)、2 週間間隔 (9~24 週目) 及び 4 週間間隔 (25 週目以降) で 24 サイクルまで皮下投与した。

注2) シクロホスファミド水和物の用法及び用量: 28 日間を 1 サイクルとし、300mg/m² (無水物換算) を 1 週間間隔で 6 サイ

クルまで経口又は静脈内投与した。なお、症状に応じ適宜減量した。

注3) ボルテゾミブの用法及び用量: 28 日間を 1 サイクルとし、1.3mg/m² を 1 週間間隔で 6 サイクルまで皮下投与した。なお、症状に応じ適宜減量した。

注4) デキサメタゾンの用法及び用量: 28 日間を 1 サイクルとし、40mg を 1 週間間隔で 6 サイクルまで経口投与した。なお、症状に応じ適宜減量した。

DCyBorD 群 193 例中 110 例 (57.0%) に副作用が認められた。主な副作用は、infusion reaction 53 例 (27.5%)、リンパ球減少 26 例 (13.5%)、貧血 21 例 (10.9%)、上気道感染 21 例 (10.9%)、注射部位反応 21 例 (10.9%)、疲労 18 例 (9.3%)、血小板減少症 16 例 (8.3%) 等であった。DCyBorD 群の 72.5% がベースライン時に全身性 AL アミロイドーシスに関連する心臓障害を有していた。心臓障害関連の有害事象は、心不全 8.3%、動悸 5.7%、心房細動 5.7% であり、重篤又は致命的な心臓障害関連の有害事象は心不全 6.2%、心停止 3.6%、心房細動 2.1% であった。重篤又は致命的な心臓障害を発現した患者はベースライン時に全身性 AL アミロイドーシスに関連する心臓障害を有していた。なお、臨床試験では Mayo Clinic Cardiac Staging System に基づく心臓病期 stage IIb (NT-proBNP > 8,500pg/mL)、NYHA 分類クラス IIb 又は IV の患者は除外された。[5.2、7.6 参照]

18. 薬効薬理

18.1 作用機序

本剤は、ダラツムマブ及びボルヒアルロニダーゼ アルファを含有する配合剤である。ダラツムマブは、ヒト CD38 に結合し、補体依存性細胞傷害 (CDC) 活性、抗体依存性細胞傷害 (ADCC) 活性、抗体依存性細胞貪食 (ADCP) 活性等により、腫瘍の増殖を抑制すると考えられている。^{11)~16)} ボルヒアルロニダーゼ アルファは、結合組織におけるヒアルロン酸を加水分解する酵素である。¹⁷⁾

本剤は、ボルヒアルロニダーゼ アルファによりヒアルロン酸が加水分解され、皮下組織における浸透性が増加することで、拡散吸収されたダラツムマブが腫瘍の増殖を抑制すると考えられている。

19. 有効成分に関する理化学的知見

19.1 ダラツムマブ (遺伝子組換え)

一般的名称: ダラツムマブ (遺伝子組換え)

[Daratumumab (Genetical Recombination)]

分子量: 約 148,000

本質: ヒト CD38 に対する遺伝子組換えヒト IgG1 モノクローナル抗体である。チャイニーズハムスター卵巣細胞により産生される。452 個のアミノ酸残基からなる H 鎖 2 本及び 214 個のアミノ酸残基からなる L 鎖 2 本で構成される糖タンパク質である。

19.2 ボルヒアルロニダーゼ アルファ (遺伝子組換え)

一般的名称: ボルヒアルロニダーゼ アルファ (遺伝子組換え)

[Vorhyaluronidase Alfa (Genetical Recombination)]

分子量: 60,000~65,000

本質: 遺伝子組換えヒトヒアルロニダーゼ PH-20 類縁体であり、ヒトヒアルロニダーゼ PH-20 のアミノ酸配列の 36~482 番目に相当する。チャイニーズハムスター卵巣細胞により産生される。447 個のアミノ酸残基からなる糖タンパク質である。

20. 取扱い上の注意

20.1 激しく振盪しないこと。

20.2 外箱開封後は遮光して保存すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

15mL [1 バイアル]

23. 主要文献

1) Chapuy CI, et al.: Transfusion. 2016; 56: 2964-2972

最新の添付文書を参照すること

(doi:10.1111/ trf.13789)

- 2) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY1008 試験) (2021年3月23日承認、CTD2.7.6.6)
- 3) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY3012 試験) (2021年3月23日承認、CTD2.7.6.1)
- 4) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY2040 試験) (2021年3月23日承認、CTD2.7.6.3)
- 5) 社内資料：ダラツムマブの全身性ALアミロイドーシス患者に対する臨床成績 (54767414AMY3001 試験) (2021年MM月DD日承認、CTDX.X.X.X)
- 6) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (20160275 試験)
- 7) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY3008 試験)
- 8) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY3007 試験)
- 9) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY3003 試験)
- 10) 社内資料：ダラツムマブの多発性骨髄腫患者に対する臨床成績 (54767414MMY3004 試験)
- 11) 社内資料：ダラツムマブの補体依存性細胞傷害作用に関する非臨床成績 (GMB3003-003)
- 12) 社内資料：ダラツムマブの抗体依存性細胞傷害作用に関する非臨床成績 (GMB3003-004)
- 13) 社内資料：ダラツムマブの抗体依存性細胞貪食作用に関する非臨床成績 (GMB3003-115)
- 14) 社内資料：ダラツムマブのアポトーシス誘導に関する非臨床成績 (GMB3003-011)
- 15) 社内資料：ダラツムマブのアポトーシス誘導に関する非臨床成績 (GMB3003-116)
- 16) 社内資料：ダラツムマブのCD38 酵素活性の調節作用に関する非臨床成績 (GMB3003-013)
- 17) Frost GI. : Expert Opin Drug Deliv 2007;4(4):427-440

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最新の添付文書を参照すること

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1.8 添付文書（案）

1.8.1 全身性 AL アミロイドーシス

1.8.1.1 効能・効果（案），用法・用量（案）及びその設定根拠

1.8.1.1.1 効能・効果（案）及び用法・用量（案）

(1) 効能・効果（案）

全身性 AL アミロイドーシス

(2) 用法・用量（案）

＜全身性 AL アミロイドーシス＞

他の薬剤との併用において，通常，成人には本剤 1 回 15 mL（ダラツムマブ（遺伝子組換え）として 1,800 mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え）として 30,000 単位（2,000 単位/mL））を皮下投与する。

投与間隔は，1 週間間隔，2 週間間隔及び 4 週間間隔の順で投与とする。

1.8.1.2 設定根拠

全身性免疫グロブリン軽鎖（AL）アミロイドーシス患者に対するダラツムマブ，シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾン（DCyBorD）療法の効能・効果（案）及び用法・用量（案）は，国際共同第Ⅲ相試験である 54767414AMY3001 試験（以下 AMY3001 試験）の結果に基づき設定した。

1.8.1.2.1 AMY3001 試験でのダラツムマブの用法・用量の設定根拠

AMY3001 試験では，シクロホスファミド水和物，ボルテゾミブ及びデキサメタゾン（CyBorD）療法にダラツムマブ皮下注製剤 [ダラツムマブ 1800 mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え） 30,000 U] を併用した DCyBorD 療法と CyBorD 療法の有効性及び安全性を比較した。

CyBorD 療法は，海外のガイドラインで未治療の全身性 AL アミロイドーシスに対する標準治療の 1 つとして推奨され^{1) 2) 3)}，汎用されている。

ダラツムマブ皮下注製剤の用量（ダラツムマブとして 1800 mg）は，多発性骨髄腫患者を対象に海外で実施した用量漸増第Ⅱb 相試験である 54767414MMY1004 試験の結果に基づき設定し，日本人に対する忍容性，安全性及び薬物動態は多発性骨髄腫患者を対象とした国内第Ⅰ相試験である 54767414MMY1008 試験で確認した。また，ダラツムマブ皮下注製剤の用法は，多発性骨髄腫に対して承認されたダラツムマブ点滴静注製剤の用法に基づき設定した。

