swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Tecvayli

International non-proprietary name:	teclistamab
Pharmaceutical form:	solution for injection
Dosage strength(s):	30 mg/3 mL, 153 mg/1.7 mL
Route(s) of administration:	subcutaneous injection
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	68747
Decision and decision date:	extension of therapeutic indication approved on 25 June 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

AE	Adverse event
BCMA	B cell maturation antigen
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
DCO	Data cut-off
DPd	Daratumumab+pomalidomide+dexamethasone
DVd	Daratumumab+bortezomib+dexamethasone
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
IRC	Independent review committee
ITT	Intention-to-treat
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MM	Multiple myeloma
MRD	Minimal residual disease
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
RMP	Risk management plan
RRMM	Relapsed or refractory multiple myeloma
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
Tec-Dara	Teclistamab+daratumumab
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 TPA.
Orphan drug status was granted on 22 March 2022.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

TECVAYLI in combination with daratumumab is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy.

2.2.2 Approved indication

TECVAYLI in combination with daratumumab is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent (see *Clinical Efficacy*).

2.2.3 Requested dosage

Summary of the requested standard dosage:
TECVAYLI Dosing Schedule for combination therapy with daratumumab

Dosing schedule	*Week/day*	*Dose*	
Step-up dosing schedule	Day 1	Only daratumumab is given	
	Day 2	Step-up dose 1	0.06 mg/kg
	Day 4	Step-up dose 2	0.3 mg/kg
	Day 8	First treatment dose	1.5 mg/kg
Weekly dosing schedule	Weeks 3 to 8	Subsequent treatment doses	1.5 mg/kg
Biweekly dosing schedule (Q2W)	Weeks 9 to 24	Subsequent treatment doses	3 mg/kg
Every 4th week schedule (Q4W)	Weeks ≥ 25	Subsequent treatment doses	3 mg/kg

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	22 December 2025
Formal control completed	5 January 2026
Preliminary decision	28 April 2026
Response to preliminary decision	28 May 2026
Final decision	25 June 2026
Decision	approval

3 Medical context

Multiple myeloma (MM) is a haematological malignancy characterised by the clonal proliferation of plasma cells in the bone marrow. In patients with relapsed or refractory multiple myeloma (RRMM), the treatment algorithm from the European Hematology Association and the European Myeloma Network (EHA-EMN) guidelines published in July 2025[1] recommends selecting subsequent therapy based on the drug combination received in the previous line and the agents to which the patient remains sensitive. Currently authorised treatment options in Switzerland for the second-line treatment of MM consist of various multi-drug combinations of anti-CD38 antibody, proteasome inhibitor, immunomodulatory agent, or anti-BCMA antibody-drug. Despite the numerous available treatments, disease recurrence remains frequent, emphasising the need for new therapeutic options.

Teclistamab is currently authorised for the treatment of patients with RRMM who have received at least three prior lines of therapy. The current application seeks an extension of the indication to include teclistamab in combination with daratumumab for the treatment of RRMM after one prior line of therapy.

1. Dimopoulos MA, Terpos E, Boccadoro M, et al. EHA-EMN Evidence-Based Guidelines for diagnosis, treatment and follow-up of patients with multiple myeloma. Nature Reviews Clinical Oncology 2025; 22(9): 680-700.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable as this extension is based on ongoing and supportive clinical studies. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

The clinical pharmacology of teclistamab has been well characterised as monotherapy for participants with relapsed/refractory multiple myeloma, as summarised in the initial application. The PK and immunogenicity data supporting this submission come from pivotal study 64007957MMY3001 (MajesTEC-3) and supportive study 64407564MMY1002 (TriMM-2). For the characterisation of PK properties, data from both studies were used. For the exposure-response analysis, only MajesTEC-3 data were used.

Pharmacokinetics
In the MajesTEC-3 study, pre-dose serum concentrations of teclistamab increased during cycles 1-2 with the 1.5 mg/kg weekly dose. After switching to 3 mg/kg Q2W, mean pre-dose concentrations of teclistamab at Cycle 3 Day 1 and Cycle 6 Day 1 were similar. When the regimen changed to 3 mg/kg Q4W after Cycle 7, teclistamab concentrations decreased and remained stable through Cycle 12 Day 1. These data are consistent with the predicted PK profile of teclistamab under the administered dosing regimen. Observed daratumumab serum concentrations in participants from the teclistamab-daratumumab (Tec-Dara) group were generally within the same range as those observed in the control (daratumumab+pomalidomide (DPd)/daratumumab+bortezomib (DVd)) group.

In TriMM-2, the observed serum teclistamab pre-dose concentrations were generally similar after 1.5 mg/kg weekly and after 3.0 mg/kg Q2W, and serum daratumumab concentrations were generally within the same ranges among the cohorts.

PK characteristics of teclistamab in Tec-Dara combination are similar to those of monotherapy, suggesting that no clinically relevant PK interaction occurs between teclistamab and daratumumab. This is supported by comparable observed PK data across Tec-Dara and teclistamab monotherapy studies.

Furthermore, teclistamab PK in MajesTEC-3 and TriMM-2 was successfully characterised using a population PK model previously developed from MajesTEC-1 monotherapy study.

None of the investigated covariates, including age, sex, race, ethnicity, country, region, body weight, albumin, hepatic and renal function, and baseline disease status such as ECOG, number of prior therapy lines, ISS stage, cytogenetic risk, sBCMA, percentage of bone marrow plasma cells, and presence of plasmacytomas, had clinically meaningful effects on teclistamab PK exposure. The type of myeloma was associated with variations in PK exposure, although these differences were deemed not clinically relevant, as supported by the exposure efficacy analysis. Therefore, no teclistamab dose adjustment is warranted based on these covariates for the Tec-Dara combination.

Exposure-Response
Within the exposure range achieved at the proposed dosing regimen, no statistically significant exposure-PFS relationship was observed for teclistamab in the Tec-Dara group for several clinically relevant exposure metrics ($C_{ave,1stdose}$, $C_{trough,4doses}$, $C_{trough,Q2W}$, and $C_{trough,Q4W}$). The exposure-safety relationship showed no apparent increase in the TEAE (Grade ≥3) rate with increasing teclistamab exposure ($C_{max,1stdose}$) for anaemia, neutropenia, thrombocytopenia, and infections, indicating an acceptable safety profile across the teclistamab exposure range.

Immunogenicity
MajesTEC-3: The incidence rate of treatment-emergent antibodies to teclistamab was <1% (2 out of 270 participants) with only 1 out of 270 participants positive for neutralising antibodies. The incidence rate of treatment-emergent antibodies to daratumumab was <1% (1 out of 268 participants in the Tec-Dara group and 1 out of 280 participants in the DPd/DVd group). TriMM-2: None out of 109

participants were identified as positive for antibodies to teclistamab. One out of 108 participants was identified as positive for antibodies to daratumumab.

5.2 Dose finding and dose recommendation

The requested dose of teclistamab combined with daratumumab was evaluated in the randomised controlled pivotal study MajesTEC-3.

5.3 Efficacy

Pivotal evidence to support the requested indication comes from a Phase 3 study, MajesTEC-3.

MajesTEC-3 is an open-label international randomised controlled trial that evaluates the combination treatment of teclistamab and subcutaneous daratumumab (Tec-Dara) versus investigator's choice (i.e. control) between two triplet combination treatments consisting of daratumumab, dexamethasone, and either bortezomib or pomalidomide (DVd or DPd), respectively. Randomisation was stratified by investigator's choice of DPd or DVd, stage of disease at screening per ISS (I versus II versus III), prior anti-CD38 monoclonal antibody exposure, and number of prior lines of therapy (1 versus 2 or 3). The study enrolled patients with RRMM who had progressive disease on or after the last regimen, and 1 to 3 prior lines of antimyeloma therapy including a proteasome inhibitor and lenalidomide. If a study subject previously received only one prior line of antimyeloma therapy, the respective study subject must have been refractory to lenalidomide. Key exclusion criteria were any prior BCMA-directed therapy and refractoriness to an anti-CD38 monoclonal antibody (subjects with prior response to an anti-CD38 monoclonal antibody were permitted).

The treatment options selected for the control arm were considered adequate for patients with RRMM at the time of trial initiation.[2] However, the RRMM treatment landscape is complex and comprises numerous multi-drug combination regimens. Given that the inclusion of all available treatment options would likely have resulted in a highly heterogeneous study population, the restricted selection of DPd and DVd as comparator regimens is acceptable.

The primary endpoint of MajesTEC-3 is progression-free survival (PFS), as assessed by an Independent Review Committee (IRC). Secondary endpoints controlled for Type I error were a response of Complete Response (CR) or better, Overall response (Partial response or better), Minimal Residual Disease (MRD) negativity, Overall Survival (OS), and Time to Worsening of Symptoms in the MySIm-Q total symptom score. These endpoints were hierarchically tested in the order listed above. Overall, the selection of study endpoints is acceptable.

The applicant summited the results from the pre-specified interim PFS analysis with a DCO (data cut-off) date of 01 August 2025. In total, 283 of the 291 randomised participants in the Tec-Dara arm, and 290 of the 296 randomised to the DPd/DVd (control) group were treated. Among treated participants in the control group, the investigator's choice of study treatment was DPd for 90.7% of participants and DVd for 9.3% of participants.

In the overall study population, the median age was 64 years (range: 25-88), with 38.2% of participants aged 65 to <75 years and 9.5% aged ≥75 years. The proportion of participants by ISS was 62.5% for Stage I, 29.5% for Stage II, and 8.0% for Stage III. Of the participants with baseline cytogenetic data available, 35.9% had at least 1 high-risk abnormality. Overall, 14.0% of participants

2. M.A. Dimopoulos, P. Moreau, E. Terpos, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):309-322.

had presence of soft tissue plasmacytoma. Study participants had received a median of 2 prior lines of therapy, with 37.8% having received 1 prior line of therapy.

At the presented DCO, the median duration of follow-up in the overall study population was 34.5 months. MajesTEC-3 met its primary endpoint, with Tec-Dara demonstrating a statistically significant improvement in PFS, as assessed by IRC, compared with DPd/DVd as control. The hazard ratio (HR) for PFS for Tec-Dara versus control was 0.17 (95% CI: 0.12, 0.23; p<0.0001). Median PFS was not reached in the Tec-Dara group and was 18.1 months in the control group. The 36-month PFS rate was 83.4% (95% CI: 78.2%, 87.4%) in the Tec-Dara group and 29.7% (95% CI: 23.6%, 36.0%) in the control group.

