A Phase 1, Open-Label Study to Assess the Relative Bioavailability, Effect of Food, and Gastric pH Modification on the Pharmacokinetics of TAK-931 in Patients with Advanced Solid Tumors

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Primary Objectives:Part 1- Estimate the relative bioavailability of the tablet formulation of TAK-931 in reference to the PIC formulation.Part 2- Assess the effect of a high-fat meal on the single dose PK of TAK-931 administered as the tablet...

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON45823

Source
ToetsingOnline

Brief title
TAK-931-1003

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
advanced cancer, Advanced solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Millenium Pharmaceuticals
Source(s) of monetary or material Support: Millennium Pharmaceuticals;Inc;a wholly owned subsidiary of Takeda Pharmaceutical Company Limited

Intervention

Keyword: Solid tumors

Outcome measures

Primary outcome

Part 1

* Ratio of geometric mean of the following PK parameters for TAK-931 tablets in

reference to PIC and

associated 90% CIs:

* Maximum observed concentration (Cmax).

* AUC from time 0 to time of the last quantifiable concentration (AUClast).

* AUC from time 0 to infinity (AUC*).

Part 2

* Ratio of geometric mean of the following PK parameters for TAK-931 tablets

under fed and fasted conditions and associated 90% CIs:

* Cmax.

* AUClast.

* AUC*.

* Ratio of geometric mean of the following PK parameters for TAK-931 tablets in

the presence and absence of esomeprazole and associated 90% CIs:

* Cmax.

* AUClast.

* AUC*.

* Summary statistics of the following PK parameters for TAK-931:

* Cmax.

* AUClast.

* AUC*.

Secondary outcome

Part 1

* PK parameters of TAK-931 following single-dose administrations as PIC and

tablets at 80 mg:

* Time of first occurrence of Cmax (tmax).

* Apparent clearance after extravascular administration (CL/F).

* Terminal disposition phase half-life (t1/2z).

* Antitumor activity:

* Overall response rate (ORR).

* PFS.

* Disease control rate (DCR).

* Duration of response (DOR).

* Safety:

* Percentage of serious adverse events (SAEs), treatment-emergent adverse

events (TEAEs), Grade *3 TEAEs, TEAEs leading to discontinuation or dose

modification, and percentage of laboratory abnormalities.

Part 2

* PK parameters:

* tmax, CL/F, and t1/2z of TAK-931 tablets following single-dose administration under fasting and fed conditions.

* tmax, CL/F, and t1/2z of TAK-931 tablets following single-dose administration in the absence and in the presence of esomeprazole.

* Antitumor activity:

* ORR.

* PFS.

* DCR.

* DOR.

* Safety:

* Percentage of serious adverse events (SAEs), treatment-emergent adverse events (TEAEs), Grade *3 TEAEs, TEAEs leading to discontinuation or dose modification, and percentage of laboratory abnormalities.

Study description

Background summary

Millennium Pharmaceuticals, Inc, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, the study Sponsor is paying the study hospital and the investigator to carry out this research study.

TAK-931, the study drug, is an investigational drug. This means that it has not been approved by the FDA (US Food and drug Administration), EMA (European

Medicines Agency) or other regulatory authorities for use by the general public and is still being tested. This study is not intended to improve the health but is necessary for the further development of TAK-931.

TAK-931 is being studied as a new medication in humans with advanced solid tumors. TAK-931 decreases the activity of a chemical in the body that is called CDC7 kinase, which is important for the survival of cancer cells.

This study is an open-label study, which means that both the patient and the study doctor know which treatment the patient is receiving.

The study consists of 2 parts. Approximately 20 patients will participate in part 1 and 24 patients in part 2 of this research study. The doctor will tell the patient if he/she is being invited to participate in Part 1 or in Part 2. Patients cannot participate in both parts. The study will only be conducted in the Netherlands.

Study objective

Primary Objectives:

Part 1
- Estimate the relative bioavailability of the tablet formulation of TAK-931 in reference to the PIC formulation.

Part 2
- Assess the effect of a high-fat meal on the single dose PK of TAK-931 administered as the tablet formulation.
- Assess the effect of esomeprazole, a proton pump inhibitor (PPI) on the single dose PK of TAK-931 administered as the tablet formulation.