1.8.1.2.2 AMY3001 試験結果に基づく設定根拠

AMY3001 試験の DCyBorD 群では、いずれの治験薬投与も 28 日間を 1 サイクルとし、疾患進行又は全身性 AL アミロイドーシスに対する次治療開始まで、ダラツムマブは最長 24 サイクル（約 2 年）、ボルテゾミブ、シクロホスファミド水和物及びデキサメタゾン（無水物換算）は最長 6 サイクル投与することとした。ダラツムマブはサイクル 1～2 は 1 週間隔、サイクル 3～6 は 2 週間隔、サイクル 7 以降は 4 週間隔で 1800 mg を皮下投与した。ボルテゾミブは 1 週間隔で 1.3 mg/m² を皮下投与した。なお、ボルテゾミブの投与により注射部位反応が発現した被験者では、ボルテゾミブの静脈内投与を可とした。シクロホスファミド水和物は 1 週間隔で 300 mg/m²（無水物換算）を経口又は静脈内投与した。ただし、週間投与量は、体表面積にかかわらず 500 mg（無水物換算）までとした。デキサメタゾンは 1 週間隔で 40 mg を経口投与した。ダラツムマブ投与日にデキサメタゾンを投与する場合は前投薬として 20 mg を経口又は静脈内投与し、その翌日にも 20 mg を投与した。なお、ダラツムマブ投与日以外（サイクル 3～6 の Day 8, Day 22）にデキサメタゾンを投与する場合でも、40 mg を 20 mg ずつに分割して 2 日間にわたる投与を可とした。また、70 歳超、体格指数（BMI）18.5 未満、血液量増加症、コントロール不良の糖尿病、又はステロイドに対する不耐症／有害事象の既往のある被験者に対しては、1 週間隔で 20 mg のデキサメタゾン投与を可とした。CyBorD 群では、DCyBorD 群で投与した治験薬のうち、ボルテゾミブ、シクロホスファミド水和物及びデキサメタゾンを同一の用法・用量で投与した。

有効性

主要評価項目である complete response（CR）率は、CyBorD 群（18.1%）と比較して DCyBorD 群（53.3%）で統計学的に有意な改善が認められ {オッズ比 [95% 信頼区間（CI）] : 5.13（3.22, 8.16）, p<0.0001} , CyBorD 療法に対するダラツムマブの上乗せ効果が示された。主な副次評価項目である、主要な臓器機能低下－無増悪生存期間（MOD-PFS）は、CyBorD 群と比較して DCyBorD 群で延長傾向がみられた。CR 率及び MOD-PFS の結果は、感度分析及び補足的解析でも一貫しており、いずれの部分集団でも CyBorD 群と比較して DCyBorD 群で改善が認められた。また、CR までの期間及び very good partial response（VGPR）以上までの期間は CyBorD 群と比較して DCyBorD 群でいずれも短縮傾向がみられ、VGPR 以上の奏効が認められた被験者の割合及び臓器奏効（心臓及び腎臓）でも CR 率及び MOD-PFS と同様、DCyBorD 群で良好な結果であった。

日本人集団に対する有効性については、主要評価項目である CR 率で全体集団との一貫性が示された。主な副次評価項目も全体集団と同様の結果であった。DCyBorD 群の MOD-PFS は CyBorD 群と比較して延長傾向がみられ、DCyBorD 群の CR までの期間及び VGPR 以上までの期間は CyBorD 群と比較して短縮傾向が示された【CTD 2.5.4.6】。

安全性

DCyBorD 群の安全性プロファイルは、原疾患である全身性 AL アミロイドーシスの合併症に関連するものが含まれており、その他はダラツムマブ、ボルテゾミブ、シクロホスファミド水和物及びデキサメタゾンの既知の安全性プロファイルと比較したときと大きな差はみられず、忍容性は良好であった。DCyBorD 群の日本人集団の安全性プロファイルは、全体集団と同様であった【CTD 2.5.5.8】。

薬物動態

未治療の全身性 AL アミロイドーシス患者に対してダラツムマブ 1800 mg を CyBorD 療法との併用で反復皮下投与した結果、母集団薬物動態解析及び曝露-応答（ER）解析によりダラツムマブの推奨用量を 1800 mg とすることが支持された。また、被験者背景による用量調節は不要と考えられた。詳細を以下に示す。

- ・ 未治療の全身性 AL アミロイドーシス患者に対して固定用量としてダラツムマブ 1800 mg を反復皮下投与したときの血清中ダラツムマブ曝露量は、低体重の被験者では高値を、高体重の被験者では低値を示す傾向が認められた。しかし、体重別の部分集団解析の結果、CR 率は体重区分によらず一定であったこと、及び安全性に関する ER 解析の結果、検討した曝露量範囲においてダラツムマブの曝露量と安全性に明らかな相関は認められなかったことから、ダラツムマブの曝露量に対する体重の影響は臨床的に意義のあるものではないと考えられた【CTD 2.7.2.3.3.1(2)1】。
- ・ 有効性に関する ER 解析の結果、未治療の全身性 AL アミロイドーシス患者に対してダラツムマブ 1800 mg を CyBorD 療法との併用で反復皮下投与した場合、大部分の被験者で血液学的奏効を得るのに十分な曝露量が得られており、血液学的奏効が不十分な被験者でダラツムマブの投与量を増量しても血液学的奏効の改善は期待できないと考えられた【CTD 2.7.2.3.3.2(1)】。
- ・ 安全性に関する ER 解析の結果、検討したダラツムマブの曝露量範囲では、曝露量と有害事象 [infusion related reaction (IRR) , 血球減少症に関する有害事象 (好中球減少症, 血小板減少症, リンパ球減少症, 貧血) , 感染症および寄生虫症 (器官別大分類, SOC) , 心臓障害 (SOC) , 腎および尿路障害 (SOC)] の発現割合との間に明らかな関連は認められなかった【CTD 2.7.2.3.3.2(2)】。

血清中ダラツムマブ濃度の平均値は、いずれの時点でも全体集団と比較して日本人集団で高値であった。しかし、日本人集団の血清中ダラツムマブ濃度の分布は全体集団の血清中ダラツムマブ濃度の分布と重なっていた。また、全体集団と日本人集団の血清中ダラツムマブ濃度の平均値の差は体重差に起因すると考えられるが、全体集団ではダラツムマブの薬物動態に及ぼす体重の影響は臨床的に意義のあるものではないと結論づけられた。以上のことから、全身性 AL アミロイドーシス患者に対してダラツムマブ 1800 mg を CyBorD 療法との併用で反復皮下投与したときに、ダラツムマブの薬物動態に臨床的に意義のある国内外差はないと考えられた【CTD 2.7.2.3.2】。

以上のとおり、AMY3001 試験の結果、DCyBorD 療法は未治療の全身性 AL アミロイドーシス患者に対して臨床的に有用であることが示され、かつ外国人と日本人との間に薬物動態、安全性及び有効性のいずれについても臨床的に意義のある差は認められなかった。また、海外のガイドラインでは再発した全身性 AL アミロイドーシス患者に対しては、初回治療レジメンでの再治療、又はこれまでに投与していない代替併用レジメンでの治療が選択肢となるため^{1) 2) 3)}、未治療の

全身性 AL アミロイドーシス患者で有用性が検証された治療レジメンは、再発した全身性 AL アミロイドーシス患者での治療選択肢の 1 つとなると考える。

以上より、効能・効果（案）を全身性 AL アミロイドーシスと設定し、AMY3001 試験で用いたダラツムマブ皮下注製剤の用法・用量を全身性 AL アミロイドーシス患者に対する推奨用法・用量（案）として設定した。