The rate of CR or better demonstrated a statistically significant difference in favour of Tec-Dara over the control arm (81.8% versus 32.1%; odds ratio=9.56 [95% CI: 6.47, 14.14]; p<0.0001). Tec-Dara was associated with a statistically significantly higher overall response rate than control (89.0% versus 75.3%; odds ratio=2.65 [95% CI: 1.68, 4.18]; p<0.0001). The MRD negativity rate at a sensitivity threshold of 10^{-5} in the Tec-Dara group (58.4%) was higher than in the control group (17.1%) (odds ratio=6.78 [95% CI: 4.53, 10.15]; p<0.0001).

The study also demonstrated a statistically significant and clinically meaningful OS advantage of Tec-Dara compared with DPd/DVd. The HR for Tec-Dara versus control was 0.46 (95% CI: 0.32, 0.65) and a p value <0.0001. The estimated OS rates were higher in the Tec-Dara group than the control group at 36 months (83.3% [95% CI: 78.3%, 87.2%] versus 65.0% [95% CI: 58.8%, 70.5%]).

5.4 Safety

The safety profile of Tec-Dara is consistent with the known safety profiles of teclistamab monotherapy and subcutaneous formulation of daratumumab. Noteworthy known toxicities associated with teclistamab encompass cytokine release syndrome, neurological toxicity, including immune effector cell-associated neurotoxicity syndrome (ICANS), infections, neutropenia, and hepatoxicity. Of note, the revised Information for healthcare professionals includes updated guidance on immunoglobulin monitoring, when to administer immunoglobulin replacement therapy, infection prophylaxis, and management of infections.

5.5 Final clinical benefit risk assessment

The MajesTEC-3 study showed a statistically significant benefit of Tec-Dara over DPd/DVd in RRMM patients, including improvements in PFS, CR or better rates, ORR, MRD negativity, and time to symptom deterioration. Importantly, the reported OS benefit from the study was statistically significant and clinically meaningful.

The observed safety profile of Tec-Dara is consistent with the known safety profiles of both combination treatment components. The updates in the Information healthcare professionals regarding immunoglobulin replacement therapy and infection management are regarded as adequate risk mitigation measure measures. The safety profile is manageable under the care of experienced oncologists.

The benefit-risk assessment is positive.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Tecvayli was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

TECVAYLI®

Composition

Active substances

Teclistamab

Excipients

EDTA disodium salt dihydrate, Glacial acetic acid, Polysorbate 20, Sodium acetate trihydrate, Sucrose (240 mg in 3 mL vial; 140 mg in 1.7 mL vial), Water for injection

Total sodium content: 0.75 mg of sodium in 3 mL vial; 0.43 mg of sodium in 1.7 mL vial

Pharmaceutical form and active substance quantity per unit

TECVAYLI is a colorless to light yellow solution for injection.
TECVAYLI is available in the following presentations:

- Each 3 mL vial contains 30 mg of teclistamab (10 mg of teclistamab per mL)
- Each 1.7 mL vial contains 153 mg of teclistamab (90 mg of teclistamab per mL)

Indications/Uses

TECVAYLI is indicated:

- in combination with daratumumab for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least one prior line of therapy, including a proteasome inhibitor and an immunomodulatory agent (see *Clinical Efficacy*).
- as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody, and have demonstrated disease progression to the last line of therapy (see *Clinical Efficacy*).

Dosage/Administration

General

TECVAYLI should only be administered under the guidance of medical personnel experienced in the treatment of malignant haematological diseases, cytokine release syndrome (CRS) and neurologic toxicities including immune effector cell-associated neurotoxicity syndrome (ICANS).

TECVAYLI should be administered by subcutaneous injection only.

Monitoring

Administer TECVAYLI according to the step-up dosing schedule in Table 1 and 2 to reduce the incidence and severity of cytokine release syndrome (CRS). Due to the risk of CRS and ICANS, it is recommended to hospitalize patients for 48 hours after administration of both Step-up dose 1 and Step-up dose 2. Instruct patients to remain within proximity of a healthcare facility and monitor patients daily for 48 hours after the first treatment dose of the TECVAYLI step-up dosing schedule (see *Dosage/Administration – Management of severe adverse reactions* and *Warnings and Precautions*).

Failure to follow the recommended doses or dosing schedule for initiation of therapy or re-initiation of therapy after dose delays may result in increased frequency and severity of adverse events related to the mechanism of action of TECVAYLI, particularly cytokine release syndrome (see *Dosage and Administration – Dosage modifications and Warnings and Precautions – Cytokine Release Syndrome*).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.
Administer pretreatment medications prior to each dose of the TECVAYLI step-up dosing schedule (see *Dosage and Administration – Pretreatment medications*).

Recommended dosing schedule for combination therapy with daratumumab

TECVAYLI dosing schedule in Table 1 is for combination therapy with daratumumab. If TECVAYLI is used in combination with daratumumab, only the subcutaneous formulation should be administered. TECVAYLI should be administered until disease progression or unacceptable toxicity (see *Clinical Efficacy)*.

Table 1: TECVAYLI Dosing Schedule for Combination Therapy with Daratumumab

Dosing schedule	Week/Day	TECVAYLI Dosage[a]	Concomitant Therapy
	Day 0	N/A	Daratumumab
Step-up dosing schedule[b]	Day 1	Step-up dose 1 (0.06 mg/kg)[c]	N/A
	Day 3	Step-up dose 2 (0.3 mg/kg)[d]	N/A
	Day 7	First Treatment dose (1.5 mg/kg)[e,f]	Daratumumab
Weekly dosing schedule	Weeks 2 to 8	1.5 mg/kg once weekly[f,g]	Daratumumab once weekly
Biweekly (every two weeks) dosing schedule	Weeks 9 to 24	3 mg/kg every two weeks[f,h]	Daratumumab every two weeks
Every four weeks dosing schedule	Week 25 onwards	3 mg/kg every four weeks[f,i]	Daratumumab every four weeks

[a] See Table 3 for recommendations on restarting TECVAYLI after dose delays.
[b] The Step-up dosing schedule is a component of the recommended TECVAYLI dosage but is not applicable for the daratumumab dosing.
[c] Step-up dose 1 must be administered 20 hours or more after daratumumab dose.
[d] **Step-up dose 2 may be given between 2 to 4 days after step-up dose 1** and if adverse reactions occur, step-up dose 2 may be given up to 7 days after step-up dose 1 to allow for resolution of adverse reactions.
[e] **First treatment dose (1.5 mg/kg) may be given between 2 to 4 days after step-up dose 2** and if adverse reactions occur, first full treatment dose may be given up to 7 days after step-up dose 2 to allow for resolution of adverse reactions.
[f] Administer TECVAYLI at least 3 hours after the daratumumab dose for the first treatment dose. For subsequent doses, administer TECVAYLI at least 15 minutes after the daratumumab dose.
[g] Maintain a minimum of 5 days between 1.5 mg/kg once weekly doses.
[h] Maintain a minimum of 12 days between 3 mg/kg every two weeks doses.
[i] Maintain a minimum of 25 days between 3 mg/kg every four weeks doses.

For dosing and administration instructions of daratumumab, see *Clinical Efficacy* and refer to the daratumumab subcutaneous monotherapy prescribing information.

Recommended dosing schedule for monotherapy

The recommended dosing schedule for TECVAYLI is provided in Table 2. The recommended dosage of TECVAYLI is step-up doses of 0.06 mg/kg and 0.3 mg/kg followed by 1.5 mg/kg once weekly until disease progression or unacceptable toxicity. In patients who have at least a complete response (CR or better) for a minimum of 6 months, a reduced dosing frequency of 1.5 mg/kg every two weeks until disease progression or unacceptable toxicity may be considered (see *Clinical Efficacy*).

Table 2: TECVAYLI Dosing Schedule for Monotherapy

Dosing schedule	Day	Dose	
All patients			
Step-up dosing schedule[a]	Day 1	Step-up dose 1	0.06 mg/kg
	Day 4[b]	Step-up dose 2	0.3 mg/kg
	Day 7[c]	First treatment dose	1.5 mg/kg
Weekly dosing schedule[a]	One week after first treatment dose and weekly thereafter	Subsequent treatment doses	1.5 mg/kg once weekly
Patients who have at least a complete response (CR or better) for a minimum of 6 months			
Biweekly (every two weeks) dosing schedule[a]	Consider reducing the dosing frequency to 1.5 mg/kg every two weeks		

[a] See Table 3 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays)*.
[b] **Step-up dose 2 may be given between 2 to 4 days after step-up dose 1** and may be given up to 7 days after step-up dose 1 to allow for resolution of adverse reactions.
[c] **First treatment dose may be given between 2 to 4 days after step-up dose 2** and may be given up to 7 days after step-up dose 2 to allow for resolution of adverse reactions.

Refer to Tables 12, 13, 14 and 15 to determine the dosage based on predetermined weight ranges (see *Other information – Mode of Administration*).

Pretreatment medications

Administer the following pretreatment medications 1 to 3 hours before each dose of the TECVAYLI step-up dosing schedule to reduce the risk of cytokine release syndrome (see *Warnings and Precautions – Cytokine Release Syndrome* and *Undesirable effects*).

- Corticosteroid (oral or intravenous dexamethasone, 16 mg)
- H1-Antihistamine (oral or intravenous diphenhydramine, 50 mg or equivalent)

- Antipyretics (oral or intravenous acetaminophen, 650 mg to 1'000 mg or equivalent)

Administration of pretreatment medications may be required prior to administration of subsequent doses of TECVAYLI in the following patients:

- Patients who repeat doses within the TECVAYLI step-up dosing schedule following a dose delay (see *Dosage and Administration – Restarting TECVAYLI after dose delays*)
- Patients who experienced CRS following the prior dose of TECVAYLI (see *Dosage and Administration – Management of severe adverse reactions*)

Prophylaxis for herpes zoster virus reactivation

Prior to starting treatment with TECVAYLI, anti-viral prophylaxis should be considered for the prevention of herpes zoster virus reactivation per local institutional guidelines.

