EMADOC-1700519818-2266337
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Verzenios

International non-proprietary name: Abemaciclib

Procedure No. EMA/VR/0000282650

Note

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

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Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Submission deadline	4 Jul 2025	1 Jul 2025	☐
☐	Validation	20 Jul 2025	4 Jul 2025	☐
☐	Start date	21 Jul 2025	21 Jul 2025	☐
☐	CHMP Rapporteur AR	25 Aug 2025	25 Aug 2025	☐
☐	CHMP Comments	8 Sept 2025	N/A	☐
☐	Updated CHMP Rapporteur AR	11 Sept 2025	11 Sept 2025	☐
☒	CHMP Outcome	18 Sept 2025	18 Sept 2025	☐

Table of contents

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 01 July 2025 an application for a variation.

The following changes were proposed:

Variation(s) requested		Type
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of section 5.1 of the SmPC in order to update efficacy and safety information in paediatric and adult population based on final results from study J1S-MC-JP04; this is a randomized, open-label, phase 2 study evaluating abemaciclib in combination with irinotecan and temozolomide in participants with relapsed or refractory Ewing's sarcoma.

The requested variation proposed amendments to the Summary of Product Characteristics.

2. Overall conclusion and impact on the benefit/risk balance

Verzenios (abemaciclib) is a selective inhibitor of CDK4/6. CDK4/6 inhibition prevents cell cycle progression through the G1 restriction point and arrests tumour growth. Mutations or overexpression in this pathway occur frequently in human cancers and tumours that involve such alterations are potentially sensitive to CDK4/6 inhibition.

Ewing sarcoma (EWS) is an aggressive sarcoma of the bone or soft tissue, or both, with a peak incidence in adolescents, but can occur from infancy to adulthood. Long-term survivors of relapsed EWS are rare. Among the accepted regimens, irinotecan (IRN) and temozolomide (TMZ) have demonstrated some of the highest response rates of up to 63% and a 2-year OS rate of 36% in EWS patients. These outcomes highlight the need for continued improvements. This highlights a need for rationale-targeted therapies beyond conventional cytotoxic chemotherapy.

Based on the role of CDKs in the activation of DNA-damage signalling and repair, along with the evidence of CDK pathway aberrations in EWS, it was hypothesised that the addition of abemaciclib to IRN plus TMZ could be of potential benefit for the treatment of EWS.

Abemaciclib was initially authorised in the EU on 26 September 2018 and is now licensed for the treatment of early and advanced or metastatic breast cancer.

As part of the present type II variation, the MAH submitted the results of paediatric study J1S-MC-JP04 and proposed an update of section 5.1 of the SmPC. Study J1S-MC-JP04 is one of two clinical studies key binding elements in the voluntary abemaciclib PIP (EMEA- 002342-PIP01-18-M04). This voluntary PIP was intended for the development of an indication for Ewing sarcoma.

Study J1S-MC-JP04 failed to meet its primary outcome. Median PFS was 2.8 months in the abemaciclib + IRN +TMZ arm and 2.9 months in the control arm (IRN +TMZ).

Hence, add-on abemaciclib to IRN and TMZ does not lead to a favourable benefit-risk balance for patients with relapsed or refractory EWS when compared to the combination of IRN and TMZ.

The combination of abemaciclib with IRN and TMZ was generally safe and tolerated with manageable toxicities. However, the addition of abemaciclib resulted in increased high-grade toxicities notably

haematologic and gastrointestinal toxicity and required more dose reductions and omissions of all study drugs.

To inform the healthcare professionals of the available information for EWS, section 5.1 *Paediatric population* of the abemaciclib SmPC is being updated with appropriate information on study JP04.

The proposed update to section 5.1 is acceptable.

The benefit-risk balance of Verzenios, remains positive.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation(s) requested		**Type**
C.I.4	C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data	Variation type II

Update of section 5.1 of the SmPC based on the final results from study J1S-MC-JP04, a PIP study and submitted in accordance with Article 46 of Regulation (EC) No 1901/2006; study J1S-MC-JP04is a randomized, open-label, phase 2 study evaluating abemaciclib in combination with irinotecan and temozolomide in participants with relapsed or refractory Ewing's sarcoma.

