The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.
SYNOPSIS

STUDY INFORMATION

Long Title: A Multicenter, Open-label, Phase 1b Study of MLN0128 (an Oral mTORC1/2 Inhibitor) in Combination With MLN1117 (an Oral PI3Kα Inhibitor) in Adult Patients With Advanced Nonhematologic Malignancies

Short Title: MLN0128 in Combination With MLN1117

Sponsor: Millennium Pharmaceuticals, Inc (a wholly owned subsidiary of Takeda Pharmaceutical Company Limited)

Name of Active Ingredient: TAK-228 (also known as MLN0128, INK128, and sapanisertib), TAK-117 (also known as MLN1117)

Name of Finished Product: TAK-228 and TAK-117 capsules

Investigators: Five principal investigators enrolled subjects in the treatment period.

Study Sites: A total of 5 sites in Spain (1 site), the United Kingdom (1 site), and the United States (3 sites) had subjects that enrolled in the study’s treatment period.

Publication Based on the Study (Citation):

A Phase 1b multicenter, open-label study of investigational TAK-228 (MLN0128) plus TAK-117 (MLN1117) in adult patients with advanced nonhematologic malignancies. AACR-NCI-EORTC Symposium on Molecular Targets and Cancer Therapeutics; November 29-December 2, 2016; Munich, Germany.

Study Dates:

Date first subject signed informed consent form: 28 June 2013
Date of data cutoff: 31 January 2017 (4 subjects remain ongoing)

Study Phase: Phase 1b

Objectives:

Primary Objective:

The primary objectives were as follows:

- To evaluate the safety profile and to determine dose-limiting toxicities (DLTs), maximum tolerated doses (MTDs) and/or recommended phase 2 doses (RP2Ds), and dosing schedules of oral TAK-228+TAK-117 in subjects with advanced nonhematologic malignancies.

- To characterize the single- and multiple-dose plasma pharmacokinetics (PK) of TAK-228+TAK-117 in subjects with advanced nonhematologic malignancies.

Secondary Objective:

The secondary objective was as follows:

- To evaluate evidence of antitumor activity of TAK-228+TAK-117.
**Additional Objectives:**

**Methodology:**

This was a phase 1b, multicenter, open-label study evaluating the safety, PK, efficacy, and pharmacodynamics of TAK-228+TAK-117 administered to adult subjects with advanced nonhematologic malignancies.

The study consisted of 2 stages: an Escalation Stage followed by an Expansion Stage. The Escalation Stage evaluated the safety, PK, efficacy, and pharmacodynamics of 2 combination treatment schedules in 3 treatment arms to identify their MTDs and/or RP2Ds and select 1 regimen for further evaluation in the Expansion Stage. In the Escalation Stage, subjects received TAK-228+TAK-117 in 1 of the following treatment arms:

- Treatment Arm A: TAK-228 administered once daily every day (QD) plus TAK-117 administered once daily on Monday, Wednesday, and Friday of each week (MWF QW).
- Treatment Arm B: TAK-228 plus TAK-117, with both agents administered once daily on Monday, Tuesday, and Wednesday of each week (MTuW QW).
- Treatment Arm C: TAK-228 plus TAK-117, with both agents administered MTuW QW.

The initial cohorts of subjects enrolled into Treatment Arm A, B, and C received TAK-228/TAK-117 at doses of 2 mg/100 mg, 3 mg/100 mg, and 3 mg/400 mg, respectively, in the specified schedules. After the last subject in a cohort completed Cycle 1, an interim review of safety and tolerability determined the dose of TAK-228+TAK-117 to be administered for the next cohort in that treatment arm. Treatment Arms A and B were evaluated in series, with the first 2 cohorts from Treatment Arm A completed before the first cohort from Treatment Arm B began. Similarly, the safety of Treatment Arm B was confirmed before the first cohort from Treatment Arm C began.

Upon completion of the Escalation Stage, 1 combination treatment regimen was selected for further safety, tolerability, PK, and mutual drug-drug interaction (DDI) characterization in the Escalation Stage.

Subject assignments to a study stage and treatment arm were made using an interactive voice/web response system and based on cohort availability. Subjects were not allowed to switch from 1 dosing schedule to another or participate in more than 1 treatment arm or study stage at any time. During treatment, subjects in both stages received TAK-228 and TAK-117 capsules at prespecified doses in repeated 28-day cycles. TAK-228 and TAK-117 capsules were administered on an empty stomach at approximately the same time on each scheduled dosing day and were always to be taken together, at the same time, when dosed on the same day.

Assessments were made in 28-day cycles throughout the study.

**Number of Subjects:**

Planned: 101 enrolled subjects (81 to the Escalation Stage and 20 to the Expansion Stage).