Restarting TECVAYLI after dose delays

If a dose of TECVAYLI is delayed, restart therapy based on the recommendations listed in Table 3 and resume the treatment schedule accordingly (see *Dosage and Administration – Recommended dosing schedule for monotherapy* and *for combination therapy with daratumumab*). Administer pretreatment medications as indicated in Table 3 (see *Dosage and Administration – Pretreatment medications*).

Table 3: Recommendations for Restarting Therapy with TECVAYLI After Dose Delay

Last dose administered	Time since the last dose administered	Action
Step-up dose 1	More than 7 days	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Step-up dose 2	8 days to 28 days	Repeat step-up dose 2 (0.3 mg/kg)[a] and continue TECVAYLI step-up dosing schedule.
	More than 28 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Weekly treatment dose	28 days or less	Continue TECVAYLI 1.5 mg/kg once weekly.
	29 days to 56 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 2 (0.3 mg/kg).[a]
	More than 56 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]
Any biweekly (every two weeks) or every four weeks treatment dose	63 days or less[b]	Continue TECVAYLI at last dose given every two weeks or every four weeks schedule.
	64 days to 112 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 2 (0.3 mg/kg).[a]
	More than 112 days[b]	Restart TECVAYLI step-up dosing schedule at step-up dose 1 (0.06 mg/kg).[a]

[a] Administer pretreatment medications prior to TECVAYLI dose and monitor patients accordingly (see *Dosage and Administration – Pretreatment medications* and *Dosage and Administration – Monitoring*).
[b] Consider benefit-risk of restarting TECVAYLI in patients who require a dose delay of more than 28 days due to an adverse reaction.

Dosage modifications

Do not skip step-up doses of TECVAYLI.

Monotherapy: Dose reductions of TECVAYLI are not recommended.

Combination therapy: Dose modifications of TECVAYLI during the step-up dosing and the first 1.5 mg/kg treatment dose are not recommended.

Refer to the daratumumab subcutaneous prescribing information for information about dosage modifications for daratumumab.

Dose delays may be required to manage toxicities related to TECVAYLI (see *Warnings and Precautions*).

See Tables 4, 5 and 6 for recommended actions for adverse reactions of CRS, neurologic toxicity, and ICANS (see *Management of severe adverse reactions*. See Table 7 for recommended actions for other adverse reactions following administration of TECVAYLI (see *Other adverse reactions*).

Management of severe adverse reactions

Cytokine release syndrome (CRS)

Identify CRS based on clinical presentation (see *Warnings and Precautions – Cytokine Release Syndrome*). Evaluate and treat other causes of fever, hypoxia, and hypotension.
If CRS is suspected, withhold TECVAYLI until the adverse reaction resolves (see Table 4) and manage according to the recommendations in Table 4. Administer supportive care for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) as appropriate. Consider laboratory testing to monitor for disseminated intravascular coagulation (DIC), hematology parameters, as well as pulmonary, cardiac, renal, and hepatic function.

Table 4: Recommendations for Management of Cytokine Release Syndrome

Grade[a]	Presenting Symptoms	Actions
Grade 1	Temperature ≥ 38°C[b]	• Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines.
Grade 2	Temperature ≥ 38°C[b] with: Hypotension responsive to fluids and not requiring vasopressors. and/or Oxygen requirement of low-flow nasal cannula[d] or blow-by.	• Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Monitor patients for 48 hours following the next dose of TECVAYLI. Instruct patients to remain within proximity of a healthcare facility during daily monitoring and consider hospitalization.[c] (*see Dosage and Administration – Monitoring*).

Grade 3	Temperature ≥ 38°C[b] with: Hypotension requiring one vasopressor with or without vasopressin. and/or Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask.	First Occurrence of Grade 3 CRS with duration less than 48 hours: • Withhold TECVAYLI until CRS resolves. • Manage CRS per consensus guidelines. • Provide supportive therapy, which may include intensive care. • Administer pretreatment medications prior to next dose of TECVAYLI.[c] • Patients should be monitored in an inpatient setting for at least 48 hours following the next dose of TECVAYLI.[c] (see *Dosage and Administration – Monitoring*).
		Recurrent Grade 3 CRS or Grade 3 CRS with duration 48 hours or longer: • Permanently discontinue TECVAYLI. • Manage CRS per consensus guidelines. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥ 38°C[b] with: Hypotension requiring multiple vasopressors (excluding vasopressin). and/or Oxygen requirement of positive pressure (e.g., continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), intubation, and mechanical ventilation).	• Permanently discontinue TECVAYLI. • Manage CRS per consensus guidelines • Provide supportive therapy, which may include intensive care.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.
[b] Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anticytokine therapy.
[c] See Table 3 for recommendations on restarting TECVAYLI after dose delays (see *Dosage and Administration – Restarting TECVAYLI after dose delays).*
[d] Low-flow nasal cannula is ≤6 L/min, and high-flow nasal cannula is >6 L/min.

Neurologic toxicities and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Management recommendations for neurologic toxicity and ICANS are summarized in Table 5 and 6.

At the first sign of neurologic toxicity, including ICANS, withhold TECVAYLI and consider neurology evaluation. Rule out other causes of neurologic symptoms. Provide intensive care and supportive therapy for severe or life-threatening neurologic toxicities (see *Warnings and Precautions – Neurologic toxicities including ICANS*). Manage according to the recommendations in Table 5 and 6. With regard to progressive multifocal leukoencephalopathy (PML), the information in the section *Warnings and Precautions – Infections* must be considered.

Table 5: Recommendations for Management of Neurologic Toxicity (excluding ICANS)

Adverse Reaction	Severity[a]	Actions
Neurologic Toxicity[a] (excluding ICANS)	Grade 1	• Withhold TECVAYLI until neurologic toxicity symptoms resolve or stabilize.[b]
	Grade 2 Grade 3 (First occurrence)	• Withhold TECVAYLI until neurologic toxicity symptoms improve to Grade 1 or less.[b] • Provide supportive therapy.
	Grade 3 (Recurrent) Grade 4	• Permanently discontinue TECVAYLI. • Provide supportive therapy, which may include intensive care.

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
[b] See Table 3 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays)*.

Table 6: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Grade[a]	Presenting Symptoms[b]	Actions
Grade 1	ICE score 7-9[c], or depressed level of consciousness[d]: awakens spontaneously.	• Withhold TECVAYLI until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy per consensus guidelines.
Grade 2	ICE score 3-6[c], or depressed level of consciousness[d]: awakens to voice.	• Withhold TECVAYLI until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy per consensus guidelines. • Monitor patients for 48 hours following the next dose of TECVAYLI. Instruct patients to remain within proximity of a healthcare facility during daily monitoring and consider hospitalization. (see *Dosage and Administration – Monitoring*)[e]
Grade 3	ICE score 0-2[c], or depressed level of consciousness[d]: awakens only to tactile stimulus, or seizures[d], either: • any clinical seizure, focal or generalized, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, or raised intracranial pressure: focal/local edema on neuroimaging[d].	First Occurrence of Grade 3 ICANS: • Withhold TECVAYLI until ICANS resolves. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines. • Patients should be monitored in an inpatient setting for at least 48 hours following the next dose of TECVAYLI.[e] Recurrent Grade 3 ICANS: • Permanently discontinue TECVAYLI

Table 6: Recommendations for Management of Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

Grade[a]	Presenting Symptoms[b]	Actions
		• Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.
Grade 4	ICE score 0[c], or depressed level of consciousness[d]: either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, or seizures[d], either: • life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, or motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, or raised intracranial pressure/cerebral edema[d], with signs/symptoms such as: • diffuse cerebral edema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilledema, or • Cushing's triad.	• Permanently discontinue TECVAYLI. • Administer dexamethasone[f] 10 mg intravenously and repeat dose every 6 hours. Continue dexamethasone use until resolution to Grade 1 or less, then taper. • Alternatively, consider administration of methylprednisolone 1'000 mg per day intravenously and continue methylprednisolone 1'000 mg per day intravenously for 2 or more days. • Monitor neurologic symptoms and consider consultation with neurologist and other specialists for further evaluation and management, including consideration for starting non-sedating, anti-seizure medicines for seizure prophylaxis. • Provide supportive therapy, which may include intensive care, per consensus guidelines.

[a] Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
[b] Management is determined by the most severe event, not attributable to any other cause.
[c] If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: **Orientation** (oriented to year, month, city, hospital = 4 points); **Naming** (name 3 objects, e.g., point to clock, pen, button = 3 points); **Following Commands** (e.g., "show me 2 fingers" or "close your eyes and stick out your tongue" = 1 point); **Writing** (ability to write a standard sentence = 1 point; and **Attention** (count backwards from 100 by ten = 1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS) = 0 points.
[d] Not attributable to any other cause.
[e] See Table 3 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays).*
[f] All references to dexamethasone administration are dexamethasone or equivalent.

Other Adverse Reactions

Table 7: Recommended Dosage Modifications for Other Adverse Reactions

Adverse Reactions	Severity	Actions
Infections[a] *(see Warnings and Precautions)*	All Grades	• Withhold TECVAYLI in patients with active infection during the step-up dosing schedule.[b]
	Grade 3	• Withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until no evidence of an active infection.[b]
	Grade 4	• Consider permanent discontinuation of TECVAYLI. • If TECVAYLI is not permanently discontinued, withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until no evidence of active infection.[b]
Hematologic Toxicities (see *Warnings and Precautions and Undesirable effects*)	Absolute neutrophil count less than 0.5 x 10^9/L	• Withhold TECVAYLI until absolute neutrophil count is 0.5 x 10^9/L or higher.[b]
	Febrile neutropenia	• Withhold TECVAYLI until absolute neutrophil count is 1 x 10^9/L or higher and fever resolves.[b]
	Hemoglobin less than 8 g/dL	• Withhold TECVAYLI until hemoglobin is 8 g/dL or higher.[b]
	Monotherapy: Platelet count less than 25'000/µl Platelet count between 25'000/µl and 50'000/µl with bleeding Combination therapy: Platelet count less than 50'000/µl	Monotherapy: • Withhold TECVAYLI until platelet count is 25'000/µl or higher and no evidence of bleeding.[b] Combination therapy: • Withhold TECVAYLI until platelet count is 50'000/µL or higher and no evidence of bleeding.
Other Non-Hematologic Adverse Reactions[a] *(Warnings and Precautions and Undesirable effects)*	Grade 3	• Withhold TECVAYLI until adverse reaction improves to Grade 1 or less.[b]
	Grade 4	• Consider permanent discontinuation of TECVAYLI. • If TECVAYLI is not permanently discontinued, withhold subsequent treatment doses of TECVAYLI (i.e., doses administered after TECVAYLI step-up dosing schedule) until adverse reaction improves to Grade 1 or less.[b]

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

[b] See Table 3 for recommendations on restarting TECVAYLI after dose delays *(see Dosage and Administration – Restarting TECVAYLI after dose delays)*.

