Amsterdam, 25 April 2025
EMADOC-1700519818-1902684
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ibrance

International non-proprietary name: Palbociclib

Procedure No. EMA/PAM/0000250384

Note

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

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Table of contents

1. Introduction

On 7 February 2025, the MAH submitted a completed paediatric study (study A5481092: Ewing sarcoma cohort) for IBRANCE, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH has submitted the final result of study A5481092. The primary analysis of this study were previously assessed within the procedure EMEA/H/C/003853/P46/006. The MAH stated that study A5481092 is the clinical measure of the agreed palbociclib paediatric investigational plan (PIP) in the treatment of Ewing sarcoma (EWS).

The MAH does not consider that a change to the palbociclib Product Information is warranted at this stage. An update of the Product Information to include the results of all the measures agreed in the palbociclib PIP in recurrent or refractory (r/r) EWS was made as part of the Type II variation, EMEA/H/C/003853/II/0045.

2.2. Information on the pharmaceutical formulation used in the study

Palbociclib was administered either as capsule or oral solution (concentration 25 mg/ml).

2.3. Clinical aspects

2.3.1. Introduction

Palbociclib (IBRANCE®) is a small molecule inhibitor of cyclin-dependent kinases (CDK) 4 and 6, administered orally. It is approved in the EU for the treatment of patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy or in combination with fulvestrant in patients with disease progression following endocrine therapy.

Paediatric Ewing sarcoma (EWS) is an aggressive bone and soft tissue tumour mediated by somatic chromosomal translocations resulting in the expression of chimeric fusions of EWS and ETS family transcription factors. There is an increasing body of literature showing the dependency of paediatric tumour cells on CDK4/6 and cyclin D1 including EWS and myeloid and lymphoblastic leukaemia to support the use of CDK4/6 inhibitors.

The antitumor activity of palbociclib in combination with the chemotherapy regimen, temozolomide (TMZ) and irinotecan (IRN) has been investigated in 3 different patient-derived EWS models grown subcutaneously in immunocompromised mice. The findings indicated a potential antitumor benefit of adding palbociclib, a CDK4/6 inhibitor, to a combination of a topoisomerase inhibitor (e.g. IRN or topotecan (TOPO) and an alkylating agent (e.g. TMZ or cyclophosphamide [CTX]).

Study A5481092 was a phase I/II multicentre, open-label study to evaluate palbociclib in combination with either irinotecan and temozolomide or in combination with topotecan and cyclophosphamide in paediatric patients with recurrent or refractory (r/r) solid tumours. The study consisted of a non-

randomized phase I portion for r/r solid tumours followed by a potential non-randomized Tumour Specific Cohort (TSC) and a randomized phase II portion for r/r EWS.

The randomized phase II portion of the study crossed the pre-specified futility boundary at the pre-planned interim analysis (IA) and therefore did not meet its primary endpoint of EFS based on investigator assessment. The external Data Monitoring Committee (eDMC) recommended that enrolment to the phase II portion of the study be stopped for lack of efficacy.

The phase I data was reviewed within the procedure EMEA/H/C/003853/P46/006. No new data is available from this part of the study.

Also the primary analysis of the phase II portion was submitted within the previous article P46 procedure EMEA/H/C/003853/P46/006, and it was concluded that efficacy of palbociclib in combination with irinotecan and temozolomide in paediatric EWS had not been demonstrated.

With the current submission, the MAH provided the final analysis of the phase II portion of the study, and in addition the data from the TSC cohort (neuroblastoma (NB)) is submitted.

2.3.2. Clinical study - Clinical study A5481092

2.3.2.1. Description

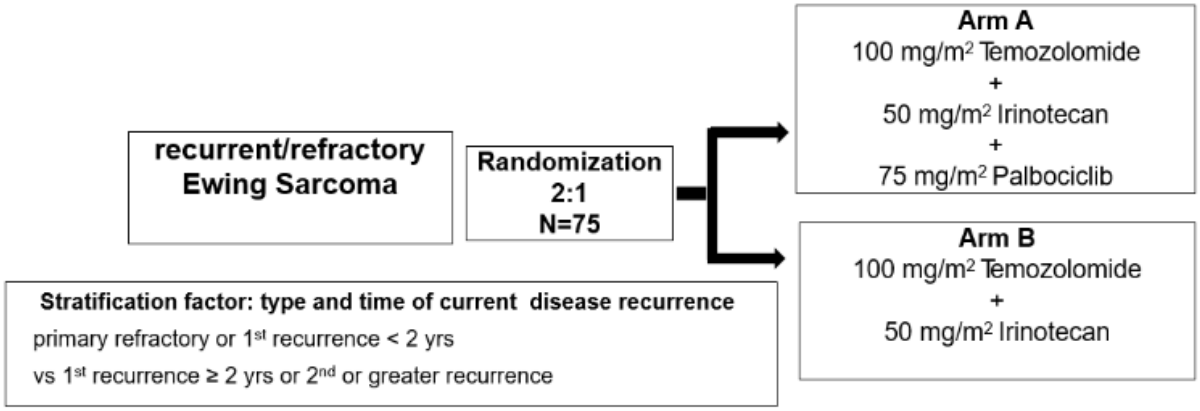
Study A5481092 is a phase I/II multicentre, open-label study to evaluate palbociclib in combination with either Irinotecan (IRN) and Temozolomide (TMZ) or Topotecan (TOPO) and Cyclophosphamide (CTX) chemotherapy in children, adolescents and young adults with r/r solid tumours. The study consists of a non-randomized phase I portion for participants with r/r solid tumours followed by potential non-randomized tumour specific cohort(s) (TSC) and a randomized phase II portion for participants with r/r Ewing sarcoma (EWS). The phase II portion is part of the agreed PIP for palbociclib in the treatment of EFS.