1.8.1.3 使用上の注意（案）及びその設定根拠

使用上の注意（案） 2021年5月作成（第1版）からの変更点	設定根拠
<p>1. 警告</p> <p>本剤の投与は、緊急時に十分対応できる医療施設において、<u>造血器悪性腫瘍又は全身性 AL アミロイドーシスの治療に対して十分な知識・経験を持つ医師のもとで、本剤の投与が適切と判断される症例のみに行うこと。</u>また、治療開始に先立ち、患者又はその家族に有効性及び危険性を十分に説明し、同意を得てから投与を開始すること。</p>	<p>抗悪性腫瘍剤使用時における一般的な注意喚起として設定した。</p> <p><u>申請効能及び効果である、全身性 AL アミロイドーシスは、造血器悪性腫瘍ではないため、追記した。</u></p>
<p>2. 禁忌（次の患者には投与しないこと）</p> <p>本剤の成分に対し過敏症の既往歴のある患者</p>	<p>一般的な注意事項として、本剤の成分に対する過敏症の既往歴のある患者を禁忌に設定した。</p>
<p>5. 効能又は効果に関連する注意</p> <p><u><多発性骨髄腫></u></p> <p>5.1 「17.臨床成績」の項及びダラツムマブ（遺伝子組換え）点滴静注製剤の添付文書の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。</p> <p>[17.1.1-17.1.7 参照]</p> <p><u><全身性 AL アミロイドーシス></u></p> <p>5.2 「17.臨床成績」の項の内容を熟知し、本剤の有効性及び安全性を十分に理解した上で、適応患者の選択を行うこと。[17.1.8 参照]</p>	<p>ダラザレックス点滴静注添付文書に準じて設定した。</p>
<p>7. 用法及び用量に関連する注意</p> <p><u><効能共通></u></p> <p>7.1 本剤を単独投与した場合の有効性及び安全性は確立していない。</p> <p>7.2 本剤投与による infusion reaction を軽減させるために、本剤投与開始 1～3 時間前に副腎皮質ホルモン、解熱鎮痛剤及び抗ヒスタ</p>	<p>ダラザレックス点滴静注添付文書に準じて設定した。</p> <p><u>全身性 AL アミロイドーシスに使用される併用薬には、造血器悪性腫瘍剤でないものも含まれるため、7.6 を追記した。</u></p>

<p>ミン剤を投与すること。また、遅発性の infusion reaction を軽減させるために、必要に応じて本剤投与後に副腎皮質ホルモン等を投与すること。 [11.1.1 参照]</p> <p>7.3 Infusion reaction が発現した場合、以下のように、本剤の投与中止、投与速度の変更等、適切な処置を行うこと。なお、Grade は NCI-CTCAE v4.0 に準じる。 [11.1.1 参照]</p> <ul style="list-style-type: none"> ・ Grade 3 の infusion reaction が 3 回発現した場合は本剤の投与を中止すること。 ・ Grade 4 の infusion reaction が発現した場合は本剤の投与を中止すること。 <p><u><多発性骨髄腫></u></p> <p>7.4 本剤の投与間隔、投与間隔の変更時期、本剤と併用する抗悪性腫瘍剤等について、「17. 臨床成績」の項及びダラツムマブ（遺伝子組換え）点滴静注製剤の添付文書の内容を熟知した上で選択すること。 [17.1.1-17.1.7 参照]</p> <p>7.5 ボルテゾミブ及びデキサメタゾン併用、又はボルテゾミブ、メルファラン及びプレドニゾン併用の場合、併用投与終了後も本剤単独投与を継続すること。</p> <p><u><全身性 AL アミロイドーシス></u></p> <p>7.6 本剤の投与間隔、投与間隔の変更時期、本剤と併用する薬剤等について、「17. 臨床成績」の項の内容を熟知した上で選択すること。 [17.1.8 参照]</p>	
<p>8. 重要な基本的注意</p> <p>8.1 骨髄抑制があらわれることがあるので、本剤の投与前及び投与中は、定期的に血液検査等を行い、患者の状態を十分に観察すること。 [9.1.3、11.1.2 参照]</p> <p>8.2 本剤は、赤血球上に発現している CD38 と結合し、間接クームス試験結果が偽陽性となる可能性がある。当該干渉は本剤最終投与より 6 ヶ月後まで持続する可能性がある。この</p>	<p>ダラザレックス点滴静注添付文書に準じて設定した。</p>

<p>ため、本剤投与前に不規則抗体のスクリーニングを含めた一般的な輸血前検査の実施をすること。輸血が予定されている場合は、本剤を介した間接クームス試験への干渉について関係者に周知すること。 [12.1 参照]</p> <p>8.3 腫瘍崩壊症候群があらわれることがあるので、血清中電解質濃度及び腎機能検査を行う等、患者の状態を十分に観察すること。 [11.1.4 参照]</p> <p>8.4 本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがあるので、本剤投与に先立って肝炎ウイルス感染の有無を確認し、本剤投与前に適切な処置を行うこと。 [9.1.2、11.1.3 参照]</p> <p>8.5 本剤の使用にあたっては、ダラツムマブ（遺伝子組換え）点滴静注製剤との取り違えに注意すること。</p>	
<p>9.特定の背景を有する患者に関する注意</p> <p>9.1 合併症・既往歴等のある患者</p> <p>9.1.1 慢性閉塞性肺疾患若しくは気管支喘息のある患者又はそれらの既往歴のある患者 本剤の投与後処置として気管支拡張剤及び吸入ステロイド剤の投与を考慮すること。本剤投与後に遅発性を含む気管支痙攣の発現リスクが高くなるおそれがある。</p> <p>9.1.2 B 型肝炎ウイルスキャリアの患者又は HBs 抗原陰性で HBc 抗体陽性若しくは HBs 抗体陽性の患者 本剤の投与開始後は継続して肝機能検査や肝炎ウイルスマーカーのモニタリングを行うなど、B 型肝炎ウイルスの再活性化の徴候や症状の発現に注意すること。本剤の投与により B 型肝炎ウイルスの再活性化による肝炎があらわれることがある。 [8.4、11.1.3 参照]</p> <p>9.1.3 体重 65kg 以下の患者 好中球減少等の骨髄抑制の発現が増加することがある。 [8.1、11.1.2 参照]</p> <p>9.4 生殖能を有する者 妊娠可能な女性及びパートナーが妊娠する可</p>	<p>ダラザレックス点滴静注添付文書に準じて設定した。</p>

<p>能性のある男性に対しては、本剤投与中及び本剤投与終了後一定期間は適切な避妊を行うよう指導すること。男性の受胎能に対する影響は検討されておらず不明である。 [9.5 参照]</p> <p>9.5 妊婦 妊婦又は妊娠している可能性のある女性には、治療上の有益性が危険性を上回ると判断される場合にのみ投与すること。本剤を用いた生殖発生毒性試験は実施されていないが、IgG1 モノクローナル抗体に胎盤通過性があることが知られている。 [9.4 参照]</p> <p>9.6 授乳婦 治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行は検討されていないが、ヒト IgG は乳汁中に移行するので、本剤も移行する可能性がある。</p> <p>9.7 小児等 小児等を対象とした臨床試験は実施していない。</p> <p>9.8 高齢者 患者の状態を観察しながら慎重に投与すること。高齢者では一般に生理機能が低下している。ダラツムマブ（遺伝子組換え）点滴静注製剤の臨床試験において、再発又は難治性の多発性骨髄腫患者のうち 65 歳未満と比較して 65 歳以上で重篤な有害事象の発現頻度は高く、主な重篤な有害事象は肺炎、敗血症であった。造血幹細胞移植の適応とならない未治療の多発性骨髄腫患者において、75 歳未満と比較して 75 歳以上で重篤な有害事象の発現頻度は高く、主な重篤な有害事象は肺炎であった。<u>未治療の全身性 AL アミロイドーシス患者において、65 歳以上における主な重篤な有害事象は肺炎であった。</u></p>	
<p>11. 副作用 次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には</p>	<p>副作用は、本剤及びダラザレックス点滴静注の臨床試験に基づき設定した。 重大な副作用及びその他の副作用の頻度は、</p>

投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 Infusion reaction

アナフィラキシー、鼻閉、咳嗽、悪寒、気管支痙攣、低酸素症、呼吸困難等の infusion reaction (25.8%) があらわれることがあり、多くの場合は、初回投与時に発現が認められたが、2回目以降の投与時にも認められている。異常が認められた場合は、本剤の投与を中断又は中止し適切な処置を行うとともに、症状が回復するまで患者の状態を十分に観察すること。重度の infusion reaction が認められた場合、本剤の投与中止等の適切な処置を行うこと。[7.2、7.3 参照]

11.1.2 骨髄抑制

好中球減少 (12.3%)、血小板減少 (12.3%)、リンパ球減少 (9.7%) 及び発熱性好中球減少症 (0.9%) 等の骨髄抑制があらわれることがある。[8.1、9.1.3 参照]