Special dosage instructions

Patients with hepatic disorders

No formal studies of TECVAYLI in patients with hepatic impairment have been conducted.

Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate hepatic impairment (see *Pharmacokinetic Properties*).

Patients with renal disorders

No formal studies of TECVAYLI in patients with renal impairment have been conducted.
Based on population pharmacokinetic analyses, no dose adjustment is recommended for patients with mild or moderate renal impairment (see *Pharmacokinetic Properties*).

Elderly patients (65 years of age and older)

No dose adjustment is necessary (see *Pharmacokinetic Properties*).

Pediatric population

TECVAYLI is not authorised for use in the paediatric population.

Contraindications

None.

Warnings and precautions

Cytokine release syndrome (CRS)

TECVAYLI can cause cytokine release syndrome (CRS), including life-threatening or fatal reactions (see *Undesirable Effects*). The majority of CRS events observed following TECVAYLI administration were Grade 1 and Grade 2 (see *Undesirable Effects*). Clinical signs and symptoms of CRS may include, but are not limited to, fever, chills, hypotension, tachycardia, hypoxia, headache, and elevated liver enzymes. Potentially life-threatening complications of CRS may include cardiac dysfunction, acute respiratory distress syndrome, neurologic toxicity, renal and/or hepatic failure, and disseminated intravascular coagulation (DIC).

Initiate therapy according to TECVAYLI step-up dosing schedule to reduce risk of CRS (see Table 1 and 2). Failure to follow the recommended doses or dosing schedule for initiation of therapy or re-initiation of therapy after dose delays may result in increased frequency and severity of adverse events related to mechanism of action. Administer pretreatment medications (corticosteroids, antihistamine, and antipyretics) prior to each dose of the TECVAYLI step-up dosing schedule to reduce risk of CRS and monitor patients following administration accordingly (see *Dosage and Administration – Pretreatment medications* and *Monitoring*). Patients who experienced CRS following their previous dose should be managed according to the recommendations in Table 4.
Counsel patients to seek medical attention should signs or symptoms of CRS occur. At the first sign of CRS, immediately evaluate patient for hospitalization and institute treatment with supportive care based on severity. Withhold treatment with TECVAYLI until CRS resolves as indicated in Table 4 (see *Dosage and Administration – Management of severe adverse reactions*).

Neurologic toxicities including ICANS

Serious, life-threatening or fatal neurological toxicities, including Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS), occurred following treatment with TECVAYLI (see *Undesirable Effects*). The majority of neurologic toxicities were Grade 1 and Grade 2 (see *Undesirable Effects*). With longer follow-up, Grade 4 seizure and fatal Guillain-Barré syndrome occurred in patients who received TECVAYLI. For described cases of progressive multifocal leukoencephalopathy (PML), see *Infections*.

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS.

Monitor patients for signs or symptoms of neurologic toxicities during treatment and treat promptly. Counsel patients to seek medical attention should signs or symptoms of neurologic toxicities occur. At the first sign of neurologic toxicities, including ICANS, immediately evaluate patient and institute treatment based on severity as indicated in Table 6 (see *Dosage and Administration – Management of severe adverse reactions*).

For neurologic toxicities (excluding ICANS) or ICANS, withhold treatment with TECVAYLI as indicated in Table 5 and 6 respectively and manage adverse reactions based on recommendations in Table 5 and 6 respectively.

Infections

Severe, life-threatening or fatal infections, including opportunistic infections, have been reported in patients receiving TECVAYLI (see *Undesirable Effects*).

Progressive Multifocal Leukoencephalopathy (PML), which can be fatal, has also been reported in patients receiving TECVAYLI (see *Undesirable effects – Infections*). Monitor any new onset of or changes in pre-existing neurological signs or symptoms. If PML is suspected, withhold treatment with TECVAYLI and initiate appropriate diagnostic testing. Discontinue TECVAYLI if PML is confirmed.

New or reactivated viral infections occurred during therapy with TECVAYLI (see *Undesirable Effects*). In patients who received TECVAYLI at the recommended dose in the clinical trial, COVID-19 including severe and fatal cases occurred (see *Undesirable Effects*).

Hepatitis B virus reactivation can occur in patients treated with drugs directed against B cells, and in some cases, may result in fulminant hepatitis, hepatic failure, and death. Before initiation of treatment with TECVAYLI, screening for HBV infection, active HCV and active HIV infection should be performed according to clinical guidelines.

Patients with evidence of positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation while receiving TECVAYLI, and for at least six months following the end of treatment.

Monitor patients for signs and symptoms of infection prior to and during treatment with TECVAYLI and treat appropriately. Infection precautions and antimicrobials, including antibiotic or antiviral

prophylaxis, should be administered according to local institutional guidelines. Withhold treatment with TECVAYLI as indicated in Table 7 (see *Dosage and Administration – Dosage modifications*).

Hypogammaglobulinemia

Hypogammaglobulinemia has been reported in patients receiving TECVAYLI (see *Undesirable Effects*).
Monitor immunoglobulin levels during treatment with TECVAYLI and treat with subcutaneous or intravenous immunoglobin (IVIG) therapy to maintain the serum levels above 400 mg/dL.

Hepatotoxicity

TECVAYLI can cause hepatotoxicity, including fatalities. In patients who received TECVAYLI at the recommended dose in the clinical trial MajesTEC-1, there was one fatal case of hepatic failure.
Monitor liver enzymes and bilirubin at baseline and during treatment as clinically indicated. Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity and manage per local institutional guidelines (see *Dosage and Administration – Dosage modifications*).

Vaccines

Immune response to vaccines may be reduced when taking TECVAYLI.
The safety of immunization with live viral vaccines during or following TECVAYLI treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 4 weeks prior to the start of treatment, during treatment, and at least 4 weeks after treatment.

Neutropenia

Neutropenia and febrile neutropenia have been reported in patients who received TECVAYLI (see *Undesirable Effects*).
Monitor complete blood cell counts at baseline and periodically during treatment and provide supportive care per local institutional guidelines.
Patients with neutropenia should be monitored for signs of infection.
Withhold treatment with TECVAYLI based on severity as indicated in Table 7 (see *Dosage and Administration – Dosage modifications*).

Women of child bearing potential/contraception

Pregnancy status of females of child bearing potential should be verified prior to initiating treatment with TECVAYLI. Females of reproductive potential should use effective contraception during treatment and for 5 months after the last dose of TECVAYLI (see *Pregnancy, lactation*).

Hypersensitivity and other administration reactions

TECVAYLI can cause both systemic administration-related reactions and local injection-site reactions (see *Undesirable Effects*). Withhold TECVAYLI or consider permanent discontinuation of TECVAYLI based on severity (see *Dosage and Administration, Other Adverse Reactions)*.

Excipients

TECVAYLI contains less than 1 mmol sodium (23 mg) per 1 vial, i.e. it is almost "sodium-free".

Interactions

No drug interaction studies have been performed with TECVAYLI.

The initial release of cytokines associated with the start of TECVAYLI treatment could suppress CYP450 enzymes. Based on physiologically based pharmacokinetic (PBPK) modelling, the highest risk of drug-drug interaction is predicted to be from initiation of TECVAYLI step-up dosing schedule up to 7 days after the first Treatment Dose or during a CRS event. During this time period, monitor for toxicity or drug concentrations (e.g., cyclosporine) in patients who are receiving concomitant CYP450 substrates with a narrow therapeutic index. The dose of the concomitant drug should be adjusted as needed.

Pregnancy, lactation

Females and males of reproductive potential

Pregnancy testing

Pregnancy status for females of child-bearing potential should be verified prior to starting treatment with TECVAYLI.

Contraception

Advise females of reproductive potential to use effective contraception during treatment and for five months after the final dose of TECVAYLI.
Advise male patients with a female partner of reproductive potential to use effective contraception during treatment and for three months after the last dose of TECVAYLI.

Pregnancy

There are no available data on the use of TECVAYLI in pregnant women or animal data to assess the risk of TECVAYLI in pregnancy. Human immunoglobulin G (IgG) is known to cross the placenta. Therefore, teclistamab has the potential to be transmitted from the mother to the developing fetus. TECVAYLI induces T-cell activation and cytokine release, which may adversely affect the course of pregnancy. TECVAYLI should not be administered to pregnant women unless clearly indicated. TECVAYLI is associated with hypogammaglobulinemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with TECVAYLI should be considered.

Lactation

It is not known whether teclistamab is excreted in human or animal milk, affects breastfed infants or affects milk production. Because of the potential for serious adverse reactions in breastfed infants

from TECVAYLI, advise patients not to breastfeed during treatment with TECVAYLI and for at least five months after the last dose.

Fertility

There are no data on the effect of TECVAYLI on fertility. Effects of TECVAYLI on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Due to the potential for neurologic events (including ICANS), patients receiving TECVAYLI are at risk of depressed level of consciousness. Patients should avoid driving or operating heavy or potentially dangerous machinery during and for 48 hours after completion of TECVAYLI step-up dosing schedule (see *Dosage and Administration*, Table 1 and 2) and in the event of new onset of any neurological symptoms until neurologic toxicity resolves.

Undesirable effects

Adverse reactions are adverse events that were considered to be reasonably associated with the use of teclistamab based on the comprehensive assessment of the available adverse event information. A causal relationship with teclistamab cannot be reliably established in individual cases. Further, 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 clinical practice.