Enrolled and participated in the study treatment period: 101 subjects, with 81 subjects in the Escalation Stage (26,
34, and 21 subjects to Treatment Arms A, B, and C, respectively) and 20 subjects in the Expansion Stage.

Analyzed: Subjects in each analysis population are shown below.

<table>
<thead>
<tr>
<th>Study Stage</th>
<th>Escalation Stage</th>
<th>Expansion Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm A (N=26)</td>
<td>Arm B (N=34)</td>
</tr>
<tr>
<td>Safety</td>
<td>26 (100)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Response-evaluable</td>
<td>20 (77)</td>
<td>27 (79)</td>
</tr>
<tr>
<td>DLT-evaluable</td>
<td>20 (77)</td>
<td>25 (74)</td>
</tr>
<tr>
<td>PK</td>
<td>26 (100)</td>
<td>34 (100)</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>19 (73)</td>
<td>22 (65)</td>
</tr>
</tbody>
</table>

NA=not applicable.

**Diagnosis and Main Criteria for Inclusion:** Male and female subjects with a diagnosis and documented disease progression of a solid tumor malignancy (excluding primary brain tumor) for which standard, curative, or life-prolonging treatment did not exist or was no longer effective were enrolled. At Screening, subjects must have been at least 18 years of age, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and had a radiographically or clinically evaluable tumor.

**Duration of Treatment:** After completing the Screening period (up to 28 days), subjects received study drug in accordance with their assigned treatment regimen and dose level in 28-day cycles. Subjects could have received study drug treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the sponsor.

Details regarding TAK-228 and TAK-117 administered during the study are provided below.

**Study Drugs, Dose and Mode of Administration, and Lot Numbers**

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Product Dose Strength and Form</th>
<th>Drug Substance</th>
<th>Manufacturer</th>
<th>Takeda Finished Goods Lot Number</th>
<th>Takeda Bulk Drug Product Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
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<td>Unmilled</td>
<td>Pharmatek</td>
<td>102477</td>
<td>102101</td>
</tr>
<tr>
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<td>Pharmatek</td>
<td>102915</td>
<td>102290</td>
</tr>
<tr>
<td>TAK-228</td>
<td>3 mg capsule</td>
<td>Unmilled</td>
<td>Pharmatek</td>
<td>102479</td>
<td>102077</td>
</tr>
<tr>
<td>TAK-228</td>
<td>1 mg capsule</td>
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<td>Haupt Pharma Amareg GbmbH</td>
<td>103527, 221862</td>
<td>103149</td>
</tr>
<tr>
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<td>Milled</td>
<td>Haupt Pharma Amareg GbmbH</td>
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<td>103150</td>
</tr>
<tr>
<td>TAK-117</td>
<td>100 mg capsule</td>
<td>NA</td>
<td>Patheon, Inc</td>
<td>102134</td>
<td>102126</td>
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<td>TAK-117</td>
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<td>222830</td>
</tr>
</tbody>
</table>

NA=not applicable, Pharmatek=Pharmatek Laboratories, Inc.
Endpoints and Criteria for Evaluation:

Efficacy:

- Measures of disease response, including objective response rate and duration of response (DOR), based on investigator’s assessment and using, if feasible, the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).

Pharmacokinetics:

- TAK-228 and TAK-117 plasma PK parameters including, but not limited to, single-dose maximum (peak) concentration (C\text{max}), single-dose time to reach maximum (peak) concentration, area under the plasma concentration versus time curve (AUC) from time 0 to the time of the last measurable concentration (AUC\text{last}), terminal phase half-life, apparent oral clearance, peak-to-trough ratio, and accumulation ratio.

Safety:

- Adverse events (AEs), serious adverse events (SAEs), assessments of clinical laboratory values, physical exam findings, electrocardiograms (ECGs), and vital sign measurements.

Statistical Methods:

Efficacy: Efficacy analyses were based on the Safety population. The best overall response for each subject was derived programmatically from the reported responses based on the investigator assessment using RECIST version 1.1. The objective response rate was defined as the percent of subjects in the Response-Evaluable population with a best response of complete response (CR) or partial response (PR). The numbers and percentages of subjects in each individual response category; with a response; and with CR, partial PR, or stable disease ([SD]; SD of any duration and SD of >6 months) were summarized. The duration of SD, defined as the number of days from Cycle 1 Day 1 until progressive disease (PD) or until the last response assessment if there was no disease progression, was calculated for the subjects with a best response of SD. The DOR, defined as the time from the date of first documented response of CR/PR to the first documented PD, was calculated for subjects with a best response of CR or PR. The DOR was censored at the last response assessment date that was SD or better for subjects who did not progress.