11.1.3 感染症

肺炎 (4.8%) や敗血症 (0.7%) 等の重篤な感染症や、B型肝炎ウイルスの再活性化があらわれることがある。[8.4、9.1.2 参照]

11.1.4 腫瘍崩壊症候群 (頻度不明)

異常が認められた場合には適切な処置 (生理食塩液、高尿酸血症治療剤等の投与、透析等) を行うとともに、症状が回復するまで患者の状態を十分に観察すること。[8.3 参照]

11.1.5 間質性肺疾患 (0.3%)

異常が認められた場合には、本剤の投与を中止し、必要に応じて、胸部 CT、血清マーカー等の検査を実施するとともに、適切な処置を行うこと。

11.2 その他の副作用

	10%未満5%以上	5%未満	頻度不明
感染症及び寄生虫症	上気道感染	気管支炎、尿路感染、インフルエンザ、サイトメガロウイルス感染	
血液及びリンパ系障害	貧血	白血球減少	

MMY3012 試験, MMY2040 試験の DVMP コホート, DRd コホート及び AMY3001 試験の結果に基づく。

代謝及び栄養障害		食欲減退、低カルシウム血症、高血糖	脱水	
精神障害			不眠症	
神経系障害		浮動性めまい、頭痛、末梢性感覚ニューロパチー、錯感覚		
心臓障害		心房細動		
血管障害		高血圧		
呼吸器、胸部及び縦隔障害		呼吸困難、咳嗽	肺水腫	
胃腸障害	下痢	便秘、悪心、嘔吐		
皮膚および皮下組織障害		そう痒症、発疹		
筋骨格系及び結合組織障害		筋痙縮、関節痛、背部痛、筋骨格系胸痛		
一般・全身障害及び投与部位の状態	疲労、発熱、注射部位反応	悪寒、無力症、注射部位紅斑、末梢性浮腫		
<p>12. 臨床検査結果に及ぼす影響</p> <p>12.1 本剤は赤血球上の CD38 と結合し、抗体スクリーニングや交差試験等の適合性試験に干渉する。本剤による間接クームス試験への干渉を回避するために、ジチオスレイトール（DTT）処理（本剤と赤血球上の CD38 との結合を阻害する）を考慮すること。Kell 血液型抗原は DTT 処理で変性するので、不規則抗体スクリーニングにおいて Kell 血液型抗原に対する抗体の評価が不能となることに注意すること。 [8.2 参照]</p> <p>12.2 本剤はヒト IgGκ 型モノクローナル抗体であり、血清中 M タンパクの血清蛋白電気泳動法及び血清免疫固定法の結果に干渉する可能性がある。IgGκ 型多発性骨髄腫細胞を有する患者における完全奏効（CR）の評価及び CR からの再発の評価に影響を及ぼす可能性があるため注意すること。</p>				<p>ダラザレックス点滴静注添付文書に準じて設定した。</p>
<p>14. 適用上の注意</p> <p>14.1 薬剤調製時の注意</p> <p>14.1.1 本剤の投与には、ポリプロピレン、ポリエチレン又はポリ塩化ビニル（PVC）の皮下投与セットとステンレス鋼製の注射針を用いること。</p>				<p>臨床試験に基づき設定した。</p>

<p>14.1.2 本剤は、無菌環境下において、調製すること。</p> <p>14.1.3 本剤を冷蔵庫から取り出し、15～30℃に戻しておくこと。未穿刺バイアルは、室温及び室内光下で最長 24 時間保管ができる。</p> <p>14.1.4 注射針の詰まりを避けるために、投与直前に皮下注射針又は皮下投与セットをシリンジに取り付ける。</p> <p>14.1.5 薬液入りシリンジを直ちに使用しない場合は、本剤調製後、室温及び室内光下で 4 時間まで保存することができる。</p> <p>14.2 薬剤投与時の注意</p> <p>14.2.1 本剤投与前に粒子や変色の有無を目視で確認すること。不透明粒子や変色又は異物が認められた場合は使用しないこと。</p> <p>14.2.2 臍から左又は右に約 7.5cm の腹部皮下に、本剤 15mL を約 3～5 分かけて投与する。他の部位への投与はデータが得られていないため行わないこと。</p> <p>14.2.3 同一部位への反復注射は行わないこと。</p> <p>14.2.4 皮膚の発赤、挫傷、圧痛、硬結又は瘢痕がある部位には注射しないこと。</p> <p>14.2.5 患者が痛みを感じた場合は、注射速度を減速又は注射を中断する。減速しても痛みが軽減しない場合は、残りを左右逆側の腹部に投与することができる。</p> <p>14.2.6 本剤投与中は、同一部位に他剤を皮下投与しないこと。</p> <p>14.2.7 本剤は 1 回使い切りである。未使用残液については適切に廃棄すること。</p>	
<p>15. その他の注意</p> <p>15.1 臨床使用に基づく情報</p> <p>本剤の投与によりダラツムマブ（遺伝子組換え）に対する抗体産生が認められた患者の割合は、0.2%（1 例）であり、この 1 例においては、ダラツムマブ（遺伝子組換え）に対する中和抗体を認めた。また、ボルヒアルロニダーゼ アルファ（遺伝子組換え）に対する抗</p>	<p>本剤の臨床試験における抗体産生の発現頻度に基づき設定した。</p>

体産生が認められた患者の割合は、 <u>6.6%</u> (41例)であった。	
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参考文献

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- 3) The Risk Adapted Approach to Management of Multiple Myeloma and Related Disorders [homepage on the Internet]. Mayo clinic; [update 2019 August]. Treatment Guidelines: Amyloidosis. Available from:
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1.10 毒薬・劇薬等の指定審査資料のまとめ

毒薬・劇薬等の指定審査に係る資料について、本申請に係る内容を次ページより示す。

化学名・別名																											
構造式																											
効能・効果	全身性 AL アミロイドーシス																										
用法・用量	他の薬剤との併用において、通常、成人には、ダラツムマブ（遺伝子組換え）として1回 1,800mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え）として 30,000 単位（2,000 単位/mL）を皮下注射する。 投与間隔は、1 週間間隔、2 週間間隔及び 4 週間間隔の順で投与とする。																										
劇薬等の指定																											
市販名及び有効成分・分量	有効成分：ダラツムマブ（遺伝子組換え）／ボルヒアルロニダーゼ アルファ（遺伝子組換え） 製剤：ダラキューロ皮下注配合皮下注 （1 バイアル中、ダラツムマブ（遺伝子組換え） 1,800 mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え） 30,000 単位を含有）																										
毒性	<p>【ダラツムマブ（遺伝子組換え）】</p> <p>単回投与毒性</p> <table border="1"> <thead> <tr> <th>動物種</th> <th>投与経路</th> <th>概略の致死量 (mg/kg) ¹⁾</th> </tr> </thead> <tbody> <tr> <td>チンパンジー</td> <td>静脈内</td> <td>♂♀：5</td> </tr> </tbody> </table> <p>1) 単回投与毒性試験を実施していないため、6 週間反復投与毒性試験の初回投与時の結果から求めた。</p> <p>反復投与毒性</p> <table border="1"> <thead> <tr> <th>動物種</th> <th>投与期間 投与経路</th> <th>投与量 (mg/kg/週)</th> <th>無毒性量 (mg/kg/週)</th> <th>主な所見</th> </tr> </thead> <tbody> <tr> <td>チンパンジー</td> <td>6 週間 (1 回/週) 静脈内</td> <td>0 → 5²⁾ 0 → 25³⁾</td> <td>< 5</td> <td> ≥5: 気管粘液↑, 排便, 好中球・APTT ↑, リンパ球・血小板・IgG・IgM ↓ 5: 死亡 (♀1) 死亡例にみられた所見：サイトカイン放出反応 (くしゃみ, TNF-α・IL-6・IFN-γ ↑, 気管及び鼻孔から泡沫状液体の大量排出) 25: サイトカイン放出反応 (くしゃみ, 粘液↑), 粘膜蒼白, 下痢, 軟便, 食欲低下 </td> </tr> </tbody> </table> <p>2) 溶媒投与の1週間後に、ダラツムマブ 5 mg/kg を 30 分間かけて静脈内持続投与（以後、1 週間ごとにダラツムマブ 5 mg/kg を計 6 回、静脈内持続投与）。</p> <p>3) 5 mg/kg の初回静脈内持続投与時にサイトカイン放出反応が認められ、雌 1 例が死亡したため、過剰なサイトカイン放出を予防する目的で、溶媒投与の2週間後にダラツムマブ 10 mg を静脈内にボラスで前投与し、その 24 時間後にダラツムマブ 25 mg/kg を 1 時間かけて静脈内持続投与。ダラツムマブの 2～6 回目の静脈内持続投与時間は 30 分間。</p> <p>【ボルヒアルロニダーゼ アルファ（遺伝子組換え）】</p> <p>単回投与毒性</p> <table border="1"> <thead> <tr> <th>動物種</th> <th>投与経路</th> <th>概略の致死量 (mg/kg) ⁴⁾</th> </tr> </thead> <tbody> <tr> <td rowspan="2">カニクイザル</td> <td>皮下</td> <td>♂：>5, ♀：>30</td> </tr> <tr> <td>静脈内</td> <td>♂：>5, ♀：>30</td> </tr> </tbody> </table> <p>4) 単回投与毒性試験を実施していないため、7 日間反復投与毒性試験の初回投与時（雄）及び単回投与薬物動態試験（雌）の結果から求めた。</p> <p>反復投与毒性</p>			動物種	投与経路	概略の致死量 (mg/kg) ¹⁾	チンパンジー	静脈内	♂♀：5	動物種	投与期間 投与経路	投与量 (mg/kg/週)	無毒性量 (mg/kg/週)	主な所見	チンパンジー	6 週間 (1 回/週) 静脈内	0 → 5 ²⁾ 0 → 25 ³⁾	< 5	≥5: 気管粘液↑, 排便, 好中球・APTT ↑, リンパ球・血小板・IgG・IgM ↓ 5: 死亡 (♀1) 死亡例にみられた所見：サイトカイン放出反応 (くしゃみ, TNF-α・IL-6・IFN-γ ↑, 気管及び鼻孔から泡沫状液体の大量排出) 25: サイトカイン放出反応 (くしゃみ, 粘液↑), 粘膜蒼白, 下痢, 軟便, 食欲低下	動物種	投与経路	概略の致死量 (mg/kg) ⁴⁾	カニクイザル	皮下	♂：>5, ♀：>30	静脈内	♂：>5, ♀：>30
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	静脈内	♂：>5, ♀：>30																									