☒ is recommended for approval.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex I are recommended.

4. EPAR changes

The table in the 'Steps after' module of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

SmPC 5.1 Pharmacodynamic properties

Paediatric population

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

The efficacy and safety of Verzenios in combination with irinotecan and temozolomide was evaluated in Study J1S-MC-JP04, a multicentre, randomised, open-label, phase 2 study in participants with relapsed or refractory Ewing sarcoma. The primary endpoint was progression-free survival (PFS) assessed by a

blinded independent review committee. 46 participants, 3 to 35 years of age, were randomised to receive Verzenios plus irinotecan and temozolomide or irinotecan and temozolomide in a 2:1 ratio. 58.7 % of patients (27 patients) were < 18 years of age. 45 participants were treated in 21-day cycles until disease progression or having met other discontinuation criteria. No difference in PFS was observed with the addition of Verzenios. The median PFS was 2.8 months in patients treated with Verzenios in combination irinotecan and temozolomide and 2.9 months in patients treated with irinotecan and temozolomide (HR 0.64 [95% CI: 0.28, 1.45]).

For more information, please refer to the Summary of Product Characteristics.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Abemaciclib (Verzenio) is a selective inhibitor of CDK4/6. CDK4/6 inhibition prevents cell cycle progression through the G1 restriction point and arrests tumour growth. Alterations in this pathway occur frequently in human cancers and involve i) loss of endogenous CDK inhibitors by mutation or epigenetic silencing, ii) mutation or overexpression of either CDK4, CDK6, or Cyclin D, or iii) inactivation of retinoblastoma. These alterations render cells less dependent on mitogenic signalling for proliferation. With few exceptions, cancers that involve CDK mutations or overexpression are potentially sensitive to CDK4/6 inhibition.

Ewing sarcoma is an aggressive sarcoma of the bone or soft tissue, or both, with a peak incidence in adolescents, but can occur from infancy to adulthood. A multidisciplinary approach of neoadjuvant chemotherapy, surgery, or radiation (reserved for unresectable tumours) has improved 5-year event-free survival and OS to 69% and 72%, respectively, in the paediatric population. However, 30% to 40% of those who present initially with localised or metastatic disease will ultimately suffer a disease recurrence. Time to relapse is typically short, with a median of only 1.4 years for patients with initial localised disease, and 12 months for those initially metastatic. The prognosis for patients after disease relapse is dismal, with a 5-year OS rate of only 13% and median OS of only 7 months following progression. Long-term survivors of relapsed EWS are rare. Among the accepted regimens, irinotecan (IRN) and temozolomide (TMZ) have demonstrated some of the highest response rates of up to 63% and a 2-year OS rate of 36% in EWS patients. These outcomes highlight the need for continued improvements. Despite large multinational studies of novel combinations, treatment of relapsed EWS relies entirely on chemotherapeutic agents. This highlights a need for rationale-targeted therapies beyond conventional cytotoxic chemotherapy.

Based on the role of CDKs in the activation of DNA-damage signalling and repair, along with the evidence of CDK pathway aberrations in EWS, it was hypothesised that the addition of abemaciclib to IRN plus TMZ could be of potential benefit for the treatment of EWS.

Abemaciclib was initially authorised in the EU on 26 September 2018 and is now indicated for the treatment of early and advanced or metastatic breast cancer. Two product-specific waivers have been agreed upon:

1. for the treatment of breast cancer (procedure EMEA-002342-PIP03-18) and
2. for the treatment of prostate cancer (EMEA-002342-PIP05-23).

Two voluntary PIPs have also been agreed upon:

1. for the treatment of EWS (**EMEA-002342-PIP01-18-M04**) and
2. for the treatment of glioma (EMEA-002342-PIP02-18).

The present variation concerns the paediatric study J1S-MC-JP04 and as part of such type II variation, the MAH proposed to update section 5.1 of the SmPC. Study J1S-MC-JP04 is one of two clinical studies key binding elements in the voluntary PIP (**EMEA- 002342-PIP01-18-M04**). This voluntary PIP was intended for the development of an indication for Ewing sarcoma. The primary outcome of the J1S-MC-JP04 study was not met. Hence, the MAH is only proposing to reflect the outcome of the study in section 5.1 of the SmPC.