PK: PK analyses were based on the PK DDI-Evaluable population. Descriptive statistics were used to summarize TAK-228 and TAK-117 plasma concentrations and calculated PK parameters. Linear and semilogarithmic plots of the mean plasma concentration versus scheduled sampling time and individual plasma concentration versus actual sampling time were provided. The following statistical analyses were performed on the data collected during the Expansion Stage: an analysis of variance with log-transformed C\text{max} and AUC as the dependent variables, treatment as the fixed effect, and subject as the random effect; and least-square mean ratios between the treatment states (TAK-228+TAK-117 [Test]) versus TAK-228 or TAK-117 alone [Reference]) along with 90% CIs. In addition, in the Expansion Stage, the amount of TAK-228 and TAK-117 excreted in urine and the renal clearance of TAK-228 and TAK-117 were determined.

Safety: Safety analyses were based on the Safety population. Exposure data were summarized by treatment group. Treatment-emergent adverse events (TEAEs) were coded using the Medical Dictionary for Regulatory Activities version 19.0, and the number and percentage of subjects experiencing TEAEs in the following categories were summarized: all TEAEs, TEAEs related to study drug, Grade 3 or greater TEAEs, Grade 3 or greater TEAEs related to study drug, most common TEAEs, TEAEs resulting in discontinuation of study drug, SAEs, SAEs related to study drug, and AEs of interest (ie, rash, renal insufficiency, mucosal inflammation, and asthenic conditions). Laboratory parameters were summarized via posttreatment shifts relative to Baseline. Vital signs, weight, and 12-lead ECG findings were summarized descriptively and by maximum/minimum change from Baseline, where appropriate.
SUMMARY OF RESULTS

Disposition of Subjects:
A total of 101 subjects were enrolled in the study and received at least 1 dose of study drug: 81 subjects in the Escalation Stage (26, 34, and 21 subjects to Treatment Arms A, B, and C, respectively) and 20 subjects in the Expansion Stage. As of the data cutoff date of 31 January 2017, all subjects in the Escalation Stage and most subjects in the Expansion Stage had discontinued study treatment. The remaining subjects (4 subjects [20%]) were ongoing in the Expansion Stage. Overall, the most common reason for treatment discontinuation in each stage and treatment arm was PD.

Demographic and Other Baseline Characteristics:
Across both study stages, mean subject age ranged from 58.4 to 63.4 years (overall range 30 to 80 years). Most subjects enrolled into the study were white and not Hispanic or Latino, and the most common disease stage for subjects in each stage was Stage IV. With the exception of a greater percentage of women in Treatment Arm A of the Escalation Stage than the other treatment arms or study stage, there were no meaningful differences in demographic characteristics, baseline disease characteristics, concomitant medication use, or prior cancer treatments between subjects enrolled into the different treatment groups.

Efficacy Results:
Overall, 2 subjects achieved an objective response during the study (both PR, and both in the Expansion Stage); these responses occurred in subjects with endometrial tumors. Four additional subjects, all in the Escalation Stage, maintained SD for at least 6 months (1 subject each with ependymoma, head/neck, cervical, and thymus tumors). There were no noteworthy trends in efficacy across the different dosing schedules or levels in the study. Overall clinical benefit rates were 51% for the Escalation Stage and 44% for the Expansion Stage.

PK Results:
During the Escalation Stage, TAK-228 and TAK-117 exhibited consistent and dose-dependent PK, with no readily apparent indications of interaction. Observed effects of TAK-228 milling on PK parameters were not consistent. During the Expansion Stage, the mutual DDI analysis demonstrated increases in the geometric mean TAK-228 $C_{\text{max}}$ and $AUC_{\text{last}}$ values of approximately 22% and 29%, respectively, for combination TAK-228 4 mg+TAK-117 200 mg versus TAK-228 4 mg alone; there were no meaningful changes in the PK of TAK-117. The urinary excretion and renal clearance of both TAK-228 and TAK-117 were low, suggesting that urinary excretion is not a major clearance route for either agent.

Safety Results:
DLTs and MTDs. DLTs varied across treatment regimens and included oral pain, diarrhea, nausea, fatigue, rash macular, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), asthenia, and vomiting. The only DLTs occurring in more than 1 subject were increased ALT and nausea, which were reported for 2 subjects each across treatment arms. On the basis of these DLTs, the MTDs were established at the following dose levels (TAK-228/TAK-117): 4 mg (milled)/200 mg MTuW QW for Treatment Arm B and 3 mg (milled)/300 mg MTuW QW for Treatment Arm C. Because of the poor tolerability of milled TAK-228+TAK-117 in Treatment Arm A, no MTD was defined for the TAK-228 QD/TAK-117 MWF QW schedule. Based on these data and the greater tolerability of the 4 mg (milled)/200 mg than 3 mg (milled)/300 mg dose combination in later treatment cycles, TAK-228 4 mg (milled)/TAK-117 200 mg MTuW QW was chosen as the RP2D for further evaluation in the Expansion Stage.