The phase I portion of the study was to estimate the MTD/potential RP2D and to confirm the RP2D of palbociclib in combination with IRN and TMZ and palbociclib in combination with TOPO and CTX in participants with r/r solid tumours for whom no standard therapy was available.

Once the RP2D was confirmed for the combination of palbociclib with IRN and TMZ in the phase I portion of the study, the phase II portion of the study was initiated to compare the efficacy of palbociclib in combination with IRN and TMZ versus IRN and TMZ alone in children, adolescents, and young adults with r/r EWS for whom no standard therapy was available. Approximately 75 participants were to be randomized in a 2:1 ratio to receive either palbociclib in combination with IRN and TMZ (Arm A: approximately 50 participants) or IRN and TMZ chemotherapy alone (Arm B: approximately 25 participants). Randomization was stratified using block randomization by type and time of current disease recurrence (primary refractory or 1st recurrence <2 years versus 1st recurrence ≥2 years since completion of 1st line treatment or 2nd or greater recurrence). The schema is shown in Figure 1.

If 2 or more patients from dose escalation / dose determination part and / or dose expansion cohorts showed a confirmed objective response in a specific tumour type (e.g. neuroblastoma, rhabdomyosarcoma, rhabdoid tumour or medulloblastoma, etc…), a TSC with a maximum of 21 patients per cohort was to be opened to further evaluate antitumor activity of palbociclib in combination with IRN and TMZ or TOPO and CTX in each specific tumour type using a modified Simon's 2-stage optimal design.

Figure 1. Study Schema – Phase 2 Palbociclib in Combination With IRN and TMZ in Ewing sarcoma (EWS)



2.3.2.2. Objective(s) and endpoints

	Primary objectives	**Endpoints**
Dose escalation/dose determination parts	To estimate the MTD for the combination of palbociclib, TMZ and IRN in children, adolescents, and young adults with r/r solid tumours. To determine the potential RP2D for palbociclib in combination with TOPO and CTX in children, adolescents, and young adults with r/r solid tumours	First cycle DLTs
Dose expansion cohort	To evaluate the safety, and confirm the RP2D for the combination of palbociclib, TMZ, and IRN at the MTD in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor. To evaluate the safety, and confirm the RP2D for the combination palbociclib CTX, and TOPO in children, adolescents and young adults with r/r solid tumours that are known to be sensitive to a CDK4/6 inhibitor.	AEs as characterized by type, frequency, severity, timing, seriousness, and relationship to study therapy; laboratory test data including HbA1c as characterized by type, frequency, severity, and timing; ECG parameters, and vital signs
	To evaluate the preliminary antitumor activity of palbociclib combined with TMZ and IRN. To evaluate the preliminary antitumor activity of palbociclib combined with TOPO and CTX	OR, as assessed by investigator using RECIST version 1.1/modified RANO for CNS malignancies/INRC for neuroblastoma
Randomised Phase 2	To compare the efficacy of palbociclib in combination with TMZ and IRN vs TMZ and IRN chemotherapy alone in the treatment of children, adolescents, and young adults with r/r EWS	EFS based on investigator assessment

Abbreviations: AEs, adverse events; DLT, dose limiting toxicity, EFS, event-free survival; OR, objective response

2.3.2.3. Participant flow

A total of 128 participants (aged ≥2 and <21 years at the time of study entry) with r/r solid tumours were enrolled at 110 centres in 19 countries.

Phase 2

As of the cut-off date of 26 August 2024, a total of 81 participants were screened, of which 63 participants were enrolled (42 to the palbociclib + IRN +TMZ arm and 21 to the IRN + TMZ arm) and 62 (98.4%) participants (41 in the palbociclib + IRN +TMZ arm and 21 in the IRN + TMZ arm) were treated. Specifically:

- A total of 42 (100%) and 21 (100%) in the palbociclib + IRN + TMZ arm and the IRN + TMZ arm, respectively, were entered into the treatment phase and all of them discontinued treatment. The most common reason for discontinuation was progressive disease (73.8% and 57.1%, respectively). No participants completed the treatment phase in either arm.
- A total of 37 (88.1%) and 20 (95.2%) participants in the palbociclib + IRN + TMZ arm and the IRN + TMZ arm, respectively, entered the follow-up period. Of these participants, 27 (64.3%) and 16 (76.2%) participants discontinued with the most common reason being death (57.1% and 61.9%, respectively); 10 (23.8%) and 4 (19.0%) participants were still under follow-up. No participants in either arm completed the follow-up period.

TSC

Two participants with r/r neuroblastoma (NB) from the phase I dose determination part and dose expansion cohort treated with palbociclib plus TOPO and CTX showed the confirmed objective responses. Therefore, per protocol a non-randomized TSC for NB was opened, including additional 5 participants enrolled in stage 1.