動物種	投与期間 投与経路	性別	投与量	無毒性量	主な所見																																								
マウス	8カ月間(生後7~30日:1回/日, 生後30~241日:1回/週) ⁵⁾ 皮下	♂♀	0, 1 mg/kg/回	1 mg/kg/回 ⁶⁾	1 mg/kg/回: 安楽死(♂: 25例中2例) ⁷⁾ , 投与部位: 皮下組織の混合 細胞性炎症を伴う混合性 細胞浸潤 ⁸⁾																																								
カニクイザル	7日間(1回/日) 皮下又は静脈内	♂♀	0, 5 mg/kg/日	5 mg/kg/日	所見なし																																								
	39週間(1回/週) 皮下 回復期間: 4週間	♂♀	0, 0.02, 0.2, 2 mg/kg/週	2 mg/kg/週	≥0.2 mg/kg/週: 投与部位: 皮下血管周囲の リンパ形質細胞浸潤 ⁸⁾ 【回復期間】 2 mg/kg/週: 投与部位: 皮下血管周囲の リンパ形質細胞浸潤(♂) ⁸⁾																																								
<p>5) 幼若マウスを用いたボルヒアルロニダーゼ アルファ及び抗薬物抗体の生涯投与毒性試験の慢性毒性評価サブセット。</p> <p>6) 当該試験では無毒性量を求めているため、忍容性が良好で、ボルヒアルロニダーゼ アルファ投与による有害な影響がみられなかった用量を示す。</p> <p>7) ボルヒアルロニダーゼ アルファ投与に関連しない。</p> <p>8) 有害ではない所見。</p>																																													
副作用	<p>副作用発現率(臨床検査値異常を含む) 134/ 260 例=51.5% [日本を含む国際共同第III相試験(54767414MMY3012 試験)]</p> <table border="1"> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr><td>Infusion related reactions</td><td>68/260 (26.2%)</td></tr> <tr><td>好中球減少症</td><td>32/260 (12.3%)</td></tr> <tr><td>血小板減少症</td><td>24/260 (9.2%)</td></tr> <tr><td>貧血</td><td>21/260 (8.1%)</td></tr> <tr><td>発熱</td><td>15/260 (5.8%)</td></tr> <tr><td>悪寒</td><td>14/260 (5.4%)</td></tr> <tr><td>疲労</td><td>14/260 (5.4%)</td></tr> <tr><td>リンパ球減少症</td><td>12/260 (4.6%)</td></tr> <tr><td>下痢</td><td>11/260 (4.2%)</td></tr> <tr><td>上気道感染</td><td>9/260 (3.5%)</td></tr> </tbody> </table> <p>副作用発現率(臨床検査値異常を含む) 110/ 193 例=57.0% [日本を含む国際共同第III相試験(54767414AMY3001 試験)]</p> <table border="1"> <thead> <tr> <th>副作用の種類</th> <th>例数</th> </tr> </thead> <tbody> <tr><td>Infusion related reactions</td><td>53/193 (27.5%)</td></tr> <tr><td>リンパ球減少症</td><td>26/193 (13.5%)</td></tr> <tr><td>貧血</td><td>21/193 (10.9%)</td></tr> <tr><td>疲労</td><td>18/193 (9.3%)</td></tr> <tr><td>血小板減少症</td><td>16/193 (8.3%)</td></tr> <tr><td>上気道感染</td><td>16/193 (8.3%)</td></tr> <tr><td>下痢</td><td>15/193 (7.8%)</td></tr> <tr><td>注射部位紅斑</td><td>10/193 (5.2%)</td></tr> </tbody> </table>					副作用の種類	例数	Infusion related reactions	68/260 (26.2%)	好中球減少症	32/260 (12.3%)	血小板減少症	24/260 (9.2%)	貧血	21/260 (8.1%)	発熱	15/260 (5.8%)	悪寒	14/260 (5.4%)	疲労	14/260 (5.4%)	リンパ球減少症	12/260 (4.6%)	下痢	11/260 (4.2%)	上気道感染	9/260 (3.5%)	副作用の種類	例数	Infusion related reactions	53/193 (27.5%)	リンパ球減少症	26/193 (13.5%)	貧血	21/193 (10.9%)	疲労	18/193 (9.3%)	血小板減少症	16/193 (8.3%)	上気道感染	16/193 (8.3%)	下痢	15/193 (7.8%)	注射部位紅斑	10/193 (5.2%)
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別紙様式 1

生物由来医薬品又は特定生物由来医薬品の指定資料のまとめ

一般名：	ダラツムマブ（遺伝子組換え）、ボルヒアルロニダーゼ アルファ（遺伝子組換え）
販売名：	ダラキューロ配合皮下注
申請者：	ヤンセンファーマ株式会社
効能・効果：	全身性 AL アミロイドーシス
用法・用量：	他の薬剤との併用において、通常、成人には、ダラツムマブ（遺伝子組換え）として 1 回 1,800mg 及びボルヒアルロニダーゼ アルファ（遺伝子組換え）として 30,000 単位（2,000 単位/mL）を皮下注射する。 投与間隔は、1 週間間隔、2 週間間隔及び 4 週間間隔の順で投与とする。
生物由来原材料の使用の有無	<input checked="" type="checkbox"/> 使用→ 使用している場合は以下の欄を記入 <input type="checkbox"/> 不使用
使用した生物由来原材料	<input type="checkbox"/> 人由来細胞・組織、 <input type="checkbox"/> 人由来成分（血液、尿、その他）、 <input checked="" type="checkbox"/> 動物由来細胞・組織、 <input type="checkbox"/> 動物由来成分（血液、その他） 原材料名；チャイニーズハムスター卵巣細胞
生物由来原料の使用目的	<input checked="" type="checkbox"/> 宿主細胞、 <input type="checkbox"/> 培地添加物、 <input type="checkbox"/> その他の製造原材料、 <input type="checkbox"/> 製剤添加物、 <input type="checkbox"/> その他（ ）
原材料の由来となる人・動物のスクリーニング・管理の内容：	合致する基準の告示・通知等があれば引用（ ）
当該生物由来原材料不活化処理等の内容：	別紙様式 2 参照
ウイルスクリアランス試験結果の概要：	別添 2 参照
製造工程の概要（フローチャート）： （不活化処理には下線を付し、処理条件を具体的に記載）	別添 1 参照
使用した生物由来原材料	<input type="checkbox"/> 人由来細胞・組織、 <input type="checkbox"/> 人由来成分（血液、尿、その他）、 <input checked="" type="checkbox"/> 動物由来細胞・組織、 <input type="checkbox"/> 動物由来成分（血液、その他） 原材料名；DHFR 欠損 CHO DG44 変異株
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原材料の由来となる人・動物のスクリーニング・管理の内容：	合致する基準の告示・通知等： ・ICH Q5A ヒト又は動物細胞株を用いて製造されるバイオテクノロジー応用医薬品のウイルス安全性評価 ・生物由来原料基準 第 4 動物由来原料総則