6. Clinical Efficacy aspects

6.1. Methods – analysis of data submitted

6.1.1. Study JP04

Figure 1. Study design

Study JP04 was a randomised, open-label, Phase 2 study evaluating abemaciclib in combination with IRN and TMZ in participants with relapsed or refractory Ewing sarcoma.

Stratification factors for the randomisation were time to first recurrence less than 2 years or at least 2 years from initial diagnosis, isolated pulmonary metastases versus other metastases at study entry, and age (less than 18 years or at least 18 years). Patients were treated until disease progression or other discontinuation criteria were met.

Under a frequentist analysis, study JP04 was powered at 82% assuming a PFS HR of 0.45 at a 1-sided alpha of 0.1, which required approximately 34 events. However, the primary analysis, which incorporated Bayesian control arm augmentation and utilised a Bayesian decision rule, namely the posterior probability of HR less than 1 being greater than 90%, was powered at 86%.

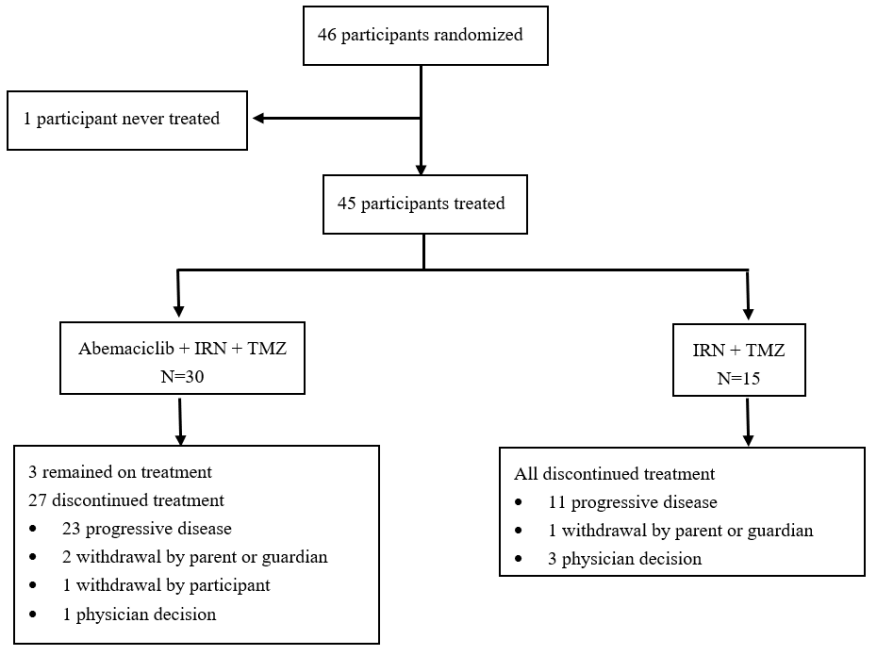
The primary objective of study JP04 was to characterise the efficacy of abemaciclib in combination with IRN and TMZ in participants with relapsed or refractory EWS by PFS by BIRC. Secondary objectives included safety, clinical activity, PK, and acceptability and palatability of the age-appropriate tablet or granule drug product, or both, of abemaciclib.

The primary analysis results are based on a database lock on 12 March 2025.

6.2. Results

6.2.1. Participant flow

Figure 2. Study participant disposition figure.