A total of 7 participants with r/r NB treated with palbociclib plus TOPO and CTX were enrolled in stage 1, including 2 participants with r/r NB from dose determination part and dose expansion cohort. All 7 participants were treated. As of the cut-off date of 26 August 2024, 5 (71.4%) participants discontinued the treatment due to withdrawal by parent/guardian (2 participants) or progressive diseases (3 participants). 1 (14.3%) participant completed the treatment phase, and 1 (14.3%) participant was still under treatment.

Of 6 (85.7%) participants who entered the follow-up period, 2 (28.6%) participants discontinued from the study due to withdrawal by subject and death, respectively, 1 participant completed the study, and 3 participants were still under follow-up.

2.3.2.4. Demographics

Phase 2

Among the 63 participants randomized, demographic characteristics and baseline characteristics are shown below:

- The median age (range) was 13.5 (5, 19) years in the palbociclib + IRN + TMZ arm and 15.0 (6, 20) years in the IRN + TMZ arm, with most participants aged <18 years old in both arms (36 [85.7%] in the palbociclib + IRN + TMZ arm and 18 [85.7%] in the IRN + TMZ arm).
- Most of the participants were male (33 [78.6%] in the palbociclib + IRN + TMZ arm and 12 [57.1%] in the IRN + TMZ arm).

- More than half of participants were White (23 [54.8%] in the palbociclib + IRN + TMZ arm and 12 [57.1%] in the IRN + TMZ arm) followed by Asian (12 [28.6%] in the palbociclib + IRN + TMZ arm and 6 [28.6%] in the IRN + TMZ arm).
- ECOG PS was examined for participants >16 years. Comparing the palbociclib + IRN + TMZ arm to the IRN + TMZ arm, 9.5% versus 14.3% of participants had a baseline ECOG PS of 0, 11.9% versus 14.3% of participants had a baseline ECOG PS of 1, and 2.4% of participants versus none had a baseline ECOG PS of 2.
- Lansky PS was examined for participants ≤16 years. Comparing the palbociclib + IRN + TMZ arm to the IRN + TMZ arm, 2.4% versus none of participants had a baseline Lansky PS of 50-60%, 31.0% versus 14.3% of participants had a baseline Lansky PS of 70-80%, and 47.6% versus 57.1% of participants had a baseline Lansky PS of 90-100%.
- In the palbociclib + IRN + TMZ arm, 12 (28.6%), 7 (16.7%), 3 (7.1%), 8 (19.0%), and 11 (26.2%) participants had Tanner stage 1, 2, 3, 4, and 5, respectively. In the IRN + TMZ arm, 4 (19.0%), 4 (19.0%), 1 (4.8%), 4 (19.0%), and 8 (38.1%) participants had Tanner stage 1, 2, 3, 4, and 5, respectively.
- Type and time of current disease recurrence were balanced between the 2 arms (both 71.4% of participants had primary refractory or first recurrence <2 years and both 28.6% of participants had first recurrence ≥2 years or second or greater recurrence).
- The majority of participants had metastatic recurrence in both arms (81.0% in the palbociclib + IRN + TMZ arm and 85.7% in the IRN + TMZ arm) and most had measurable disease (76.2% in the palbociclib + IRN + TMZ arm and 95.2% in the IRN + TMZ arm).

TSC

Most participants were female (5, 71.4%); the median age was 7.0 years (range: 3, 16), with most participants under 12 (exclusive) years old (3 [42.9%] participants in each ≤6 years old and >6 to <12, respectively); most of the participants were White (4, 57.1%) and were not Hispanic or Latino (6, 85.7%).

All participants aged 16 or younger, and most participants (6, 85.7%) had a baseline of 90-100% Lansky performance status. 1 (14.3%) participant had a baseline of 70-80% Lansky performance status.

Overall, 5 (71.4%), 1 (14.3%), and 1 (14.3%) participants had Tanner stage 1, 2, and 5, respectively.

2.3.2.5. Palbociclib exposure

Descriptive Summary of Steady-State Palbociclib Plasma PK Parameter palbociclib following 75 mg/m2 doses (administered orally QD), in combination with IRN + TMZ are summarized in the table below.

Median T_{max} of palbociclib was 4.00 hours. The palbociclib exposure on C1D5 based on AUC_T, C_{max}, and C_{trough} in EWS patients following 75 mg/m2 doses in combination with IRN + TMZ was similar to the exposure observed in this same treatment group in the non-TSC of phase I. C_{trough} palbociclib concentrations were comparable between visits C1D5, C1D6, C1D14, C2D5, and C2D14, and therefore, steady-state appeared to be achieved on C1D5. Inter-participant variability of palbociclib exposure on C1D5 based on CV% for AUC_T, C_{max},and C_{trough} was 38%, 49%, and 80%, respectively.