Summary of the safety profile

The safety data of TECVAYLI was evaluated in 448 adult patients with relapsed or refractory multiple myeloma including 165 patients from MajesTEC-1 who received TECVAYLI subcutaneous (SC) formulation as monotherapy, with a median duration of treatment of 9 (Range 0.2 to 41) months and 283 patients from MajesTEC-3 who received TECVAYLI SC formulation in combination with SC daratumumab with a median duration of treatment of 32 (Range 0.03 to 43) months.
The most frequent adverse reactions of any grade (≥ 20 %) in patients were hypogammaglobulinemia, neutropenia, cytokine release syndrome, upper respiratory tract infection, musculoskeletal pain, anemia, diarrhoea, cough, fatigue, COVID-19, injection site reaction, thrombocytopenia, pyrexia, pneumonia, pain, lymphopenia, headache, nausea, and hypokalemia. Serious adverse reactions were reported in 70 % of patients who received TECVAYLI. Serious adverse reactions reported in ≥ 2 % of patients included pneumonia (23 %), COVID-19 (18 %), upper respiratory tract infection (10 %), cytokine release syndrome (9 %), sepsis (7 %), pyrexia (5 %), febrile neutropenia (4 %), musculoskeletal pain (2.7 %), and diarrhoea (2.2 %).

List of adverse reactions

Table 8 summarizes adverse reactions reported in patients in MajesTEC-1 and MajesTEC-3.

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing frequency.

Table 8: Adverse Reactions in Patients with Multiple Myeloma in MajesTEC-1 and MajesTEC-3

System Organ Class	Adverse Reaction	Frequency (all grades)	N=448 n (%)	
			Any Grade	Grade 3 or 4
Infections and infestations	Upper respiratory tract infection[1]	Very common	287 (64 %)	49 (11 %)
	COVID-19[2]	Very common	180 (40 %)	78 (17 %)
	Pneumonia[3]	Very common	150 (33 %)	110 (25 %)
	Urinary tract infection[4]	Very common	69 (15 %)	18 (4.0 %)
	Sepsis[5]	Very common	45 (10 %)	32 (7 %)
	Progressive multifocal leukoencephalopathy	Uncommon		
Blood and lymphatic system disorders	Neutropenia	Very common	340 (76 %)	322 (72 %)
	Anemia[6]	Very common	211 (47 %)	120 (27 %)
	Thrombocytopenia	Very common	172 (38 %)	93 (21 %)
	Lymphopenia	Very common	123 (27 %)	116 (26 %)
	Leukopenia	Very common	84 (19 %)	45 (10 %)
	Febrile neutropenia	Common		
Immune system disorders	Hypogammaglobulinemia[7]	Very common	358 (80 %)	21 (4.7 %)
	Cytokine release syndrome	Very common	289 (65 %)	1 (0.2 %)
Metabolism and nutrition disorders	Hypokalemia	Very common	102 (23 %)	32 (7 %)
	Decreased appetite	Very common	77 (17 %)	4 (0.9 %)
	Hypophosphatemia	Very common	57 (13 %)	18 (4.0 %)
	Hyponatremia	Common		
	Hyperkalaemia	Common		
	Hyperamylasemia	Common		
Nervous system disorders	Headache	Very common	113 (25 %)	5 (1.1 %)
	Sensory neuropathy[8]	Very common	79 (18 %)	4 (0.9%)
	Encephalopathy[9]	Very common	47 (10 %)	2 (0.4 %)
	Immune effector cell-associated neurotoxicity syndrome	Common		
Vascular disorders	Hypertension[10]	Very common	54 (12 %)	23 (5 %)
Respiratory, thoracic and mediastinal disorders	Cough[11]	Very common	202 (45 %)	2 (0.4 %)
	Dyspnea[12]	Very common	67 (15 %)	16 (3.6 %)
Gastrointestinal disorders	Diarrhea[13]	Very common	205 (46 %)	16 (3.6 %)
	Nausea	Very common	110 (25 %)	1 (0.2 %)
	Constipation	Very common	77 (17 %)	0
	Vomiting	Very common	74 (17 %)	2 (0.4 %)
	Abdominal pain[14]	Very common	66 (15 %)	4 (0.9 %)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain[15]	Very common	229 (51 %)	18 (4.0 %)
	Fatigue[16]	Very common	189 (42 %)	17 (3.8 %)

General disorders and administration site conditions	Injection site reaction[17]	Very common	174 (39 %)	1 (0.2 %)
	Pyrexia	Very common	155 (35 %)	5 (1.1 %)
	Pain[18]	Very common	127 (28 %)	6 (1.3 %)
	Edema[19]	Very common	65 (15 %)	1 (0.2 %)
Investigations	Transaminase elevation[20]	Very Common	86 (19 %)	16 (3.6 %)
	Weight decreased	Very Common	70 (16 %)	10 (2.2 %)
	Gamma-glutamyltransferase increased	Very Common	48 (11 %)	12 (2.7 %)
	Lipase increased	Common		

Note: Adverse events are graded according to the NCI-CTCAE Version 5.0, with the exception of ICANS and CRS, which were graded by ASTCT consensus grading system (Lee et al 2019).

[1] Upper respiratory tract infection includes Acute sinusitis, Adenoviral upper respiratory infection, Bacterial rhinitis, Bronchiolitis, Bronchitis, Bronchitis bacterial, Bronchitis chronic, Bronchitis haemophilus, Bronchitis viral, Chronic sinusitis, Nasopharyngitis, Pharyngitis, Respiratory syncytial virus infection, Respiratory tract infection, Respiratory tract infection bacterial, Respiratory tract infection viral, Rhinitis, Rhinovirus infection, Sinobronchitis, Sinusitis, Sinusitis bacterial, Tracheitis, Tracheobronchitis, Upper respiratory tract infection, Upper respiratory tract infection bacterial, Viral rhinitis, Viral sinusitis and Viral upper respiratory tract infection.

[2] COVID-19 includes Asymptomatic COVID-19, COVID-19 and COVID-19 pneumonia.

[3] Pneumonia includes Atypical pneumonia, Enterobacter pneumonia, Lower respiratory tract infection, Lower respiratory tract infection bacterial, Lower respiratory tract infection viral, Metapneumovirus pneumonia, Pneumocystis jirovecii pneumonia, Pneumonia, Pneumonia adenoviral, Pneumonia bacterial, Pneumonia chlamydial, Pneumonia cytomegaloviral, Pneumonia escherichia, Pneumonia fungal, Pneumonia haemophilus, Pneumonia influenzal, Pneumonia klebsiella, Pneumonia moraxella, Pneumonia pneumococcal, Pneumonia pseudomonal, Pneumonia respiratory syncytial viral, Pneumonia staphylococcal, Pneumonia streptococcal and Pneumonia viral.

[4] Urinary tract infection includes Cystitis, Cystitis escherichia, Cystitis klebsiella, Escherichia urinary tract infection, Genitourinary tract infection, Klebsiella urinary tract infection, Pyelonephritis acute, Urinary tract infection, Urinary tract infection bacterial, Urinary tract infection enterococcal and Urinary tract infection fungal.

[5] Sepsis includes Bacteremia, Bacterial sepsis, Campylobacter bacteremia, Campylobacter sepsis, Citrobacter bacteremia, Corynebacterium bacteremia, Device related bacteremia, Enterococcal sepsis, Escherichia bacteremia, Escherichia sepsis, Haemophilus sepsis, Klebsiella sepsis, Meningococcal sepsis, Neutropenic sepsis, Pseudomonal bacteremia, Pseudomonal sepsis, Sepsis, Septic shock, Staphylococcal bacteremia, Staphylococcal sepsis, Streptococcal sepsis and Urosepsis.

[6] Anemia includes Anemia, Iron deficiency anemia, Leukoerythroblastic anemia and Microcytic anemia.

[7] Hypogammaglobulinemia includes patients with adverse events of hypogammaglobulinemia, hypoglobulinemia, immunoglobulins decreased; and/or patients with laboratory IgG levels below 400 mg/dL following treatment with TECVAYLI.

[8] Sensory neuropathy includes Dysaesthesia, Hyperaesthesia, Hypoaesthesia, Hypoaesthesia oral, Neuralgia, Neuropathy peripheral, Paraesthesia, Paraesthesia oral, Peripheral sensory neuropathy, Sciatica, Skin burning sensation and Vestibular neuronitis.

[9] Encephalopathy includes Agitation, Amnesia, Apathy, Brain fog, Cognitive disorder, Confusional state, Delirium, Depressed level of consciousness, Disturbance in attention, Hallucination, Lethargy, Memory impairment and Somnolence.

[10] Hypertension includes Blood pressure increased, Essential hypertension, Hypertension, Hypertensive crisis and Mean arterial pressure increased.

[11] Cough includes Allergic cough, Cough, Productive cough and Upper-airway cough syndrome.

[12] Dyspnea includes Acute respiratory failure, Dyspnea, Dyspnea exertional and Respiratory failure.

[13] Diarrhea includes Bacterial diarrhea and Diarrhea.

[14] Abdominal pain includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper and Gastrointestinal pain.

[15] Musculoskeletal pain includes Arthralgia, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal pain, Myalgia, Neck pain, Pain in extremity and Sacral pain.

[16] Fatigue includes Asthenia, Fatigue and Malaise.

[17] Injection site reaction includes Administration site pruritus, Administration site reaction, Application site erythema, Injection site bruising, Injection site cellulitis, Injection site discomfort, Injection site eczema, Injection site erythema, Injection site hematoma, Injection site hyperesthesia, Injection site induration, Injection site inflammation, Injection site irritation, Injection site edema, Injection site pain, Injection site pruritus, Injection site rash, Injection site reaction, Injection site swelling, Injection site vesicles and Injection site warmth.

[18] Pain includes Axillary pain, Breast pain, Chest pain, Ear pain, Eye pain, Facial pain, Flank pain, Gingival pain, Groin pain, Non-cardiac chest pain, Esophageal pain, Oral pain, Oropharyngeal pain, Pain, Pain in jaw, Pain of skin, Pelvic pain, Perineal pain, Periorbital pain, Sinus pain, Spinal pain, Toothache and Tumor pain.

[19] Edema includes Eyelid edema, Face edema, Fluid overload, Localized edema, Edema, Edema peripheral, Periorbital edema, Peripheral swelling, Skin edema, Swelling, Swelling face and Testicular swelling.

[20] Transaminase elevation includes Alanine aminotransferase increased, Aspartate aminotransferase increased, Hypertransaminasaemia and Transaminases increased.

Description of specific adverse reactions and additional information

Cytokine release syndrome (CRS)

In clinical trials (monotherapy and combination therapy; N=448), CRS was reported in 65 % of patients following treatment with TECVAYLI. Twenty seven percent (27 %) of patients experienced

more than one CRS event. Most patients experienced CRS during the initial step-up dosing schedule (Step-up dose 1 (38 %), Step-up dose 2 (32 %), or the initial treatment dose (20 %)). Most CRS events were Grade 1 (46 %) and Grade 2 (18 %). 0.2% of CRS events were Grade 3.