6.2.2. Baseline data

Table 1. Demographic Summary

Characteristics	Abemaciclib + IRN + TMZ N=30	IRN + TMZ N=16	Total N=46
Sex, n (%)			
Female	9 (30.0)	4 (25.0)	13 (28.3)
Male	21 (70.0)	12 (75.0)	33 (71.7)
Age (years)			
Mean (SD)	16.7	17.1	16.8
Median	16.5	16.0	16.0
Min-Max	3-35	7-32	3-35
Age categories			
<12 years	6 (20.0)	3 (18.8)	9 (19.6)
12-<18 years	12 (40.0)	6 (37.5)	18 (39.1)
≥18 years	12 (40.0)	7 (43.8)	19 (41.3)
Race, n (%)			
White	18 (60.0)	11 (68.8)	29 (63.0)
Asian	7 (23.3)	2 (12.5)	9 (19.6)
Black or African American	0	1 (6.3)	1 (2.2)
Not Reported	5 (16.7)	2 (12.5)	7 (15.2)
Country, n (%)			
Australia	1 (3.3)	0	1 (2.2)

Characteristics	Abemaciclib + IRN + TMZ N=30	IRN + TMZ N=16	Total N=46
France	4 (13.3)	3 (18.8)	7 (15.2)
Germany	1 (3.3)	2 (12.5)	3 (6.5)
Italy	5 (16.7)	0	5 (10.9)
Japan	7 (23.3)	2 (12.5)	9 (19.6)
Spain	9 (30.0)	7 (43.8)	16 (34.8)
United States	3 (10.0)	2 (12.5)	5 (10.9)
Weight (kg)			
Mean (SD)	54.52 (21.96)	56.23 (23.79)	55.11 (22.36)
Median	52.65	51.60	51.60
Min-Max	14.6-107.8	15.6-95.3	14.6-107.8
Body surface area (m^2)			
Mean (SD)	1.53 (0.40)	1.55 (0.40)	1.54 (0.39)
Median	1.54	1.52	1.52
Min-Max	0.6-2.3	0.7-2.1	0.6-2.3

Abbreviations: IRN = irinotecan; Min = minimum; Max = maximum; n = number of participants in the specified category; N = number of participants in population; SD = standard deviation; TMZ = temozolomide.

[a] Number of participants with nonmissing data, used as denominator.

Source: Table 6.1, clinical overview

Table 2. Baseline Disease Characteristics

Characteristics	Abemaciclib + IRN + TMZ N=30 n (%)	IRN + TMZ N=16 n (%)	Total N=46 n (%)
Pathological diagnosis			
Ewing Sarcoma[a]	25 (83.3)	14 (87.5)	39 (84.8)
Ewing-Like Sarcoma	5 (16.7)	2 (12.5)	7 (15.2)
Time from Initial Diagnosis to First Recurrence			
<2 years	26 (86.7)	11 (68.8)	37 (80.4)
≥2 years	4 (13.3)	5 (31.3)	9 (19.6)
Disease Status at Study Entry			
Relapsed	24 (80.0)	13 (81.3)	37 (80.4)
Refractory	6 (20.0)	3 (18.8)	9 (19.6)
Original Disease Location			
Axial Skeleton	15 (50.0)	3 (18.8)	18 (39.1)
Non Axial	15 (50.0)	13 (81.3)	28 (60.9)
Metastases at Study Entry			
Isolated Pulmonary Metastases	6 (20.0)	5 (31.3)	11 (23.9)
Other Metastases	22 (73.3)	10 (62.5)	32 (69.6)
No Metastases	2 (6.7)	1 (6.3)	3 (6.5)
Disease Stage at Study Entry			
Stage II	1 (3.3)	0	1 (2.2)
Stage III	0	1 (6.3)	1 (2.2)
Stage IV	28 (93.3)	15 (93.8)	43 (93.5)
Missing	1 (3.3)	0	1 (2.2)
Disease Stage at Initial diagnosis			
Stage I	0	2 (12.5)	2 (4.3)
Stage II	5 (16.7)	2 (12.5)	7 (15.2)
Stage III	5 (16.7)	2 (12.5)	7 (15.2)
Stage IV	17 (56.7)	8 (50.0)	25 (54.3)
Unknown	3 (10.0)	1 (6.3)	4 (8.7)
Missing	0	1 (6.3)	1 (2.2)

Abbreviations: IRN = irinotecan; N = number of participants in population; n = number of participants in the specified category; N = number of participants in population; TMZ = temozolomide.

[a] One participant randomized to the abemaciclib + IRN + TMZ treatment arm was retrospectively diagnosed with lymphoblastic lymphoma of the bone instead of Ewing Sarcoma after enrollment.