Table 1 Descriptive Summary of Steady-State Palbociclib Plasma PK Parameters (Phase 2) – PK Parameter Analysis Set (Protocol A5481092)

Parameter (Units)[a]	n	Palbociclib 75 mg/m2 + IRN 50 mg/m2 + TMZ 100 mg/m2 (N=38) Statistics
AUCTAU (h*ng/mL)	25	1525 (38)
CL/F (L/h/m2)	25	49.19 (38)
CL/F (L/h)	25	63.65 (53)
CMAX (ng/mL)	27	114.4 (49)
CTROUGH (ng/mL)	28	26.09 (80)
TMAX (h)	27	4.00 (1.68-8.00)

Source: Table 14.4.5.1.2.1.2
N = Total number of participants in the treatment group in the indicated population.
n = number of participants contributing to the summary statistics.
a. Geometric mean (geometric %coefficient of variation) for all except median (range) for Tmax.
Individual values are listed when there are less than 3 evaluable measurements.
Summaries include parameters derived from profiles that meet steady state criteria.
Samples with more than 30 mins time deviation when nominal TPD=0H are excluded from CTROUGH summaries.
Profiles with vomit comments from Dosing CRF page are excluded.
Make-up visits are included only if Cycle 1 Day 5 is not available/reportable.
PFIZER CONFIDENTIAL SDTM Creation: 29OCT2024 (00:45) Source Data: adpp Table Generation: 14NOV2024 (22:14)
Output File: ./A5481092/A5481092_CSR2_PK_Ph2/adpp_s101_1i

2.3.2.6. Efficacy results

Phase 2

Primary endpoint: Event-Free Survival Based on Investigator Assessment

Sensitivity Analyses for Event-Free Survival (EFS)

Per-protocol analysis of EFS in participants with molecularly confirmed EWS at initial diagnosis or relapse by pathology report (Sensitivity Analysis 4), a sensitivity analysis was performed excluding participants who were not confirmed by pathology report or central testing for molecularly confirmed EWS diagnosis.

Secondary Efficacy Endpoint: Overall Survival

As of the data cut-off date 26 August 2024, 24 (57.1%) deaths reported in the palbociclib + IRN + TMZ arm and 13 (61.9%) deaths were reported in the IRN + TMZ arm. The median OS was 10.64 months (95% CI: 8.44, 20.83) in the palbociclib + IRN + TMZ arm and 11.43 months (95% CI: 7.46, 19.02) in the IRN + TMZ arm. The HR of palbociclib + IRN + TMZ arm was 0.98 (95% CI: 0.50, 1.96). The median duration of follow-up for OS was 18.2 (95% CI: 11.17, 20.40) months for the palbociclib + IRN + TMZ arm and 18.33 (13.31, NE) for the IRN + TMZ arm.

TSC

Primary Efficacy Endpoint: Objective Response

The confirmed OR rates based on investigator assessment were 28.6% (2 participants, 80% CI: 12.5%, 52.8%) in TSC.

Secondary Efficacy Endpoint: Duration of Response

The analysis of DoR in TSC was limited by a small sample size of responders and could not be meaningfully interpreted.

Secondary Efficacy Endpoint: Progression-Free Survival

Of all 7 participants, 4 (57.1%) participants had progressive disease and 3 (42.9%) participants were still ongoing without an event. The median PFS was 1.97 months (95% CI: 1.08, NE).

Secondary Efficacy Endpoint: Overall Survival

As of the data cut-off date of 26 August 2024, OS data were immature. 1 (14.3%) death out of 7 participants was reported in TSC.

2.3.2.7. Safety results

Exposure

Phase 2

In the palbociclib + IRN + TMZ arm, the median duration of treatments was 1.8 months (range: 0.3, 8.5). The median relative dose intensity was 94.85% (range: 65.0%, 107.7%) for palbociclib, 94.11% (range: 60.0%, 102.4%) for IRN, and 93.93% (range: 31.9%, 102.4%) for TMZ.

In the IRN + TMZ arm, the median duration of treatment was 2.9 months (range: 0.2, 8.4). The median relative dose intensity was 100.0% (range: 73.3%, 102.4%) for IRN and 94.74% (range: 73.3%, 102.4%) for TMZ.

TSC

The median duration of treatments for all participants was 1.8 months (range: 0.3, 24.0). The median relative dose intensity was 95.0% (range: 66.7%, 100.0%) for palbociclib, 96.9% (range: 66.7%, 100.0%) for TOPO, and 96.9% (range: 66.7%, 100.0%) for CTX.

Summary of adverse events

Phase 2

As of the data cut-off date (26 August 2024), all treated 62 participants were evaluable for treatment emergent adverse events (TEAEs). Most participants experienced at least 1 all-causality TEAEs (92.7% in the palbociclib + IRN + TMZ arm and 95.2% in the IRN + TMZ arm) and treatment-related TEAEs (87.8% in the palbociclib + IRN + TMZ arm and 90.5% in the IRN + TMZ arm). Most participants experienced at least 1 non-serious TEAEs (92.7% in the palbociclib + IRN + TMZ arm and 95.2% in the IRN + TMZ arm)

- The incidence of participants who had all-causality serious adverse events (SAEs) in the palbociclib + IRN + TMZ arm (36.6%) was higher than the IRN + TMZ arm (19.0%); the incidence of treatment-related SAEs was similar between the palbociclib + IRN + TMZ arm (17.1%) and the IRN + TMZ arm (14.3%).
- The incidence of participants that had all-causality and treatment-related maximum Grade 3 or 4 TEAEs were similar between the palbociclib + IRN + TMZ arm and the IRN + TMZ arm (all-causality: 82.9% versus 81.0%, treatment-related: 78.0% versus 76.2%).