TEAEs. Overall, treatment was generally well tolerated in both study stages at the schedules and dose levels explored during the study. Nearly all subjects reported at least 1 TEAE. The most frequently occurring TEAEs were nausea, vomiting, fatigue, and diarrhea across all treatment regimens in the Escalation Stage and nausea, asthenia, vomiting, and stomatitis in the Expansion Stage. There were no meaningful differences in the incidence or pattern of commonly reported TEAEs or treatment-related TEAEs across treatment schedules or dose levels. Similarly, there were no consistent trends across treatment schedules or dose levels in the overall incidence or pattern of Grade 3 or
greater TEAEs or study drug-related Grade 3 or greater TEAEs.

Deaths, Other SAEs, and AEs of Interest. A total of 6 deaths, 2 each in Treatment Arm A (Escalation Stage), Treatment Arm B (Escalation Stage), and the Expansion Stage, occurred during the study or within 30 days of the final dose of study drug. Causes of death included dyspnea, intestinal perforation, endometrial cancer, salivary gland cancer, intestinal obstruction, and malignant neoplasm progression. None of these deaths were considered related to study treatment.

The overall incidence of SAEs was 28% in the Escalation Stage and 45% in the Expansion Stage. Most SAEs were Grade 3 or lower in severity, and no Grade 4 SAE was reported for more than 1 subject overall. The only SAE preferred terms reported in more than 1 subject during the Escalation and Expansion Stages were dyspnea and general physical health deterioration; all other SAEs were reported for no more than 1 subject in either study stage. No study drug-related SAE preferred terms were reported for more than 1 subject. Although the incidence of SAEs varied, no meaningful trends in the incidence of SAEs or study drug-related SAEs were observed across treatment schedules or dose levels during this study.

TEAEs leading to study drug discontinuation occurred in 22% of Escalation Stage and 10% of Expansion Stage subjects. TEAE preferred terms leading to study drug discontinuation for more than 1 subject in either stage included nausea, vomiting, diarrhea, fatigue, stomatitis, increased AST, and hyperglycemia. There were no consistent trends in the incidence of TEAEs resulting in study drug discontinuation across treatment schedules or dose levels.

On the basis of class effects and previous experience with TAK-228 and TAK-117, rash, renal insufficiency, mucosal inflammation, and asthenic conditions were prespecified as AEs of interest during the study. The incidence of TEAEs of interest varied across treatment regimens, but serious AEs of interest and study drug discontinuation due to AEs of interest were infrequent. The majority of AEs of interest were Grade 1 or 2 in severity. Although there were no consistent trends indicative of overall differences in tolerability between regimens, the incidence of rash events was higher for subjects receiving TAK-228 QD/TAK-117 MWF QW in Treatment Arm A. TEAEs of interest that met the criteria for DLT included macular rash and asthenia (1 subject/1 event each). Because pneumonitis has been identified as a potential risk of mTOR inhibitor treatment, symptoms of pneumonitis were closely monitored; the incidence of pneumonitis was low during the study.

Other Safety Measures. Few subjects had shifts from a Grade 0 or 1 laboratory value at Baseline to a Grade 3 or 4 value during the study. The most frequent shifts to Grade 3 or 4 chemistry values were increased ALT and AST during the Escalation Stage and increased ALT, increased bilirubin, and decreased sodium during the Expansion Stage. The most frequent shifts to Grade 3 or 4 hematology values were increased activated partial thromboplastin time, decreased lymphocytes, and hemoglobin during the Escalation Stage and decreased lymphocytes during the Expansion Stage. TEAEs associated with laboratory values were infrequent. With the exception of a mildly increased incidence of laboratory shifts and/or TEAEs for subjects receiving milled TAK-228, there were generally no consistent trends in these parameters across treatment schedules or dose levels. Similarly, there were no meaningful trends in vital signs or ECG changes across treatment schedules or dose levels during the study.

CONCLUSIONS

Based on the results of Study C32001, the MTDs of combination TAK-228+TAK-117 treatment were established at the following doses (TAK-228/TAK-117): 4 mg (milled)/200 mg MTuW QW for Treatment Arm B and 3 mg (milled)/300 mg MTuW QW for Treatment Arm C. The RP2D evaluated during the Expansion Stage was TAK-228 4 mg (milled)/TAK-117 200 mg MTuW QW. Study drug was generally well tolerated at these dosing levels during the study. With the exception of increased ALT and nausea, no specific DLT was reported in more than 1 subject across all treatment regimens. TAK-228 and TAK-117 exhibited consistent and dose-dependent PK, with no readily apparent indications of interaction. Mutual DDI analysis demonstrated a modest increase in TAK-228 plasma exposure with TAK-117 co-administration. Preliminary efficacy results were encouraging, with no notable differences in response across treatment regimens.

REPORT DATE: 31 August 2017