The median time to onset of CRS was 2 (Range: 1 to 9) days after the most recent dose and the median duration of CRS was 2 (Range: 1 to 22) days.

The most frequent (≥ 3 %) signs and symptoms associated with CRS were fever (64 %), hypotension (14 %), chills (9 %), hypoxia (8 %), headache (5 %), and sinus tachycardia (3.6 %).

Neurologic toxicities including ICANS

In the clinical trials (monotherapy and combination therapy trials; N=448), neurologic toxicity occurred in 61 % of patients who received TECVAYLI at the recommended dose, with Grade 3 or 4 neurologic toxicity in 7 %. Neurologic toxicities reported in ≥5 % of patients included headache (25 %), insomnia (12 %), dizziness (9 %), muscle spasms (9 %), peripheral sensory neuropathy (7 %) and paraesthesia (5 %). Fatal neurologic toxicity occurred in 0.4 % of patients. Grade 4 seizure and fatal Guillain-Barré syndrome occurred in one patient each.

In MajesTEC-1 (N=165) ICANS was reported in 3 % of patients receiving TECVAYLI at the recommended dose. Recurrent ICANS occurred in 1.2 % of patients. Most patients experienced ICANS following step-up dose 1 (0.6 %), or the initial treatment dose (1.2 %). Less than 2.5 % of patients developed first occurrence of ICANS following subsequent doses of TECVAYLI. The median time to onset of ICANS was 4 (range: 2 to 5) days after the most recent dose with a median duration of 3 (range: 1 to 20) days.

The most frequent clinical manifestations of ICANS reported were confusional state (1.2 %) and dysgraphia (1.2 %).

In MajesTEC-3 (N=283), ICANS was reported in 1.1 % of patients receiving TECVAYLI in combination with daratumumab at the recommended dose. Grade 1 events occurred in 2 patients, and a Grade 4 event occurred in 1 patient. The clinical manifestations of ICANS reported were amnesia (0.4 %), encephalopathy (0.4 %) and delirium (0.4 %).

Infections

In MajesTEC-1 (N=165), opportunistic infections occurred in 9.1 % of patients with Grade 3 or higher infections in 7.9 %. The most common opportunistic infection was Pneumocystis jirovecii pneumonia (4.2 %). There was one fatal case of PML in the MajesTEC-1 trial and two fatal cases reported in trials in which Teclistamab was combined with another antimyeloma therapy (see Table 8). New or reactivated viral infections occurring during therapy with TECVAYLI included adenovirus (2.4 %), hepatitis B virus (HBV) (0.6 %) and cytomegalovirus (CMV) (1.8 %).

In patients who received TECVAYLI at the recommended dose in the clinical trial, COVID-19 occurred in 30 % (50/165) of patients and were fatal in 11 % (18/165) of patients.

In MajesTEC-3 (N=283), in patients who received TECVAYLI in combination with daratumumab at the recommended dose, serious infections occurred in 54 % of patients, with Grade 3 or Grade 4 infections in 54 % of patients and fatal infections in 4.6 %.

Hypersensitivity and other administration reactions

Systemic Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trials (monotherapy and combination therapy; N=448), 2.5 % of patients experienced systemic-administration reactions, which included Grade 1 recurrent pyrexia and Grade 1 swollen tongue.

Local Reactions

In patients who received TECVAYLI at the recommended dose in the clinical trials (monotherapy and combination therapy; N=448), injection-site reactions occurred in 37 % of patients, with Grade 1 injection-site reactions in 29 % and Grade 2 in 9 %.

Elderly patients (65 years of age and older)

Of the 203 patients treated with TECVAYLI in MajesTEC-1 monotherapy at the recommended dose, 47 % were 65 years of age or older, and 13 % were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. However, the number of patients aged 75 years or older was insufficient to determine differences in safety or efficacy.

Of the 291 patients treated with TECVAYLI in MajesTEC-3 at the recommended dose in combination with daratumumab, 51 % were younger than 65 years of age, 39 % were 65 to 74 years of age, and 11 % were 75 years of age or older. No overall differences in effectiveness were observed between patients 65 to 74 years of age compared to younger patients. However, the number of patients 75 years of age or older was insufficient to assess whether there are differences in effectiveness compared to younger patients. There was a higher incidence of serious adverse reactions in patients 75 years of age or older (83 %) and in patients 65 to 74 years of age (77 %) as compared to patients younger than 65 years of age (63 %).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

The maximum tolerated dose of teclistamab has not been determined. In clinical trials, doses of up to 6 mg/kg have been administered.

Treatment

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.

Properties/Effects

ATC code

L01FX24

Mechanism of action

Teclistamab is a bispecific IgG4 antibody that targets the CD3 receptor expressed on the surface of T cells and B cell maturation antigen (BCMA), which is expressed mainly on the surface of malignant multiple myeloma B-lineage cells, as well as late-stage B cells and plasma cells. Binding to T cells and BCMA results in T cell activation and subsequent lysis of $BCMA^+$ cells.

Pharmacodynamics

Within the first month of treatment with teclistamab, activation and redistribution of T-cells, reduction of B-cells and induction of serum cytokines were observed.
Within one month, the majority of responders had reduction in soluble BCMA.

Immunogenicity

Patients treated with subcutaneous TECVAYLI were evaluated for antibodies to teclistamab using an electrochemiluminescence-based immunoassay. One patient (0.4%) in TECVAYLI monotherapy (N=238) and two patients (0.5 %) in TECVAYLI in combination with daratumumab (N=379) developed antibodies to teclistamab. One patient in TECVAYLI monotherapy and one patient in TECVAYLI in combination with daratumumab developed neutralizing antibodies to teclistamab.

Effect on QT/QTc interval and cardiac electrophysiology

No clinical QT study has been conducted. At the recommended treatment dose of TECVAYLI, no clinically relevant QTc prolongation has been reported.

Clinical efficacy

In combination with daratumumab (MajesTEC-3)

The efficacy of TECVAYLI in combination with daratumumab (TECVAYLI-Dara) versus the control arm of either daratumumab, pomalidomide and dexamethasone (DPd) or daratumumab, bortezomib

and dexamethasone (DVd) in patients with relapsed or refractory multiple myeloma, was evaluated in a randomized, open-label, multi-center study (MajesTEC-3). The study included patients who had previously received one to three prior lines of therapy including a proteasome inhibitor (PI) and lenalidomide. Patients who had received only one prior line of therapy must have been refractory to lenalidomide.

Patients received TECVAYLI administered subcutaneously consisting of initial step-up doses of 0.06 mg/kg and 0.3 mg/kg, followed by a treatment dose schedule of 1.5 mg/kg weekly through Week 8, then 3 mg/kg once every two weeks through Week 24, and then 3 mg/kg once every four weeks thereafter until disease progression or unacceptable toxicity. Daratumumab was administered subcutaneously at a dose of 1800 mg weekly in Week 1 to Week 8, and then 1800 mg once every two weeks through Week 24, and then once every four weeks thereafter until disease progression or unacceptable toxicity (see *Dosage and Administration*).

A total of 587 patients were randomized: 291 to the TECVAYLI-Dara arm and 296 to the control arm. Randomization was stratified by investigator's choice of DPd or DVd, stage of disease at screening per International Staging System (ISS) (I vs II vs III), prior anti-CD38 monoclonal antibody exposure (yes vs no), and number of prior lines of therapy (1 vs 2 or 3). The baseline disease characteristics were similar between the TECVAYLI-Dara arm and the control arm. The median age was 64 years (range: 25 to 88) years with 10 % aged ≥75 years; 55 % were male, 65 % were White, 6 % were Black or African American, and 22 % were Asian. The ISS was 62.5 % in Stage I, 29.5 % in Stage II, and 8.0 % in Stage III. High-risk cytogenetics (presence of del(17p). t(4;14) or t(14; 16)) were present in 35.9 % of patients. Additionally, 14 % of patients had soft tissue plasmacytomas.

The median number of prior lines of therapy was 2 (range: 1 to 3), with 37.8 % of patients who received one prior line of the therapy. All patients were previously exposed to lenalidomide and a PI. Additionally, 85.3 % of patients were refractory to their last line of therapy and 31.9 % were double-class refractory (refractory to a PI, and an IMiD). 5.3 % of patients received a prior anti-CD38 monoclonal antibody. There is limited data with TECVAYLI in combination with daratumumab in patients who have received or are refractory to prior anti-CD38 monoclonal antibody therapy.

With a median follow-up of 34.5 months in the Intent to treat (ITT) population, the primary analysis of Progression-Free Survival (PFS) in MajesTEC-3 demonstrated a clinically meaningful and statistically significant improvement in the TECVAYLI-Dara arm compared with the control arm (HR=0.17; 95 % CI: 0.12, 0.23; p-value <0.0001). The median PFS was not reached in the TECVAYLI-Dara arm and was 18.1 months (95 % CI: 14.6, 22.8) in the control arm. The estimated PFS rate at 36 months was 83.4 % (95 % CI: 78.2, 87.4) in the TECVAYLI-Dara arm and 29.7 % (95 % CI: 23.6, 36.0) in the control arm.

MajesTEC-3 demonstrated a clinically meaningful and statistically significant improvement in overall survival (OS) in the TECVAYLI-Dara arm as compared to the control arm (HR= 0.46; 95 % CI: 0.32, 0.65; p-value <0.0001); the median OS was not reached in either the TECVAYLI-Dara arm or the

control arm. The estimated OS rate at 36 months was 83.3 % (95 % CI: 78.3, 87.2) in the TECVAYLI-Dara arm and 65.0 % (95 % CI: 58.8, 70.5) in the control arm.

Efficacy results were determined by the Independent Review Committee (IRC) assessment using International Myeloma Working Group (IMWG) 2016 criteria (see Table 9).