- One (2.4%) participant in the palbociclib + IRN + TMZ arm had all-causality Grade 5 AEs, which were not related to the study treatments.
- The incidence of participants with all-causality and treatment-related TEAEs leading to permanent treatment discontinuation were low in the palbociclib + IRN + TMZ and the IRN + TMZ arm (all-causality: 4.9% versus 9.5%, treatment-related: 2.4% versus 9.5%).
- One (2.4%) participant in the palbociclib + IRN + TMZ and 4 (19.0%) participants in the IRN + TMZ arm had all-causality TEAEs leading to dose reduction of any study treatments; all TEAEs were treatment related.
- The incidence of participants who had both all-causality and treatment-related TEAEs leading to dose interruption of any study treatments was higher in the palbociclib + IRN + TMZ arm than in the IRN + TMZ arm (all-causality: 68.3% versus 47.6%, treatment-related: 61.0% versus 47.6%).

TSC

As of the data cut-off date (26 August 2024):

- All 7 participants were evaluable for TEAEs and had at least 1 all-causality and treatment related TEAEs. A total of 124 all-causality TEAEs were reported, of which 70 TEAEs were considered treatment-related. All 7 participants had non-serious TEAEs.
- All-causality SAEs were reported in 4 (57.1%) participants, and 2 (28.6%) participants had treatment-related SAEs.
- All 7 participants had maximum Grade 3 or 4 all-causality and treatment related TEAEs. No participants had Grade 5 TEAEs
- No participants discontinued from the study intervention due to TEAEs.

All-Causality AEs and Treatment-related AEs

Phase 2

The incidence of all-causality and treatment-related TEAEs were generally similar across 2 arms, except that the incidence of neutropenia was reported more in the palbociclib + IRN + TMZ arm than in the IRN + TMZ arm (65.9% versus 42.9% for all-causality neutropenia and 63.4% versus 42.9% for treatment-related neutropenia).

Specifically, among all-causality TEAEs:

- The most common (reported in ≥25% participants) TEAEs (by either CLUSTER or PT) in the palbociclib + IRN + TMZ arm were neutropenia (65.9%), vomiting (36.6%), leukopenia (31.7%), diarrhoea (31.7%), anaemia (29.3%), nausea (26.8%) and thrombocytopenia (24.4%).
- The most common (reported in ≥25% participants) TEAEs (by either CLUSTER or PT) in the IRN + TMZ arm were neutropenia, diarrhoea (both were 42.9%), leukopenia, anaemia, thrombocytopenia (all were 28.6%).
- 1 participant in the palbociclib + IRN + TMZ arm reported a Grade 5 all-causality TEAE of Neoplasm progression that leading to death.

Among treatment-related TEAEs,

- The most common (reported in ≥25% participants) TEAEs (by either CLUSTER or PT) in the palbociclib + IRN + TMZ were neutropenia (63.4%), leukopenia, vomiting (both were 31.7%), and Diarrhoea (29.3%).
- The most common (reported in ≥25% participants) TEAEs (by either CLUSTER or PT) in the IRN + TMZ arm were neutropenia, diarrhoea (both were 42.9%), leukopenia and thrombocytopenia (both were 28.6%).

TSC

All treated 7 participants were evaluable for TEAEs and they all had at least 1 all-causality TEAE and at least 1 treatment-related TEAEs. All participants had at least 1 maximum Grade 4 TEAEs. No Grade 5 TEAEs were reported.

Among all-causality TEAEs, the most common (reported in ≥50% participants) TEAEs (by either CLUSTER or PT) were anaemia, thrombocytopenia (both were 100.0%), neutropenia (85.7%), infections and Nausea (both were 71.4%), Aspartate aminotransferase increased, diarrhoea, leukopenia, vomiting (all were 57.1%).

Among treatment-related TEAEs, the most common (reported in ≥50% participants) TEAEs (by either CLUSTER or PT) were anaemia, thrombocytopenia (both were 100.0%), neutropenia (85.7%), diarrhoea, leukopenia, and nausea (all were 57.1%).

All-Causality SAEs and Treatment-related SAEs

Phase 2

The incidence of participants with all-causality SAEs in the palbociclib + IRN + TMZ arm (15 [36.6%] participants) was higher than the IRN + TMZ arm (4 [19.0%] participants). The incidence of participants with maximum Grade 3 or 4 SAEs were 24.4% in the palbociclib + IRN + TMZ arm and 19.0% in the IRN + TMZ arm. 1 (2.4%) participant in the palbociclib + IRN + TMZ arm reported maximum Grade 5 SAE.

Treatment-related SAEs occurred in 7 (17.1%) participants in the palbociclib + IRN + TMZ arm and 3 (14.3%) participants in the IRN + TMZ arm, and all treatment-related SAEs were maximum Grade 3 or 4.

Most all-causality and treatment-related SAEs occurred in 1 participant each in both arms.

All-causality SAEs (by either CLUSTER or PT) reported in >1 participant were infections (6 [14.6%] participants in the palbociclib + IRN + TMZ arm and 1 [4.8%] participant in the IRN + TMZ arm), febrile neutropenia (4 [9.8%] participants in the palbociclib + IRN + TMZ arm and none in the IRN + TMZ arm).

Treatment-related SAEs (by either CLUSTER or PT) reported in >1 participant were febrile neutropenia (4 [9.8%] participants in the palbociclib + IRN + TMZ arm and none the IRN + TMZ arm), infections (2 [4.9%] participants in the palbociclib + IRN + TMZ arm and none in the IRN + TMZ arm).