Secondary Objectives:

Part 1
- Further characterize the PK of TAK-931 administered as PIC or the tablet formulation.
- Assess the safety and tolerability of TAK-931 administered as the tablet and PIC formulations.
- Assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

Part 2
- Further characterize the PK of TAK-931 administered as the tablet formulation under fasted and fed conditions.
- Further characterize the PK of TAK-931 administered as the tablet formulation in the presence or absence of esomeprazole, a PPI.
- Assess the safety and tolerability of TAK-931 administered as the tablet

formulation under fed and fasted conditions.
- Assess the antitumor activity of TAK-931 in patients with locally advanced or metastatic solid tumors.

Study design

Part 1: Assessment of Relative Bio-availability of TAK-931 Tablets in Reference to Powder-in-Capsule

Approximately 20 patients (to ensure 14-16 patients evaluable for pharmacokinetics [PK]) will be randomized in a crossover fashion to receive in Cycle 0 a single dose of TAK-931 80 mg powder-in-capsule (PIC) or tablet on Day 1 and a single dose of TAK-931 80 mg with the alternate formulation on Day 3 (PIC to tablet, or tablet to PIC; n of ~10/sequence). Blood samples will be collected predose and up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to evaluate the relative bioavailability of TAK-931 tablets in reference to the PIC formulation. There will be no TAK-931 dosing on Day 2 or Day 4. Starting on Day 5, patients will continue to receive TAK-931 50 mg PIC once daily (QD) for 12 days followed by a 7-day rest period.

Starting at Cycle 1, patients will 50 mg PIC QD for 14 days, followed by 7-day rest period, in 21-day treatment cycles until one of the discontinuation criteria is met.

Part 2: Assessment of the Effect of Food and Esomeprazole, a Proton Pump Inhibitor, on the PK of TAK-931 as a Tablet

After the preliminary PK data from part 1 have been analyzed to estimate the relative bioavailability of the tablet formulation in reference to PIC, the dose of TAK-931 tablet will be calculated to provide total exposure (area under the concentration-time curve [AUC]) comparable to the 80-mg dose of PIC. In part 2, approximately 24 patients (to ensure 14-16 patients evaluable for PK) will be randomized in a crossover fashion to receive in Cycle 0 a single dose of the TAK-931 tablet formulation with or without a standard high-fat breakfast on Day 1, with the alternate food intake condition and dosing on Day 3 (fasted to fed or fed to fasted; n of ~12/sequence). Blood samples will be collected predose and for up to 48 hours postdose at predetermined time points to measure plasma drug concentrations to characterize the effect of food on the PK profile of TAK-931 tablet. Starting from Day 5, patients will receive esomeprazole 40 mg QD through Day 13. On Day 12, each patient will receive a single dose of the TAK-931 tablet formulation, and PK samples will be collected up to 48 hours postdose (Day 14 predose). Starting on Day 14, patients will continue to receive TAK-931 tablets at a dose expected to achieve exposures comparable to 50 mg PIC QD for
11 days, followed by a 7-day rest period, until a discontinuation criterion is met.

Starting at Cycle 1, patients will receive the TAK-931 tablet formulation at a dose expected to achieve exposures comparable to 50 mg PIC QD for 14 days, followed by 7-day rest period, in 21-day treatment cycles.

Intervention

Part 1: 80 mg single dose on Day1 and Day 3 respectively followed by 50 mg QD thereafter.

Part 2: Tablet single dose providing an AUC comparable to the 80-mg single dose of PIC on Day 1, Day 3, and Day 12 followed by a tablet QD dose providing an AUC comparable to 50-mg dose of PIC.

Study burden and risks

During the study, the patient may have discomforts and risks from TAK-931 and from the study procedures. Most of these are listed here, but there may be others that we cannot predict.

Discomforts and risks may vary from person to person. Everyone taking part in the study will be watched carefully for side effects; however, doctors do not know all the discomforts and risks that may happen. There is always the possibility that unknown risks may occur. These may be mild or very serious, and in some cases may be very serious, long-lasting, or may never go away. There is also a risk of death. Serious adverse reaction may occur upon resumption of TAK-931 treatment even after dose reduction or dose interruption. If any discomforts or risks occur, the patient must tell the study doctor.