	<p>DHFR 欠損 CHO DG44 変異株は、GIBCO/Invitrogen 社により無血清化学合成培地への馴化、核型解析、特性解析及びウイルス試験が実施されたものである。また、マスターセルバンク、ワーキングセルバンク及び製造後細胞でウイルス安全性を確認している。</p>
<p>当該生物由来原材料不活化処理等の内容：</p>	<p>原薬ボルヒアルロニダーゼ アルファの製造の精製工程にて有機溶媒／界面活性剤処理によるウイルス不活化工程を実施している。</p>
<p>ウイルスクリアランス試験結果の概要：</p>	<p>原薬ボルヒアルロニダーゼ アルファの製造の精製工程について、ウイルス不活化工程（有機溶媒／界面活性剤処理）、カラムクロマトグラフィー精製工程及びナノろ過工程のスケールダウンモデルを用いたウイルスクリアランス試験を実施した。結果を以下に示す。</p> <p>【総対数減少度】</p> <p>異種指向性マウス白血病ウイルス：≥ 20.82 レオウイルス 3 型：9.74 仮性狂犬病ウイルス：≥ 11.89 マウスマイニュートウイルス：8.63</p>
<p>製造工程の概要（フローチャート）： （不活化処理には下線を付し、処理条件を具体的に記載）</p>	<p>原薬ボルヒアルロニダーゼ アルファの製造工程の概要を示す。</p> <p style="text-align: center;">＜製造工程＞</p> <p style="text-align: center;">細胞培養及びハーベスト清澄化工程 ↓ ハーベスト液の濃縮及び緩衝液交換工程 ↓ <u>ウイルス不活化工程</u> <u>（有機溶媒／界面活性剤処理）</u> ↓ クロマトグラフィー工程（1） ↓ クロマトグラフィー工程（2） ↓ クロマトグラフィー工程（3） ↓ クロマトグラフィー工程（4） ↓ ナノろ過工程 ↓ 最終濃縮及び緩衝液交換工程 ↓ 充填及び試験工程 ↓ 保管</p> <p>ウイルス不活化工程の有機溶媒／界面活性剤処理では、液温 15°C 以上で合計 30 分以上攪拌する。</p> <p>さらなる情報が必要な場合は、医薬品等原薬 ボルヒアルロニダーゼ アルファ（遺伝子組換え）の原薬等登録原簿をご参照頂くか、国内管理人までご連絡ください。</p> <p>原薬等登録原簿 登録番号 302MF10030 国内管理人 コアメッド株式会社 住所：大阪府中央区北浜二丁目 1 番 21 号 担当者 1：今村 恵子</p>

	<p>担当者 2 : 石井 篤史 TEL : 06-6221-1352 FAX : 06-6221-1357</p>
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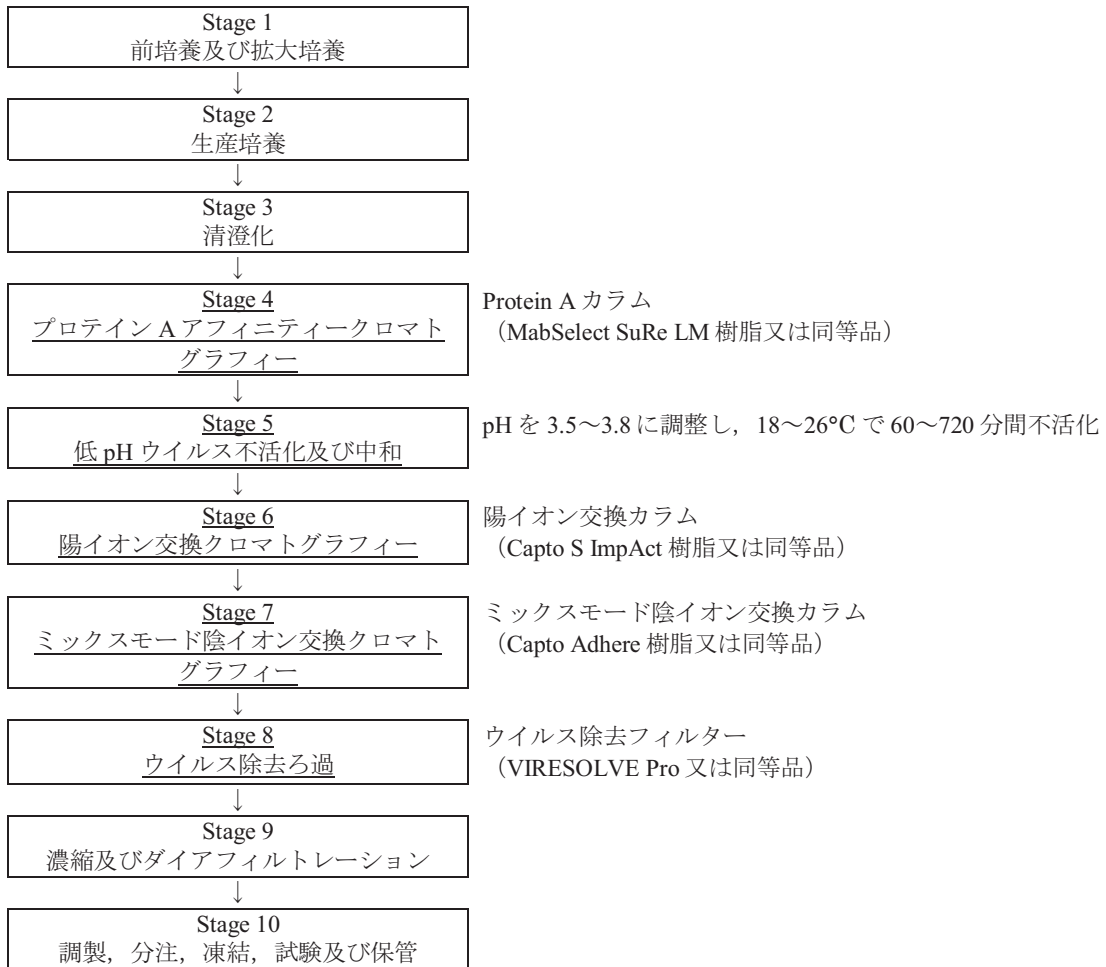
別紙様式 2