TSC

- A total of 5 all-causality SAEs were reported in 4 (57.1%) participants, of which 3 SAEs reported in 2 (28.6%) participants were considered treatment-related.
- Grade 3 or 4 all-causality SAEs were reported in 3 participants, of which 2 participants reported treatment-related SAEs. No Grade 5 SAEs were reported. None of SAEs led to permanent discontinuations or dose reduction of any study treatments.

Deaths

Phase 2

As of the data cut-off date (26 August 2024), 1 (2.4%) death in the palbociclib + IRN + TMZ arm was within 35 days after last dose of study treatments due to disease under study (neoplasm progression) and was not treatment-related. No deaths were reported in the IRN + TMZ arm.

During the follow-up period (greater than 35 days after last dose), a total of 36 (58.1%) deaths were reported including 23 (56.1%) deaths in the palbociclib + IRN + TMZ arm and 13 (61.9%) deaths in the IRN + TMZ arm. The primary cause of death for both arms was disease under study (22/23 in the palbociclib + IRN + TMZ arm and 13/13 in the IRN + TMZ arm).

TSC

There was 1 (14.3%) participant who died during follow-up period occurring greater than 35 days after last dose of study treatment due to disease under study which was not associated with any TEAEs.

Dose Modification and Discontinuations from Study Intervention Due to Adverse Events

Permanent Discontinuation of Study Intervention Due to AEs

Phase 2

There were 4 (6.5%) participants who had TEAEs leading to permanent discontinuation (2 [4.9%] participants in the palbociclib + IRN + TMZ arm and 2 [9.5%] participants in the IRN + TMZ arm), of which 3 (4.8%) were considered treatment-related (1 in the palbociclib + IRN + TMZ arm and 2 in the IRN + TMZ arm):

- One participant in the palbociclib + IRN + TMZ arm had a Grade 3 alanine aminotransferase increased and Grade 3 aspartate aminotransferase increased leading to permanent discontinuation of palbociclib, IRN, and TMZ. Both events were considered related to palbociclib, IRN, and TMZ. The event of aspartate aminotransferase increased was resolved, while alanine aminotransferase increased was not resolved at the time of the last report.
- One participant in the palbociclib + IRN + TMZ arm had a Grade 3 Swelling face leading to permanent discontinuation of palbociclib, IRN, and TMZ. This event was considered unrelated to palbociclib, IRN, and TMZ. This participant died due to progressive disease. This event was not resolved when the participant's death.
- One participant in the IRN + TMZ arm had a Grade 3 alanine aminotransferase increased leading to permanent discontinuation of IRN and TMZ. This event was considered related to IRN and TMZ. The participant withdrew consent by parent/guardian. Aspartate aminotransferase increased was resolved, while alanine aminotransferase increased was not resolved when the participant withdrew from the study.
- One participant in the IRN + TMZ arm had 2 periods of Grade 3 diarrhoea during Cycle 1, leading to a dose reduction of IRN and interruption of TMZ, then the Grade 3 diarrhoea was improved to Grade 2 after Cycle 2. The Grade 2 diarrhoea led to permanent discontinuation of IRN and TMZ. All 3 periods of diarrhoea were considered SAEs. This event was considered related to IRN but not related to TMZ. The outcome of this event was resolved.

TSC

No participants discontinued from the study intervention due to TEAEs. There was 1 (14.3%) participant who had a Grade 3 treatment-related TEAE of anaemia which was reported as the TEAE

leading to permanent discontinuation of palbociclib. This is corrected by an erratum due to this participant being withdrawn from study interventions by patient's parents and not due to a TEAE.

Dose Reduction Due to AEs

Phase 2

In the palbociclib + IRN + TMZ arm, there was 1 (2.4%) participant who had dose reduction of any study drug due to TEAEs of diarrhoea, nausea, and vomiting, all of which were considered treatment-related and leading to dose reduction of palbociclib.

In the IRN + TMZ arm, there were 4 (19.0%) participants who had dose reduction of either IRN or TMZ due to TEAEs of thrombocytopenia and diarrhoea, all of which were considered treatment-related.

TSC

A total of 2 (28.6%) participants had dose reduction of any study drugs due to TEAEs of neutropenia and thrombocytopenia, respectively. Both events were considered treatment-related. There was 1 participant who had dose reduction of palbociclib due to thrombocytopenia.

Dose Interruption Due to AEs

Phase 2

There were 28 (68.3%) participants in the palbociclib + IRN + TMZ arm who experienced all-causality TEAEs leading to dose interruption of any study treatments with most of TEAEs were considered treatment-related. The most common all-causality and treatment-related TEAEs (in ≥10% participants) were neutropenia (both were 48.8%) and thrombocytopenia (both were 14.6%).

- All participants (28 [68.3%] participants) had all-causality TEAEs leading to dose interruption of palbociclib. Among them, 25 (61.0%) participants had treatment-related TEAEs. The most common all-causality and treatment-related TEAEs (in ≥10% participants) were neutropenia (48.8% and 46.3%, respectively) and thrombocytopenia (both were 14.6%).

There were 10 (47.6%) participants in the IRN + TMZ arm who experienced all-causality TEAEs leading to dose interruption of any study treatments with most of TEAEs were considered treatment-related. The most common all-causality and treatment-related TEAEs (in ≥10% participants) in the IRN + TMZ were the same to the palbociclib + IRN + TMZ arm, which were neutropenia (both were 28.6%) and thrombocytopenia (both were 23.8%).