[b] Participant with "missing" Lansky score had a Lansky score of 100% during screening but never started study treatment and, therefore, does not have a calculable baseline score.

6.2.3. Efficacy

The primary outcome analysis for PFS by BIRC implemented a Bayesian model with control arm augmentation using historical control data from the following publications: Blanchette et al. 2015, Casey et al. 2009, and Kurucu et al. 2015. In total, 42 PFS events from 64 sarcoma patients were extracted from the publications.

Table 3. Summary of efficacy

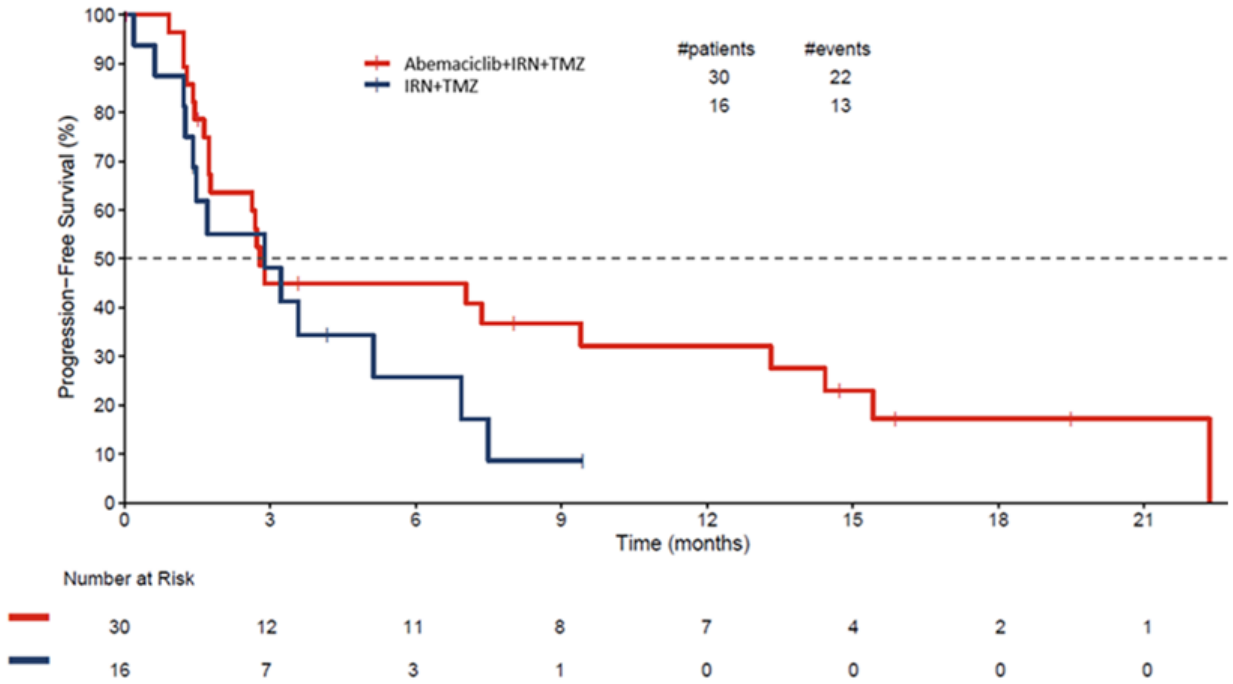
	Abemaciclib + IRN +TMZ N = 30	**IRN + TMZ N = 16**	**Effect Size Abemaciclib + IRN + TMZ vs. IRN + TMZ**	
			Bayesian Control Arm Augmentation	Frequentist Cox PH
PFS by BIRC				
Number of events (%)	22 (73.3)	13 (81.3)	HR = 0.53 80% CI: (0.32, 0.78) Prob (HR <1) = 0.97	HR = 0.64 95% CI: (0.28, 1.45) Nominal p=0.28
Median PFS, months	2.8	2.9		
PFS by Investigator				
Number of events (%)	24 (80.0)	13 (81.3)	HR = 0.68 80% CI: (0.41, 1.01) Prob (HR <1) = 0.90	HR = 0.71 95% CI: (0.32, 1.58) Nominal p=0.40
Median PFS, months	2.9	3.8		
Overall Survival				
Number of events (%)	15 (50.0)	9 (56.3)	NA	HR = 0.67 95% CI: (0.26, 1.75) Nominal p=0.41
ORR by BIRC (%)	3 (10.0)	4 (25.0)	NA	NA
ORR by Investigator (%)	5 (16.7)	3 (18.8)	NA	NA
DCR by BIRC (%)	18 (60.0)	8 (50.0)	NA	NA
DCR by Investigator (%)	18 (60.0)	9 (56.3)	NA	NA