<p>使用した生物由来原料又は材料の名称^{注1)}、^{注2)}</p>	<p>チャイニーズハムスター卵巣 (CHO) 細胞</p>
<p>使用した生物由来原料又は材料の分類</p>	<p><input type="checkbox"/>人血液由来成分、<input type="checkbox"/>人細胞組織、<input type="checkbox"/>人尿由来成分、<input type="checkbox"/>人由来成分 (血液、細胞組織又は尿を除くもの)、<input type="checkbox"/>反芻動物由来成分、<input checked="" type="checkbox"/>動物細胞組織、<input type="checkbox"/>動物由来成分、<input type="checkbox"/>その他 ()</p>
<p>生物由来原料又は材料の使用目的</p>	<p><input type="checkbox"/>製剤有効成分、<input checked="" type="checkbox"/>宿主細胞、<input type="checkbox"/>培地添加物、<input type="checkbox"/>その他の製造原料又は材料 ()、<input type="checkbox"/>製剤添加物、<input type="checkbox"/>その他 ()</p>
<p>生物由来原料又は材料の由来となる人・動物のスクリーニング・管理の内容^{注3)}</p>	<p>宿主細胞 (CHO 細胞) を用いてダラツムマブ産生細胞株 CD3806 を作製し、MCB 及び WCB を構築した。MCB 及び WCB は、ICHQ5A 及び Q5D に従って純度試験を行い、いずれも細菌、真菌、マイコプラズマ及びウシ又は外来性ウイルスの混入は認められなかった。</p>
<p>生物由来原料又は材料のウイルス等の不活化及び除去処理等の内容^{注4)}</p>	<p>実施せず</p>
<p>製造工程の概要 (フローチャート)^{注5)} ^{注6)} (不活化及び除去処理には下線を付し、条件を具体的に記載)</p>	<p>別添 1 参照</p>
<p>ウイルスクリアランス試験結果の概要^{注7)}</p>	<p>別添 2 参照</p>

別紙様式 2

<p>使用した生物由来原料又は材料の名称^{注1)}、^{注2)}</p>	<p>DHFR 欠損 CHO DG44 変異株 (チャイニーズハムスター卵巣細胞由来)</p>
<p>使用した生物由来原料又は材料の分類</p>	<p><input type="checkbox"/>人血液由来成分、<input type="checkbox"/>人細胞組織、<input type="checkbox"/>人尿由来成分、<input type="checkbox"/>人由来成分(血液、細胞組織又は尿を除くもの)、<input type="checkbox"/>反芻動物由来成分、<input checked="" type="checkbox"/>動物細胞組織、<input type="checkbox"/>動物由来成分、<input type="checkbox"/>その他()</p>
<p>生物由来原料又は材料の使用目的</p>	<p><input type="checkbox"/>製剤有効成分、<input checked="" type="checkbox"/>宿主細胞、<input type="checkbox"/>培地添加物、<input type="checkbox"/>その他の製造原料又は材料()、<input type="checkbox"/>製剤添加物、<input type="checkbox"/>その他()</p>
<p>生物由来原料又は材料の由来となる人・動物のスクリーニング・管理の内容^{注3)}</p>	<p>合致する基準の告示・通知等： ・ICH Q5A ヒト又は動物細胞株を用いて製造されるバイオテクノロジー応用医薬品のウイルス安全性評価 ・生物由来原料基準 第4 動物由来原料総則</p> <p>DHFR 欠損 CHO DG44 変異株は、GIBCO/Invitrogen 社により無血清化学合成培地への馴化、核型解析、特性解析及びウイルス試験が実施されたものである。また、マスターセルバンク、ワーキングセルバンク及び製造後細胞でウイルス安全性を確認している。</p>
<p>生物由来原料又は材料のウイルス等の不活化及び除去処理等の内容^{注4)}</p>	<p>なし。</p>
<p>製造工程の概要(フローチャート)^{注5)}^{注6)} (不活化及び除去処理には下線を付し、条件を具体的に記載)</p>	<p>別紙様式 1 の原薬ボルヒアルロニダーゼ アルファの製造工程の概要を参照する。</p>
<p>ウイルスクリアランス試験結果の概要^{注7)}</p>	<p>原薬ボルヒアルロニダーゼ アルファの製造工程についてウイルスクリアランス試験を実施している。概要については別紙様式 1 を参照する。</p>

別添 1 ダラツムマブ FB の製造工程の概要（フローチャート）



_____ : ウイルスの不活化及び除去工程

別添 2 ダラツムマブ FB のウイルスクリアランス試験結果の概要

ダラツムマブ FB の製造工程におけるウイルスクリアランス能は、ICH Q5A に従いウイルスクリアランス試験を実施し、評価した。特異的モデルウイルスとしては、CHO 細胞株に存在する内在性レトロウイルスと同じ科に属する異種指向性マウス白血病ウイルス (XMuLV) を、非特異的モデルウイルスとしては、特性の異なる様々なウイルスとしてマウスマイニュートウイルス (MMV)、仮性狂犬病ウイルス (PRV) 及びレオウイルス 3 型 (REO) を選択した。

ダラツムマブ FB の製造工程のうちプロテイン A アフィニティークロマトグラフィー (Stage 4) 工程、ウイルス不活化及び中和 (Stage 5) 工程、陽イオン交換クロマトグラフィー (Stage 6) 工程、陰イオン交換クロマトグラフィー (Stage 7) 工程及びウイルス除去ろ過 (Stage 8) 工程において、それぞれスケールダウンした装置にウイルスストックを添加し、ウイルスクリアランス能を評価した。

各工程におけるウイルスクリアランス指数を表 1 に示す。なお、ワーストケースでのウイルスクリアランス能を評価するため、測定結果のうち最も低い値で評価した。

表 1 ウイルスクリアランス指数

工程	ウイルスクリアランス指数 ¹⁾ (log ₁₀)			
	XMuLV	MMV	PRV	REO
プロテイン A アフィニティークロマトグラフィー (Stage 4)	1.5 (0.1)	1.5 (0.4)	2.4 (0.2)	2.0 (0.4)
ウイルス不活化及び中和 (Stage 5)	5.3 (0.3)	試験せず ²⁾	>6.9 (0.5)	試験せず ²⁾
陽イオン交換クロマトグラフィー (Stage 6)	3.9 (0.3)	1.7 (0.4)	>6.3 (0.6)	4.6 (0.6)
陰イオン交換クロマトグラフィー (Stage 7)	7.1 (0.7)	3.9 (0.4)	>6.3 (0.5)	6.8 (0.3)
ウイルス除去ろ過 (Stage 8)	>6.1 (0.6)	>6.4 (0.6)	>6.4 (0.6) ³⁾	>6.4 (0.6) ³⁾
総クリアランス指数	>23.9 (1.0)	>13.5 (0.9)	>21.9 (0.5)	>13.4 (0.3)

¹⁾: 片側 95%信頼区間を () に示す。

²⁾: 外被の無いウイルスはウイルス不活化及び中和による不活化が期待されないため、MMV 及び REO に対して試験を実施しなかった。

³⁾: ウイルス除去ろ過工程について、PRV 及び REO を用いた試験は実施していないが、サイズがより小さい MMV の値 (>6.4) をワーストケースとして換算に用いた際の PRV 及び REO の総クリアランス指数はそれぞれ>28.3 (1.1)及び>19.8 (0.9)となる。

以上より、ダラツムマブ FB の製造工程は十分なウイルスクリアランス能を有することが確認された。

添付資料番号	タイトル	掲載誌	評価資料 参考資料
4.2 試験報告書			
4.2.1 薬理試験			
4.2.1.1 効力を裏付ける試験			
	該当資料なし		
4.2.1.2 副次的薬理試験			
	該当資料なし		
4.2.1.3 安全性薬理試験			
	該当資料なし		
4.2.1.4 薬力学的薬物相互作用試験			
	該当資料なし		
4.2.2 薬物動態試験			
4.2.2.1 分析法及びバリデーション報告書			
	該当資料なし		
4.2.2.2 吸収			
	該当資料なし		
4.2.2.3 分布			
	該当資料なし		
4.2.2.4 代謝			
	該当資料なし		
4.2.2.5 排泄			
	該当資料なし		
4.2.2.6 薬物動態学的薬物相互作用（非臨床）			
	該当資料なし		
4.2.2.7 その他の薬物動態試験			
	該当資料なし		
4.2.3 毒性試験			
4.2.3.1 単回投与毒性試験			
	該当資料なし		
4.2.3.2 反復投与毒性試験			
	該当資料なし		
4.2.3.3 遺伝毒性試験			
4.2.3.3.1 In Vitro 試験			
	該当資料なし		
4.2.3.3.2 In Vivo 試験			
	該当資料なし		
4.2.3.4 がん原性試験			
4.2.3.4.1 長期がん原性試験			
	該当資料なし		
4.2.3.4.2 短期又は中期がん原性試験			
	該当資料なし		
4.2.3.4.3 その他の試験			
	該当資料なし		
4.2.3.5 生殖発生毒性試験			
4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験			
	該当資料なし		
4.2.3.5.2 胚・胎児発生に関する試験			
	該当資料なし		
4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験			
	該当資料なし		
4.2.3.5.4 新生児を用いた試験			
	該当資料なし		
4.2.3.6 局所刺激性試験			
	該当資料なし		
4.2.3.7 その他の毒性試験			
4.2.3.7.1 抗原性試験			

添付資料番号	タイトル	掲載誌	評価資料 参考資料
	該当資料なし		
4.2.3.7.2 免疫毒性試験			
	該当資料なし		
4.2.3.7.3 毒性発現の機序に関する試験			
	該当資料なし		
4.2.3.7.4 依存性試験			
	該当資料なし		
4.2.3.7.5 代謝物の毒性試験			
	該当資料なし		
4.2.3.7.6 不純物の毒性試験			
	該当資料なし		
4.2.3.7.7 その他の試験			
	該当資料なし		
4.3 参考文献			
4.3.1-AMY	参考文献	参考文献一覧表及び参考文献を添付	参考資料

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.2 全臨床試験一覧表				
5.3 臨床試験報告書				
5.3.1 生物薬剤学試験報告書				
5.3.1.1 バイオアベイラビリティ (BA) 試験報告書				
	該当資料なし		—	—
5.3.1.2 比較BA試験及び生物学的同等性 (BE) 試験報告書				
	該当資料なし		—	—
5.3.1.3 In Vitro-In Vivo の関連を検討した試験報告書				
	該当資料なし		—	—
5.3.1.4 生物学的及び理化学的分析法検討報告書				
5.3.1.4.1-AMY	Full Validation of an Electrochemiluminescence-Based Immunoassay for the Quantification of JNJ-54767414 (Daratumumab) in Human Serum on the Meso Scale Discovery Platform	ヤンセンファーマ 社内資料： CP2015V-012	参考資料	無
5.3.1.4.2-AMY	Validation of a Method to Detect Antibodies to JNJ-54767414 (Daratumumab) in Human Serum Samples	ヤンセンファーマ 社内資料： CP2014V-052	参考資料	無
5.3.1.4.3-AMY	Validation of a Method to Detect Antibodies to JNJ-54767414 (Daratumumab) in Serum Samples from Humans - Enhanced Drug Tolerance Method	ヤンセンファーマ 社内資料： CP2019V-041	参考資料	無
5.3.1.4.4-AMY	Validation of a Cell-based Binding Assay to Detect Neutralizing Antibodies to JNJ-54767414 (Daratumumab) in Human Serum	ヤンセンファーマ 社内資料： CP2014V-049	参考資料	無
5.3.1.4.5-AMY	An Electrochemiluminescent Immunoassay for the Detection of Anti-rHuPH20 Antibodies in Human EDTA Plasma	ヤンセンファーマ 社内資料： R09099	参考資料	無
5.3.1.4.6-AMY	Validation of a Method for the Detection of Neutralizing Antibodies to rHuPH20 in Human Plasma	ヤンセンファーマ 社内資料： 15122	参考資料	無
5.3.2 ヒト生体試料を用いた薬物動態関連の試験報告書				
5.3.2.1 血漿蛋白結合試験報告書				
	該当資料なし		—	—
5.3.2.2 肝代謝及び薬物相互作用試験報告書				
	該当資料なし		—	—
5.3.2.3 他のヒト生体試料を用いた試験報告書				
	該当資料なし		—	—
5.3.3 臨床薬物動態 (PK) 試験報告書				
5.3.3.1 健康被験者におけるPK及び初期忍容性試験報告書				
	該当資料なし		—	—
5.3.3.2 患者におけるPK及び初期忍容性試験報告書				
	該当資料なし		—	—
5.3.3.3 内因性要因を検討したPK試験報告書				
	該当資料なし		—	—
5.3.3.4 外因性要因を検討したPK試験報告書				
	該当資料なし		—	—

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.3.3.5 ポピュレーションPK試験報告書				
5.3.3.5.1-AMY	Population Pharmacokinetics and Exposure-response Analysis Report for Daratumumab Subcutaneous Administration for the Treatment of Subjects with AL Amyloidosis	ヤンセンファーマ 社内資料:	参考資料	有
5.3.4 臨床薬力学 (PD) 試験報告書				
5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書				
	該当資料なし		—	—
5.3.4.2 患者におけるPD試験及びPK/PD試験報告書				
	該当資料なし		—	—
5.3.5 有効性及び安全性試験報告書				
5.3.5.1 申請する適応症に関する比較対照試験報告書				
5.3.5.1.1-AMY	A Randomized Phase 3 Study to Evaluate the Efficacy and Safety of Daratumumab in Combination with Cyclophosphamide, Bortezomib and Dexamethasone (CyBorD) Compared with CyBorD in Newly Diagnosed Systemic AL Amyloidosis	ヤンセンファーマ 社内資料 試験番号: 54767414AMY3001	評価資料	有
5.3.5.2 非対照試験報告書				
5.3.5.2.1-1-AMY	An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab with the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma (Primary Analysis)	ヤンセンファーマ 社内資料 試験番号: 54767414MMY1004 (Primary Analysis)	参考資料	無
5.3.5.2.1-2-AMY	An Open-label, Multicenter, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Daratumumab with the Addition of Recombinant Human Hyaluronidase (rHuPH20) for the Treatment of Subjects with Relapsed or Refractory Multiple Myeloma (12-month update)	ヤンセンファーマ 社内資料 試験番号: 54767414MMY1004 (12-month update)	参考資料	無
5.3.5.2.2-1-AMY	A Phase 1 Study of Subcutaneous Delivery of JNJ-54767414 (Daratumumab) in Japanese Subjects With Relapsed or Refractory Multiple Myeloma (Interim Analysis)	ヤンセンファーマ 社内資料 試験番号: 54767414MMY1008 (Interim Analysis)	参考資料	無
5.3.5.3 複数の試験成績を併せて解析した報告書				
	該当資料なし		—	—
5.3.5.4 その他の試験報告書				
	該当資料なし		—	—
5.3.6 市販後の使用経験に関する報告書				
5.3.6.1-AMY	Cumulative Review of Daratumumab Post-marketing Spontaneous Reports Through 31 March 2020 DARZALEX™ (Daratumumab)	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.2-AMY	Daratumumab SAE Listing	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.3-AMY	rHuPH20 PSUR	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.4-AMY	rHuPH20 SAE Listing	ヤンセンファーマ 社内資料	参考資料	無

添付資料番号	タイトル	掲載誌	評価資料 参考資料	申請電子 データ 有無
5.3.6.5-AMY	Bortezomib Periodic Benefit Risk Evaluation Report_26apl2018-25apl2020	ヤンセンファーマ 社内資料	参考資料	無
5.3.6.6-AMY	Bortezomib 市販後に報告された重篤な有害事象一覧	ヤンセンファーマ 社内資料	参考資料	無
5.3.7 患者データ一覧表及び症例記録				
5.3.7.1 用量設定の根拠となった主要な試験及び主要な有効性の検証試験の症例一覧表				
	該当資料なし		—	—
5.3.7.2 実施された全ての臨床試験において副作用が観察された症例の一覧表				
5.3.7.2.1-AMY	副作用一覧表（試験番号：54767414AMY3001）	ヤンセンファーマ 社内資料 試験番号： 54767414AMY3001	評価資料	無
5.3.7.3 実施された全ての臨床試験において重篤な有害事象が観察された症例の一覧表				
5.3.7.3.1-AMY	重篤な有害事象一覧表（試験番号：54767414AMY3001）	ヤンセンファーマ 社内資料 試験番号： 54767414AMY3001	評価資料	無
5.3.7.4 実施された全ての臨床試験において臨床検査値異常変動が観察された症例の一覧表				
5.3.7.4.1-AMY	臨床検査値異常変動一覧表 （試験番号：54767414AMY3001）	ヤンセンファーマ 社内資料 試験番号： 54767414AMY3001	評価資料	無
5.3.7.5 実施された全ての臨床試験において観察された臨床検査値の変動を適切に示した図				
	該当資料なし		—	—
5.4 参考文献				
5.4.1-AMY	参考文献	参考文献一覧表及び 参考文献を添付	参考資料	無