TSC

There were 5 (71.4%) participants who experienced all-causality TEAEs leading to dose interruption of any study interventions with 4 out of 5 having treatment-related TEAEs. All those TEAEs led to dose interruption of palbociclib. The most common all-causality and treatment-related TEAEs (in >1 participant) were thrombocytopenia (both were reported in 4 participants [57.1%]) and neutropenia (both were reported in 2 participants [28.6%]).

Clinical Laboratory Evaluation

Phase 2

<u>Haematology</u>

- In the palbociclib + IRN + TMZ arm:

- The most frequently reported (>50% participants) Grades 1-4 haematology laboratory abnormalities were anaemia (38/41, 92.7%), neutrophil count decreased (36/41, 87.8%), lymphocyte count decreased (29/39, 74.4%), and platelet count decreased (28/41, 68.3%).
- Grade 3 abnormal values included anaemia (12/41, 29.3%), lymphocyte count decreased (13/39, 33.3%), lymphocyte count increased (5/39, 12.8%), neutrophil count decreased (15/41, 36.6%), and platelet count decreased (6/41, 14.6%).
- Grade 4 abnormal values included lymphocyte count decreased (3/39, 7.7%), neutrophil count decreased (12/41, 29.3%), and platelet count decreased (2/41, 68.3%).
- Shifts from Grade ≤2 at baseline to Grade 3 post-baseline occurred for 9 participants for anaemia, 12 participants for lymphocyte count decreased, 4 participants for lymphocyte count increased, 15 participants for neutrophil count decreased, and 6 participants for platelet count decreased. Shifts from Grade ≤3 at baseline to Grade 4 post-baseline occurred for 3 participants for lymphocyte count decreased, 12 participants for neutrophil count decreased, 2 participants for platelet count decreased.

- In the IRN + TMZ arm:
  - The most frequently reported (>50% participants) Grades 1-4 haematology laboratory abnormalities were lymphocyte count decreased (16/19, 84.2%), anaemia (17/21, 81.0%), neutrophil count decreased (14/21, 66.7%), and platelet count decreased (12/21, 57.1%).
  - Grade 3 abnormal values included anaemia (4/21, 19.0%), lymphocyte count decreased (3/19, 15.8%), lymphocyte count increased (2/19, 10.5%), neutrophil count decreased (7/21, 33.3%), and platelet count decreased (2/21, 9.5%).
  - Grade 4 abnormal values included lymphocyte count decreased (4/19, 21.1%), neutrophil count decreased (3/21, 14.3%), and platelet count decreased (1/21, 4.8%).
  - Shifts from Grade ≤2 at baseline to Grade 3 post-baseline occurred for 4 participants for anaemia, 3 participants for lymphocyte count decreased, 2 participants for lymphocyte count increased, 7 participants for neutrophil count decreased, and 2 participants for platelet count decreased. Shifts from Grade ≤3 at baseline to Grade 4 post-baseline occurred for 4 participants for lymphocyte count decreased, 2 participants for neutrophil count decreased, 1 participant for platelet count decreased.

<u>Chemistries</u>

- In the palbociclib + IRN + TMZ arm:
  - The most frequently reported (>50% participants) Grades 1-4 chemistry laboratory abnormalities were creatinine increased (36/41, 87.8%), hyponatremia (21/41, 51.2%), and GGT increased (7/14, 50.0%).
  - Grade 3 abnormal values included alanine aminotransferase increased (2/41, 4.9%), aspartate aminotransferase increased (2/41, 4.9%), GGT increased (1/14, 7.1%), hypermagnesemia (1/41, 2.4%), and hyponatremia (1/41, 2.4%).
  - Grade 4 abnormal values included hypocalcaemia (1/41, 2.4%).

- Most chemistry laboratory abnormalities were Grades 0 or 1. Shifts from Grade ≤2 at baseline to Grade 3 post-baseline occurred for 2 participants for alanine aminotransferase increased, 2 participants for aspartate aminotransferase increased, 1 participant for GGT increased, 1 participant for hypermagnesemia, 1 participant for hyponatremia. Shifts from Grade ≤3 at baseline to Grade 4 post-baseline occurred for 1 participant for hypocalcaemia.

- In the IRN + TMZ arm:
  - The most frequently reported (>50% participants) Grades 1-4 chemistry laboratory abnormalities were creatinine increased (18/21, 85.7%), GGT increased (6/8, 75.0%), alanine aminotransferase increased (14/21, 66.7%), and aspartate aminotransferase increased (11/21, 52.4%).
  - Grade 3 abnormal values included alanine aminotransferase increased (5/21, 23.8%), hypokalaemia (3/21, 14.3%), aspartate aminotransferase increased (1/21, 4.8%), hypermagnesemia (1/21, 4.8%), and hypocalcaemia (1/21, 4.8%).
  - Grade 4 abnormal values included lymphocyte count decreased (4/19, 21.1%), neutrophil count decreased (3/21, 14.3%), and platelet count decreased (1/21, 4.8%).
  - No Grade 4 chemistry laboratory abnormalities were reported.
  - Most chemistry laboratory abnormalities were Grades 0 or 1. Shifts from Grade ≤2 at baseline to Grade 3 post-baseline occurred for 4 participants for alanine aminotransferase increased, 1 participant for hypermagnesemia, 1 participant for hypocalcaemia, and 3 participants for hypokalaemia. No Shifts from Grade ≤3 at baseline to Grade 4 post-baseline occurred.

TSC

Haematology

- All 7 (100.0%) participants reported Grades 1-4 anaemia, lymphocyte count decreased, and platelet count decreased, 6 (85.7%) participants reported Grades 1-4 neutrophil count decreased, and 2 (28.6%) participants reported Grades 1-4 Lymphocyte count increased.
- Grade 3 abnormal values included anaemia (6/7, 85.7%), lymphocyte count decreased (2/7, 28.6%), lymphocyte count increased (2/7, 28.6%), and neutrophil count decreased (1/7, 14.3%).
- Grade 4 abnormal values included lymphocyte count decreased (5/7, 71.4%), neutrophil count decreased (4/7, 57.1%), and platelet count decreased (6/7, 85.7%).

Chemistries

- The most frequently reported (>50% participants) Grades 1-4 chemistry laboratory abnormalities were aspartate aminotransferase increased (6/7, 85.7%), creatinine increased (6/7, 85.7%), alanine aminotransferase increased (5/7, 71.4%), and hypocalcaemia (4/7, 57.1%).
- Grade 3 abnormal values included alanine aminotransferase increased (1/7, 14.3%), and hypokalaemia (1/7, 14.3%).
- No Grade 4 chemistry laboratory abnormalities were reported.

Other Safety Evaluations

Electrocardiograms

Phase 2

In the palbociclib + IRN + TMZ arm, ECG findings included QT interval ≤450 msec (97.6%), QT interval >450 and ≤480 (2.4%), QTcF ≤450 msec (90.2%), QTcF >450 msec and ≤480 msec (7.3%), and QTcF >480 msec and ≤500 msec (2.4%). There were 80.5% participants who had QTcF change from baseline ≤30 msec, 17.1% participants who had QTcF change from baseline >30 msec and ≤60 msec, and 2.4% participant who had QTcF change from baseline >60 msec.

In the IRN + TMZ arm, ECG findings included QT interval ≤450 msec (100.0%), QTcF ≤450 msec (95.2%), and QTcF >480 msec and ≤500 msec (4.8%). There were 85.7% participants who had QTcF change from baseline ≤30 msec, and 14.3% participants who had QTcF change from baseline >30 msec and ≤60 msec.

TSC

ECG findings included QT interval ≤450 msec (100.0%), QTcF ≤450 msec (100.0%). There were 2 (28.6%) participants who had QTcF change from baseline ≤30 msec and 2 (28.6%) participants who had QTcF change from baseline >30 msec and ≤60 msec.

Physical Examination Findings

Phase 2

At baseline, 20 (64.5%) participants had bone age < calendar age (16 [72.7%] versus 4 [44.4%] participants in the palbociclib + IRN + TMZ arm and IRN + TMZ arm, respectively) and 10 (32.3%) had bone age◦> calendar age (5 [22.7%] versus 5 [55.6%] participants in the palbociclib + IRN + TMZ arm and IRN + TMZ arm, respectively).

At the end of treatment, 6 (19.4%) participants had bone age < calendar age (4 [18.2%] versus 2 [22.2%] participants in the palbociclib + IRN + TMZ arm and IRN + TMZ arm, respectively) and 3 (9.7%) had bone age > calendar age (1 [4.5%] versus 2 [22.2%] participants in the palbociclib + IRN + TMZ arm and IRN + TMZ arm, respectively).

TSC

At baseline, 5 (83.3%) participants had bone age < calendar age and 1 (16.7%) had bone age > calendar age.

At the end of treatment, 1 (16.7%) participant was assessed and had bone age < calendar age.

2.3.3. Discussion on clinical aspects

Non-clinical data have indicated that the addition of a CDK4/6 inhibitor to a combination of a topoisomerase inhibitor and an alkylating agent may improve tumour growth inhibition in Ewing sarcoma (EWS) tumour models. The agreed PIP for palbociclib therefore includes the evaluation of palbociclib in the treatment of paediatric EWS.

The primary analysis of the results of the randomised phase II part of study A5481092 (assessed within the procedure EMEA/H/C/003853/P46/006) did not show an improved EFS by adding palbociclib to the combination of IRN and TMZ in the treatment of paediatric r/r EWS, and the enrolment to the phase II part was stopped prematurely for lack of efficacy. The updated EFS and OS data submitted with the current application do not alter the previous conclusions.

Additionally, the stage 1 neuroblastoma (NB) tumour-specific data with ineffective treatment of palbociclib + TOPO + CTX, submitted with the current application, does not support a favourable benefit/risk profile in this patient population, although the low number of subjects in the study (n=7) preclude definite conclusions.

The safety profile for the combination of palbociclib and IRN+TMZ in the paediatric EWS and NB population was as expected from the known safety profiles of palbociclib, IRN and TMZ, respectively. Although the combination appeared poorly tolerated, with a high rate of dose interruptions for palbociclib, no new safety signals were identified.

The IBRANCE SmPC was recently updated with paediatric data from all measures within the PIP, as part of type II variation EMEA/H/C/003853/II/0045. The final data from study A5481092 does not warrant further update of the SmPC.

3. CHMP's overall conclusion and recommendation

The final data from study A5481092 does not support a positive benefit risk for the addition of palbociclib to the combination of irinotecan and temozolomide in the treatment of paediatric Ewing sarcoma or neuroblastoma, and does not warrant further update of the SmPC.

☒ **Fulfilled:**

No regulatory action required.