The doctor may give the patient medications to help lessen some of the discomforts and risks. If a severe reaction to TAK-931 occurs, the doctor may stop TAK-931.

TAK-931 has been given to some patients already, however, the exact effects are unknown.

The following discomforts and risks have been reported in the limited number of patients taking TAK-931 in a single agent clinical trial studying the drug in humans:

Very common (Incidence 10% and above)
* Decrease in the number of white blood cells which may increase the patients risk of infection and may be associated with fever
* Decrease in the number of red blood cells, which may make the patient feel tired or lose your energy; have pale skin; or experience shortness of breath and/or a faster heart rate.
* Hair loss

* Nausea
* Vomiting
* Decreased appetite
* Diarrhoea: watery and frequent bowel movements
* Tiredness
* Fever
* Low levels of blood protein called albumin which can cause generalized swelling
* Swelling of arms or legs
* Constipation
* A vague feeling of bodily discomfort

Contacts

Public
Millenium Pharmaceuticals

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US
Scientific
Millenium Pharmaceuticals

Landsdowne Street 40
Cambridge MA 02139
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Adult patients with histologically or cytologically confirmed metastatic or locally advanced or metastatic solid tumors for whom there is no available standard treatment with proven survival benefit, this therapy is not indicated, or it is refused by the patient.
2. Eastern Cooperative Oncology Group performance status of 0 to 1.
3. Adequate bone marrow reserve and renal and hepatic function based on the following laboratory parameters:
* Absolute neutrophil count *1.5 × 109/L, platelet count *75.0 × 109/L, and hemoglobin *85 g/L.
* Total bilirubin *1.5 times the institutional upper limit of the normal range (ULN) or total bilirubin <3.0 times ULN in patients with well documented Gilbert*s Syndrome.
* Serum alanine aminotransferase or aspartate aminotransferase *3.0 times the ULN (<5 times ULN if liver enzyme elevations are due to hepatocellular cancer, biliary tract cancer, or metastatic disease in the liver).
* Creatinine <1.5 times the institutional ULN or estimated creatinine clearance using the Cockcroft-Gault formula *30 mL/min for patients with serum creatinine concentrations above institutional limits.
4. Left ventricular ejection fraction *50% as measured by echocardiogram or multiple gated acquisition scan within 4 weeks before receiving the first dose of study drug.
5. Recovered to Grade 1 or baseline from all toxic effects of previous therapy (except alopecia or neuropathy).

Exclusion criteria

1. Patients who require continuous use of PPIs or histamine-2 receptor antagonists and patients who are taking PPIs within 5 days before the first dose of study drug.
2. Treatment with clinically significant enzyme inducers, such as phenytoin, carbamazepine, enzalutamide, mitotane, ritonavir, rifampin, or St John's wort within 14 days before the first dose of study drug.
3. Treatment with systemic anticancer treatments or any investigational products within 28 days before the first dose of study drug or 5 half-lives, whichever is shorter.
4. Patients with hypertension that is unstable or not controlled despite appropriate medical therapy.
5. Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after central nervous system-directed treatment, as ascertained by clinical examination and brain imaging (magnetic resonance imaging or computed tomography) during the screening period.
6. Known history of HIV infection.
7. Known hepatitis B (HBV) surface antigen seropositive or detectable hepatitis C infection viral load. Note: Patients who have positive hepatitis B core antibody or hepatitis B surface antigen antibody can be enrolled but must have an undetectable hepatitis B viral load.
8. Known gastrointestinal (GI) disease or GI procedure that could interfere with the GI absorption of study drug, such as total gastrectomy or GI conditions that could substantially

modify gastric pH or GI transit.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-04-2019
Enrollment:	44
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	TAK-931
Generic name:	TAK-931

Ethics review

Approved WMO Date:	17-08-2018
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-06-2019
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-004629-34-NL
CCMO	NL66709.091.18

Study results

Date completed:	03-12-2019
Results posted:	06-01-2021

First publication
10-09-2020