Abbreviations: BIRC = blinded independent review committee; BOR = best overall response; CI = confidence interval; CR = complete response; DCR = disease control rate; HR = hazard ratio; IRN = IRN; N = total number of participants in the population within the treatment arm; NA = not applicable; ORR = overall response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PH = proportional hazard; PR = partial response; SD = stable disease; TMZ = temozolomide.

Note: ORR corresponds to BOR of CR or PR. DCR corresponds to BOR of CR, PR, SD, or non-CR/non-PD.

Figure 3 summarises PFS by BIRC using the Kaplan-Meier method with median PFS estimates of 2.8 and 2.9 months in the abemaciclib plus IRN and TMZ and IRN and TMZ arms, respectively.

Figure 3. Kaplan-Meier curves of PFS by BIRC



Abbreviations: BIRC = blinded independent review committee; CI = confidence interval; HR = hazard ratio; IRN = irinotecan; PFS = progression-free survival; TMZ = temozolomide.

6.3. Discussion

A total of 46 participants were included in the efficacy analyses. Most participants had relapsed disease, stage IV at study entry, and had received a median of 2 prior lines of systemic therapy. Baseline demographics and disease characteristics were generally well balanced. The median age was 16.0 (range: 3 to 35) years, with 58.7% of participants aged less than 18 years. The abemaciclib plus IRN and TMZ arm had more participants with axial skeleton disease as original disease location (50.0% and 18.8%, respectively) and more participants with time from initial diagnosis to first recurrence less than 2 years (86.7% and 68.8%, respectively).

Although study JP04 for EWS met its primary objective with respect to PFS by BIRC under Bayesian analysis using a control arm augmented with historical data, the prespecified Bayesian exponential model appears to overestimate the PFS curve in the abemaciclib arm, thus biasing effect size estimation relative to the control arm. In addition, sensitivity analysis of the primary efficacy endpoint using traditional frequentist approach did not demonstrate improved PFS by BIRC. Median PFS was 2.8 months in the abemaciclib + IRN +TMZ arm and 2.9 months in the IRN +TMZ control arm. Taken together, the primary analysis results should be interpreted with caution.

Furthermore, other efficacy endpoints including ORR failed to show benefit with add-on abemaciclib in this patient population. OS data were immature and did not indicate survival benefit (HR = 0.67, 95% CI: (0.26, 1.75).

No benefit was seen with the add-on of abemaciclib to IRN+TMZ.

The proposed update to section 5.1 is considered acceptable.

6.4. Conclusion

The totality of evidence indicates that add-on abemaciclib to IRN and TMZ does not lead to a favourable benefit-risk balance for patients with relapsed or refractory EWS when compared to the combination of IRN and TMZ.

To inform the healthcare professionals of the available information for EWS, section 5.1 *Paediatric population* of the abemaciclib SmPC is being updated with appropriate information on the study JP04.