Table 9: Efficacy results for MajesTEC-3

	TECVAYLI-Dara Arm (N=291)	Control Arm (N=296)
Progression-free survival (PFS)[a]		
Number of events, n (%)	44 (15.1)	187 (63.2)
Median, months (95 % CI)	NR (NE, NE)	18.10 (14.6, 22.8)
Hazard ratio (95 % CI)[b] ; p-value[c]	0.17 (0.12, 0.23); <0.0001	
24-month PFS rate, % (95 % CI)	85.2 (80.4, 88.9)	42.2 (36.3, 48.0)
36-month PFS rate, % (95 % CI)	83.4 (78.2, 87.4)	29.7 (23.6, 36.0)
Complete response or better (sCR+CR)[a], n (%)	238 (81.8)	95 (32.1)
95 % CI (%)	(76.9, 86.0)	(26.8, 37.7)
Odds ratio (95 % CI)[d]; p-value[e]	9.56 (6.47, 14.14); <0.0001	
Overall response (ORR: sCR+CR+VGPR+PR)[a], n (%)	259 (89.0)	223 (75.3)
95 % CI (%)	(84.8, 92.4)	(70.0, 80.1)
Odds ratio (95 % CI) [d]; p-value[e]	2.65 (1.68, 4.18); <0.0001	
Stringent complete response (sCR), n (%)	225 (77.3)	69 (23.3)
Complete response (CR), n (%)	13 (4.5)	26 (8.8)
Very good partial response (VGPR), n (%)	14 (4.8)	74 (25.0)
Partial response (PR), n (%)	7 (2.4)	54 (18.2)
MRD negativity[f,g], n/N (%)	153/262 (58.4)	46/269 (17.1)
95 % CI (%)	(52.2, 64.4)	(12.8, 22.1)
Odds ratio (95 % CI)[d]; p-value[h]	6.78 (4.53, 10.15); <0.0001	
Overall survival (OS)[a]		
Number of events, n (%)	46 (15.8)	98 (33.1)
Median, months (95 % CI)	NR (NE, NE)	NR (41.40, NE)
Hazard ratio (95 % CI)[b]; p-value[c]	0.46 (0.32, 0.65); <0.0001	
24-month survival rate, % (95 % CI)	86.5 (81.9, 90.0)	76.4 (71.1, 80.9)
36-month survival rate, % (95 % CI)	83.3 (78.3, 87.2)	65.0 (58.8, 70.5)

CI = confidence interval; NE = not estimable; NR = not reached; MRD = minimal residual disease; Control arm = DPd or DVd
Median duration of follow-up = 34.5 months

[a] Based on intent-to-treat analysis set
[b] Stratified Cox proportional hazard model. For all stratified analyses, stratification was based on ISS staging (I vs. II or III) and number of prior lines (1 vs. 2 or 3), as randomized
[c] Stratified log-rank test
[d] Mantel-Haenszel estimate of the common odds ratio for stratified tables is used
[e] Cochran Mantel-Haenszel Chi-Squared test
[f] Based on MRD next-generation sequencing (NGS) primary analysis set, defined as all randomized patients in the study except for those recruited in China.
[g] Based on a threshold of 10^{-5} using a next generation sequencing assay (clonoSEQ).
[h] Fisher's exact test

For the 15 patients who had received a prior anti-CD38 monoclonal antibody, the ORR was 93.3 % (95 % CI: 68.1, 99.8) and the PFS HR was 0.19 (95 % CI: 0.05, 0.67).

Monotherapy (MajesTEC-1)

The efficacy of TECVAYLI monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in a single-arm, open-label, multicenter, study (MajesTEC-1). The study included patients who had previously received at least three prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent and an anti-CD38 monoclonal antibody. The study excluded patients with

hypercalcemia (> 3.5 mmol/L), renal insufficiency (serum creatinine > 1.5 mg/dL or creatinine clearance < 40 mL/min), anemia (hemoglobin < 80 g/L), ECOG performance status > 1, CNS involvement, other plasma cell / monoclonal protein disorders, infections (HIV, AIDS, HBV, HCV) / active or documented history of autoimmune diseases (with the exception of vitiligo, Type 1 diabetes and prior autoimmune thyroiditis), cardiac disorders (congestive heart failure NYHA class III or IV, myocardial infarction or CABC ≤ 6 months prior to enrollment, history of clinically significant ventricular arrhythmia or unexplained syncope, history of severe non-ischemic cardiomyopathy), stroke or seizure within the last six months and patients who have received live, attenuated vaccines within 4 weeks prior to the first dose of TECVAYLI.

Patients received initial step-up doses of 0.06 mg/kg and 0.3 mg/kg of TECVAYLI administered subcutaneously followed by the treatment dose of TECVAYLI 1.5 mg/kg administered subcutaneously once weekly thereafter until disease progression or unacceptable toxicity (see *Dosage and Administration*).

Patients who had at least a complete response (CR) or better for a minimum of 6 months were eligible to reduce dosing frequency to 1.5 mg/kg subcutaneously every two weeks until disease progression or unacceptable toxicity (see *Dosage and Administration – Recommended dosing schedule*).

The efficacy population included 163 patients, consisting of 125 patients without prior anti-BCMA therapy and 38 patients with prior anti-BCMA therapy. The median age was 64 (Range: 32-83) years with 13 % of patients ≥ 75 years of age; 58 % were male; 82 % were White, 14 % were Black, 2 % were Asian. The International Staging System (ISS) at study entry was 50 % in Stage I, 34 % in Stage II, and 16 % in Stage III. High-risk cytogenetics (presence of del(17p), t(4;14) or t(14; 16)) were present in 26 % of patients. 19 % of patients had extramedullary plasmacytomas.

The median time since initial diagnosis of multiple myeloma to enrollment was 6.4 (Range: 0.9-24.1) years. The median number of prior lines of therapy was 5 (range: 2-14) with 20 % of patients who received 3 prior lines of therapy and 79 % were triple-class refractory (refractory to PI, an IMiD agent and an anti-CD38 monoclonal antibody). 83 % of patients received prior stem cell transplantation, 23 % received prior anti-BCMA therapy (27/38 patients received antibody drug conjugate (ADC) and 15/38 patients received chimeric antigen receptor T cells (CAR-T)).

The median duration of exposure was 4.6 (range: 0.03 to 10.15) months, the median duration of follow-up was 6.4 (range: 0.03 to 10.71) months.

Efficacy results were based on overall response rate (ORR, primary endpoint) as determined by the Independent Review Committee (IRC) assessment using International Myeloma Working Group (IMWG) 2016 criteria (see Table 10, cut-off date 07 September 2021).

Table 10: Efficacy Results for MajesTEC-1

	N=163
Overall response rate (ORR: sCR+CR+VGPR+PR) n (%)	93 (57 %)
95 % CI (%)	(49.1 %, 64.8 %)
Complete response or better[a]	33 (20 %)
Very good partial response (VGPR)	47 (29 %)
Partial response (PR)	13 (8 %)

[a] Complete response or better = Stringent complete response (sCR) + complete response (CR)

In a separate evaluation of the primary endpoint for patients without prior anti-BCMA therapy (n=125) the ORR was 61.6 % (77/125; 95 % CI: 52.5 %, 70.2 %), and 42.1 % (16/38; 95 % CI: 26.3 %, 59.2 %) for patients with prior anti-BCMA therapy, at a median follow-up of 6.5 and 6.1 months respectively.

At an updated clinical cut-off of 16 March 2022 at a median follow-up of 12.7 months, the median time to first response (TTR) was 1.2 months (range: 0.2 to 5.5 months), the median duration of response (DOR) was 14.9 months (95 % CI: 14.9 to NE (not estimable)) and the median progression free survival (PFS) was 8.8 months (95 % CI: 5.8 to 11.5) in the overall efficacy population (N=163). Estimated median overall survival (OS) was not mature at 16.0 months (95 % CI: 12.2 to NE).

At the updated clinical cut-off, in patients without prior exposure to an anti-BCMA therapy (N=125) at a median follow-up of 12.9 months the median TTR was 1.2 months (range: 0.2 to 5.5 months), the median DOR was 14.9 months (95 % CI: 14.9 to NE) and the median PFS was 9.8 months (95 % CI: 6.8 to 16.0). Estimated median OS was not mature at 16.0 months (95 % CI: 12.1 to NE).

At the updated clinical cut-off, in patients with prior anti-BCMA therapy (N=38) at a median follow-up of 12.5 months the median TTR was 1.2 months (range: 0.2 to 4.9 months), the median DOR was not estimable and the median PFS was 4.5 months (95 % CI: 1.3 to NE). Estimated median OS was not mature at 14.4 months (95 % CI: 8.3 to NE).

At the final clinical cut-off of 22 August 2023 at a median follow-up of29.4 months, the median time to first response (TTR) was 1.2 months (range: 0.2 to 5.5 months), the median duration of response (DOR) was 18.7 months (95 % CI: 14.5 to 28.4) and the median progression free survival (PFS) was 9.2 months (95 % CI: 6.9 to 13.8) in the overall efficacy population (N=165). Estimated median overall survival (OS) was 17.7 months (95 % CI: 13.1 to 26.3).

At the final clinical cut-off, in patients without prior exposure to an anti-BCMA therapy (N=125) at a median follow-up of 29.5 months the median TTR was 1.2 months (range: 0.2 to 5.5 months), the median DOR was 21.6 months (95 % CI: 14.9 to NE (not estimable)) and the median PFS was 10.8 months (95 % CI: 7.6 to 16.2). Estimated median OS was 19.8 months (95 % CI: 12.7 to 29.9).

At the final clinical cut-off, in patients with prior anti-BCMA therapy (N=40) at a median follow-up of 28.0 months the median TTR was 1.2 months (range: 0.2 to 4.9 months), the median DOR was 14.8

months (95 % CI: 8.0 to 22.6) and the median PFS was 4.5 months (95 % CI: 1.3 to 11.6). Estimated median OS was 15.5 months (95 % CI: 8.3 to 27.9).

Pharmacokinetics

Teclistamab exhibited approximately dose-proportional pharmacokinetics following subcutaneous administration across a dose range of 0.08 mg/kg to 3 mg/kg in monotherapy. Following the recommended dose of teclistamab monotherapy, 90 % of steady state exposure was achieved after 12 weekly treatment doses. The mean accumulation ratio between the first and 13th weekly treatment dose of teclistamab 1.5 mg/kg was 4.2-fold for C_{max}, 4.1-fold for C_{trough}, and 5.3-fold for C_{avg}.

The pharmacokinetic characteristics of teclistamab were consistent whether used as monotherapy or in combination with daratumumab.

The C_{max}, C_{trough}, and C_{avg} of teclistamab are presented in Table 11.

Table 11: Pharmacokinetic Parameters of Teclistamab for the Recommended Dose in Patients with Relapsed or Refractory Multiple Myeloma

	C_{max} (µg/mL)	C_{trough} (µg/mL)	C_{avg} (µg/mL)
Teclistamab Monotherapy			
First 1.5 mg/kg dose	6.34 (60 %)	5.77 (63 %)	4.98 (61 %)
Steady state of 1.5 mg/kg weekly dosing[a]	23.8 (55 %)	21.1 (63 %)	22.8 (57 %)
Teclistamab in Combination with Daratumumab			
First 1.5 mg/kg dose	6.36 (54 %)	5.79 (59 %)	4.96 (55 %)
End of 1.5 mg/kg weekly dosing[b]	19.6 (54 %)	17.3 (62 %)	18.6 (56 %)
End of 3.0 mg/kg every two weeks dosing[c]	29.9 (55 %)	19.8 (85 %)	26.2 (62 %)
Steady state of 3.0 mg/kg every 4 weeks dosing[d]	20.2 (52 %)	5.82 (152 %)	13.7 (67 %)

C_{avg} = average serum teclistamab concentration over a dosing interval; C_{max} = maximum serum teclistamab concentration; C_{trough} = serum teclistamab concentration prior to next dose

[a] Steady-state exposure for the 13th weekly dose.

[b] Exposure for the 7th weekly dose.

[c] Exposure for the 8th biweekly dose.

[d] Steady-state exposure for the 5th 4 weekly dose.

Note: Data are presented as geometric mean (CV %).

Absorption

The mean bioavailability of teclistamab was 72 % when administered subcutaneously. The median (range) T_{max} of teclistamab after the first and 13th treatment doses in monotherapy were 139 (19 to 168) hours and 72 (24 to 168) hours, respectively.

Distribution

Based on the population pharmacokinetic model, mean volume of distribution was 5.63 L (29 % coefficient of variation (CV)).

Metabolism

No data.

Elimination

Population pharmacokinetic analysis showed that teclistamab clearance decreases over time, with a mean (CV %) maximal reduction from baseline to the 13th weekly treatment dose in monotherapy of 40.8 % (56 %). The geometric mean (CV %) clearance is 0.472 L/day (64 %) at the 13th weekly treatment dose in monotherapy. Patients who discontinue teclistamab after the 13th weekly treatment dose in monotherapy are expected to have a 50 % reduction from C_{max} in teclistamab concentration at a median (5th to 95th percentile) time of 15 (7 to 33) days after T_{max} and a 97 % reduction from C_{max} in teclistamab concentration at a median time of 69 (32 to 163) days after T_{max}.

Population pharmacokinetic analysis showed that soluble BCMA did not impact teclistamab serum concentrations.

Kinetics in specific patient groups

Hepatic impairment

No formal studies of TECVAYLI in patients with hepatic impairment have been conducted.
Results of population pharmacokinetic analyses indicate that mild or moderate hepatic impairment did not significantly influence the pharmacokinetics of teclistamab. No data are available from patients with severe hepatic impairment.

Renal impairment

No formal studies of TECVAYLI in patients with renal impairment have been conducted.
Results of population pharmacokinetic analyses indicate that mild or moderate renal impairment did not significantly influence the pharmacokinetics of teclistamab. Limited data are available from patients with severe renal impairment.

Age and sex

The pharmacokinetics of TECVAYLI in pediatric patients have not been investigated.
Results of population pharmacokinetic analyses indicate that age (24 to 84 years) and sex did not influence the pharmacokinetics of teclistamab.

Preclinical data

No effects on clinical or immunological parameters and safety pharmacology were seen in the 5-week toxicity study in cynomolgus monkeys with weekly intravenous administration of doses up to 30 mg/kg/week (equivalent to 22 times the maximum recommended human dose based on AUC exposure). Due to the lower binding affinity to monkey BCMA compared to human BCMA, and lack of pharmacodynamic activity at clinically relevant doses, clinical safety margins cannot be established from the nonclinical studies and the study cannot adequately inform on safety in humans

Carcinogenicity/Mutagenicity

No genotoxicity or carcinogenicity studies have been performed.

Reproductive toxicity

No reproductive, developmental toxicity and fertility animal studies have been conducted to evaluate the potential effects of teclistamab.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

Chemical and physical in-use stability of TECVAYLI after drawing up in the ready-to-use syringe (PP, PC) has been demonstrated for 20 hours at 2 - 8°C in the refrigerator and at room temperature (15 - 30°C). For microbiological reasons, TECVAYLI should be used immediately after opening, unless controlled and validated aseptic conditions have been applied. If TECVAYLI is not used immediately after opening, storage times and conditions are the responsibility of the user.
Discard after 20 hours, if not used.

Special precautions for storage

Store in the refrigerator (2 - 8°C).
Store in the original carton in order to protect from light.
Do not freeze.
Keep out of the sight and reach of children.

Instructions for handling

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

Mode of administration

TECVAYLI solution for injection for subcutaneous use is colorless to light yellow. Visually inspect TECVAYLI for particulate matter and discoloration prior to administration. Do not use if the solution is discolored, or cloudy, or if foreign particles are present.
TECVAYLI 10 mg/mL vial and TECVAYLI 90 mg/mL vial are supplied as ready-to-use solution for injection that do not need dilution prior to administration.

TECVAYLI vials of different concentrations should not be combined to achieve treatment dose.

Use aseptic technique to prepare and administer TECVAYLI.

Preparation of TECVAYLI

- Verify the prescribed dose for each TECVAYLI injection. To minimize errors, use the following tables to prepare TECVAYLI injection.
  - Use Table 12 to determine total dose, injection volume and number of vials required based on patient's actual body weight for step-up dose 1 using TECVAYLI 10 mg/mL.

Table 12: Injection Volumes of TECVAYLI 10 mg/mL for Step-up Dose 1 (0.06 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 3 mL)
Step-Up Dose 1 0.06 mg/kg	35-39.9	2.2	0.22	1
	40-44.9	2.5	0.25	1
	45-49.9	2.8	0.28	1
	50-59.9	3.3	0.33	1
	60-69.9	3.9	0.39	1
	70-79.9	4.5	0.45	1
	80-89.9	5.1	0.51	1
	90-99.9	5.7	0.57	1
	100-109.9	6.3	0.63	1
	110-119.9	6.9	0.69	1
	120-129.9	7.5	0.75	1
	130-139.9	8.1	0.81	1
	140-149.9	8.7	0.87	1
	150-160	9.3	0.93	1

  - Use Table 13 to determine total dose, injection volume and number of vials required based on patient's actual body weight for Step-up Dose 2 using TECVAYLI 10 mg/mL.

Table 13: Injection Volumes of TECVAYLI 10 mg/mL for Step-up Dose 2 (0.3 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 3 mL)
Step-Up Dose 2 0.3 mg/kg	35-39.9	11	1.1	1
	40-44.9	13	1.3	1
	45-49.9	14	1.4	1
	50-59.9	16	1.6	1
	60-69.9	19	1.9	1
	70-79.9	22	2.2	1
	80-89.9	25	2.5	1
	90-99.9	28	2.8	1
	100-109.9	31	3.1	2
	110-119.9	34	3.4	2
	120-129.9	37	3.7	2
	130-139.9	40	4.0	2
	140-149.9	43	4.3	2
	150-160	47	4.7	2

  - Use Table 14 to determine total dose, injection volume and number of vials required based on patient's actual body weight for the 1.5 mg/kg Treatment Dose using TECVAYLI 90 mg/mL.

Table 14: Injection Volume of TECVAYLI 90 mg/mL for Treatment Dose (1.5 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.7 mL)
Treatment Dose 1.5 mg/kg	35-39.9	56	0.62	1
	40-44.9	64	0.71	1
	45-49.9	71	0.79	1
	50-59.9	83	0.92	1
	60-69.9	99	1.1	1
	70-79.9	108	1.2	1
	80-89.9	126	1.4	1
	90-99.9	144	1.6	1
	100-109.9	153	1.7	1
	110-119.9	171	1.9	2
	120-129.9	189	2.1	2
	130-139.9	198	2.2	2
	140-149.9	216	2.4	2
	150-160	234	2.6	2

- Use Table 15 to determine total dose, injection volume and number of vials required based on patient's actual body weight for the 3 mg/kg Treatment Dose using TECVAYLI 90 mg/mL.

Table 15: Injection Volume of TECVAYLI 90 mg/mL for Treatment Dose (3 mg/kg)

	Body Weight (kg)	Total Dose (mg)	Volume of Injection (mL)	Number of Vials (1 vial = 1.7 mL)
Treatment Dose 3 mg/kg	35-39.9	108	1.2	1
	40-44.9	126	1.4	1
	45-49.9	144	1.6	1
	50-59.9	162	1.8	2
	60-69.9	198	2.2	2
	70-79.9	225	2.5	2
	80-89.9	252	2.8	2
	90-99.9	288	3.2	2
	100-109.9	315	3.5	3
	110-119.9	342	3.8	3
	120-129.9	378	4.2	3
	130-139.9	405	4.5	3
	140-149.9	432	4.8	3
	150-160	468	5.2	4

- Remove the appropriate strength TECVAYLI vial from refrigerated storage [2 - 8°C] and equilibrate to ambient temperature [15 - 30°C], as needed, for at least 15 minutes. Do not warm TECVAYLI in any other way.
- Once equilibrated, gently swirl the vial for approximately 10 seconds to mix. Do not shake.
- Withdraw the required injection volume of TECVAYLI from the vial(s) into an appropriately sized syringe using a transfer needle.
  - Each injection volume should not exceed 2.0 mL. Divide doses requiring greater than 2.0 mL equally into multiple syringes.
- TECVAYLI is compatible with stainless steel injection needles and polypropylene or polycarbonate syringe material.
- Replace the transfer needle with an appropriately sized needle for injection.

Administration of TECVAYLI

- Inject the required volume of TECVAYLI into the subcutaneous tissue of the abdomen (preferred injection site). Alternatively, TECVAYLI may be injected into the subcutaneous tissue at other sites (e.g., thigh). If multiple injections are required, TECVAYLI injections should be at least 2 cm apart.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard or not intact.
- Any unused medicinal product or waste material should be disposed in accordance with local requirements.

Authorisation number

68747 (Swissmedic)

Packs

Carton with 1 vial of 30 mg/3 mL (Step-up Dose) [A].
Carton with 1 vial of 153 mg/1.7 mL (Treatment Dose) [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug, ZG

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