7. Clinical Safety aspects

7.1. Adverse events

Table 4. Overview of adverse events

Participants[a]	Abemaciclib + IRN + TMZ N=30 n (%)	IRN + TMZ N=15 n (%)	Total N=45 n (%)
≥1 TEAE	30 (100.0)	15 (100.0)	45 (100.0)
Related to Study Treatment[b]	30 (100.0)	15 (100.0)	45 (100.0)
≥1 CTCAE Grade ≥3 TEAE	24 (80.0)	11 (73.3)	35 (77.8)
Related to Study Treatment[b]	23 (76.7)	6 (40.0)	29 (64.4)
≥1 CTCAE Grade ≥4 TEAE	14 (46.7)	2 (13.3)	16 (35.6)
Related to Study Treatment[b]	11 (36.7)	2 (13.3)	13 (28.9)
≥1 SAE	12 (40.0)	5 (33.3)	17 (37.8)
Related to Study Treatment[b]	8 (26.7)	3 (20.0)	11 (24.4)
Discontinued study treatment due to AE	0	0	0
Discontinued study treatment due to SAE	0	0	0
Died due to AE on study treatment	0	0	0
Died due to AE within 30 days of discontinuation from study treatment	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; IRN = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; N = number of participants in safety population; n = number of participants in the specified category; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TMZ = temozolomide.

[a] Participants may be counted in more than 1 category.

[b] Includes events that were considered related to study treatment as judged by the investigator.

Note: Discontinued study treatment refers to discontinuation of all study drug. For example, discontinuation of only 1 study drug would not be counted.

MedDRA Version 27.1; CTCAE Version 5.

Table 5. Summary of All Causality TEAEs by Consolidated Term in at Least 10% of Participants

Consolidated Term	Abemaciclib + IRN + TMZ N=30			IRN + TMZ N=15			Total N=45		
	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)	Any Grade n (%)	Grade 3 n (%)	Grade 4 n (%)
Participants with ≥1 TEAE	30 (100)	10 (33.3)	14 (46.7)	15 (100)	9 (60.0)	2 (13.3)	45 (100)	19 (42.2)	16 (35.6)
Diarrhoea	29 (96.7)	3 (10.0)	0	13 (86.7)	0	0	42 (93.3)	3 (6.7)	0
Thrombocytopenia	22 (73.3)	6 (20.0)	5 (16.7)	5 (33.3)	2 (13.3)	0	27 (60.0)	8 (17.8)	5 (11.1)
Abdominal pain	18 (60.0)	2 (6.7)	0	8 (53.3)	1 (6.7)	0	26 (57.8)	3 (6.7)	0
Anaemia	19 (63.3)	11 (36.7)	1 (3.3)	6 (40.0)	2 (13.3)	0	25 (55.6)	13 (28.9)	1 (2.2)
Nausea	17 (56.7)	2 (6.7)	0	7 (46.7)	0	0	24 (53.3)	2 (4.4)	0
Neutropenia	18 (60.0)	6 (20.0)	9 (30.0)	5 (33.3)	2 (13.3)	1 (6.7)	23 (51.1)	8 (17.8)	10 (22.2)
Vomiting	16 (53.3)	3 (10.0)	0	5 (33.3)	0	0	21 (46.7)	3 (6.7)	0
Pyrexia	12 (40.0)	0	0	6 (40.0)	1 (6.7)	0	18 (40.0)	1 (2.2)	0
Leukopenia	12 (40.0)	5 (16.7)	0	4 (26.7)	3 (20.0)	0	16 (35.6)	8 (17.8)	0
Hypokalaemia	10 (33.3)	2 (6.7)	0	1 (6.7)	0	1 (6.7)	11 (24.4)	2 (4.4)	1 (2.2)
Lymphopenia	7 (23.3)	5 (16.7)	0	4 (26.7)	2 (13.3)	1 (6.7)	11 (24.4)	7 (15.6)	1 (2.2)
ALT increased	7 (23.3)	0	0	3 (20.0)	2 (13.3)	0	10 (22.2)	2 (4.4)	0
AST increased	7 (23.3)	0	0	3 (20.0)	0	0	10 (22.2)	0	0
Fatigue	7 (23.3)	0	0	3 (20.0)	0	0	10 (22.2)	0	0
Decreased appetite	6 (20.0)	2 (6.7)	0	3 (20.0)	0	0	9 (20.0)	2 (4.4)	0
Hyponatraemia	6 (20.0)	1 (3.3)	0	2 (13.3)	0	0	8 (17.8)	1 (2.2)	0
Headache	5 (16.7)	0	0	2 (13.3)	0	0	7 (15.6)	0	0
Blood creatinine increased	6 (20.0)	0	0	0	0	0	6 (13.3)	0	0
Constipation	2 (6.7)	0	0	3 (20.0)	0	0	5 (11.1)	0	0
Hypoalbuminaemia	4 (13.3)	0	0	1 (6.7)	0	0	5 (11.1)	0	0
Insomnia	5 (16.7)	0	0	0	0	0	5 (11.1)	0	0
Nasopharyngitis	3 (10.0)	0	0	2 (13.3)	0	0	5 (11.1)	0	0
Pain in extremity	2 (6.7)	0	0	3 (20.0)	1 (6.7)	0	5 (11.1)	1 (2.2)	0

Abbreviations: ALT = alanine aminotransferase increased; AST = aspartate aminotransferase increased; CTCAE = Common Terminology Criteria for Adverse Events; IRN = irinotecan; MedDRA = Medical Dictionary for Regulatory Activities; n = number of participants in the specified category; N = number of participants in safety population; TEAE = treatment-emergent adverse event; TMZ = temozolomide.

7.2. Deaths

	Abemaciclib + IRN + TMZ N=30 n (%)	IRN + TMZ N=15 n (%)	Total N=45 n (%)
All Deaths	15 (50.0)	8 (53.3)	23 (51.1)
Deaths on treatment	0	0	0
Deaths within 30 days of treatment discontinuation	3 (10.0)	0	3 (6.7)
Reasons for death: study disease	3 (10.0)	0	3 (6.7)
Deaths after 30 days of treatment discontinuation	12 (40.0)	8 (53.3)	20 (44.4)
Reasons for death: study disease	12 (40.0)	8 (53.3)	20 (44.4)

7.3. Discontinuation due to AE

Table 6. Summary of Treatment Discontinuations and or Dose Modifications due to AEs

	Abemaciclib + IRN + TMZ N=30			IRN + TMZ N=15	
Category, n (%)	Abemaciclib	IRN	TMZ	IRN	TMZ
Participants with ≥1 Dose Reduction due to AE	14 (46.7)	11 (36.7)	8 (26.7)	2 (13.3)	0
Participants with ≥1 Dose Omission due to AE	22 (73.3)	2 (6.7)	1 (3.3)	2 (13.3)	1 (6.7)
AE leading to discontinuation of individual drug	1 (3.3)	0	3 (10.0)	0	0

Abbreviations: AE = adverse event; IRN = irinotecan; n = number of participants; N = total number of participants in the population within the treatment arm; TMZ = temozolomide.

7.4. Discussion

TEAEs of at least Grade 3 related (per investigator assessment) to study treatment were more prevalent in the abemaciclib plus IRN and TMZ group (76.7%) compared to the IRN and TMZ group (40.0%).

Most TEAEs were low-grade. Notably, the group receiving abemaciclib plus IRN and TMZ experienced a higher incidence of haematological and gastrointestinal toxicities. Additionally, the abemaciclib group showed a higher rate of Grade 4 haematological toxicity (46.7% vs. 13.3%). Diarrhoea was the most common TEAE, affecting 96.7% of participants in the abemaciclib plus IRN and TMZ group and 86.7% in the IRN and TMZ group.

There were more dose modifications and treatment discontinuations of IRN or TMZ, or both, due to AEs in the abemaciclib group.

Dose modifications and discontinuations of IRN or TMZ, or both, due to AEs were more frequent in the abemaciclib arm.

Safety data were generally consistent with the known abemaciclib, IRN, and TMZ profiles.

8. Changes to the Product Information

As a result of this variation, section 5.1 of the SmPC is being updated to include results from the paedistric study J1S-MC-JP04.

9. Request for supplementary information

9.1. Major objections

None.

9.2. Other concerns

Clinical aspects

10. Assessment of the responses to the request for supplementary information (within round 1)

10.1. Major objections

N/A

10.2. Other concerns

Clinical aspects

Question 1. The proposed addition to 5.1 requires revision in line with the annotated SmPC.

Summary of the MAH's response

Section 5.1 has been amended in accordance with the CHMP Rapporteur's comments.

Assessment of the MAH's response

The MAH has amended the proposed addition to section 5.1 in accordance with the comments.

Conclusion

☒ Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance