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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

Radiolabeled BYL719

Trial Indication(s)

Not applicable.

Protocol Number

CBYL719X2107

Protocol Title

A single-center, open-label study to investigate the Absorption, Distribution, Metabolism and Excretion (ADME) of BYL719 after a single oral dose of 400 mg [^{14}C]BYL719 in healthy male volunteers

Clinical Trial Phase

Phase I

Phase of Drug Development

Phase I

Study Start/End Dates

15-April-2013 to 08-May-2013

Reason for Termination (If applicable)

Not applicable.

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Study Design/Methodology

This study was a single-center, open-label study to investigate the Absorption, Distribution, Metabolism and Excretion (ADME) of BYL719 after a single oral administration of 400 mg [14C]BYL719 in male healthy volunteers.

Centers

1 center in 1 country: Netherlands (1)

Objectives:

Primary objective(s)

Primary Objective: • To determine the rates and routes of excretion of [^{14}C]BYL719 related radioactivity, including mass balance of total drug-related radioactivity in urine and feces following the administration of a single 400 mg oral dose of [^{14}C]BYL719 in healthy male volunteers
• To determine the pharmacokinetics of total radioactivity in blood and plasma
• To identify and quantify BYL719 and its metabolites in excreta (urine and feces) in order to elucidate key biotransformation pathways and clearance mechanisms of BYL719 in humans
• To characterize the plasma pharmacokinetics of BYL719 and its metabolites

Secondary objective(s)

• To assess the safety and tolerability of a single 400 mg dose of [^{14}C]BYL719 administered to healthy male volunteers.

Test Product (s), Dose(s), and Mode(s) of Administration

Each subject received a single, oral dose of 400 mg [14C]BYL719 in two gelatin capsules of 200 mg BYL719 each.

Statistical Methods

No statistical hypotheses were tested.

The PK data of BYL719 and 14C-radioactivity in plasma were presented with descriptive statistics for the PAS. Descriptive statistics of PK parameters include n (number of non-missing values), range (given as minimum and maximum), median, geometric and arithmetic means, standard deviation (SD), coefficient of variation (CV% and CV% geometric-mean,). For Tmax only median, minimum and maximum were provided. BYL719 concentrations in plasma were summarized at each scheduled time point for the PAS. Figures of individual BYL719 plasma concentrations over time with median were presented for the FAS. Listings of BYL719 concentrations in plasma and PK parameters were provided for FAS.
All summaries and listings of demographic and baseline characteristics were provided for the FAS.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Healthy male between 18 and 55 years of age; healthy was defined as an absence of clinically significant abnormalities, as identified by a detailed medical history, complete physical examination, vital signs, 12-lead ECG and clinical laboratory tests at screening through baseline visit; understand and sign the written informed consent.
- Subjects, who weighed at least 55 kg and not more than 90 kg and had body mass index (BMI) within the range of 18 to 29 kg/m2, had laboratory values (hematology and baseline) within the following ranges: body temperature (≥ 35.0 and ≤ 37.5°C); systolic blood pressure (≥ 100 and ≤ 140 mmHg); diastolic blood pressure (≥ 50 and ≤ 90 mmHg); pulse rate (≥ 40 and ≤ 90 beats per minute) were included in the study

Exclusion criteria

Subjects eligible for this study did not meet **any** of the following criteria:

- Sexually active males not using a condom during intercourse while taking the drugs and for at least 3 months after stopping treatment and fathering a child in this period. A condom was required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
- Subjects having a significant illness, including infections, or hospitalization within the 2 weeks prior to dosing. Invasive systemic fungal infections needed to be fully resolved prior to study entry.
- Subjects having had any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of drugs, or which might jeopardize the subject in case of participation in the study. The PI made this determination in consideration of the subject's medical history and/or clinical or laboratory evidence of any of the following:
    - History of inflammatory bowel disease, ulcers, gastrointestinal or rectal bleeding
    - History of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy,or bowel resection
    - History of pancreatic injury or pancreatitis as indicated by an abnormal serum lipase or amylase test result. Clinical evidence of liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), γ-GT, alkaline phosphatase, or total bilirubin

- History or presence of impaired renal function as indicated by clinically significantly abnormal creatinine, urea or clinically significant abnormal urinary constituents (*e.g.*, albuminuria or hematuria). Evidence of urinary obstruction or difficulty in voiding at screening

Participant Flow Table

Subject disposition (FAS)

Disposition reason	All subjects (N=4) n(%)
Completed	4 (100.0)

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Baseline Characteristics

Demographics (FAS)

Age/Sex/Race	Ethnicity	Weight (kg)	Height (cm)	BMI (kg/m^2)
32/M/CA	Other	78.4	184	23.16
48/M/CA	Other	89.1	185	26.03
47/M/CA	Other	87.5	197	22.55
39/M/CA	Other	78.6	176	25.37

FAS = Full Analysis Set, BMI = Body Mass Index, M = Male, CA = Caucasian,

Primary Outcome Result(s)

Pharmacokinetic Result: Summary of PK, metabolism and excretion results

Result	Parameters (unit)	Mean ± SD or median [and range]
Plasma BYL719	AUCinf (ng*hr/ml) AUClast (ng*hr/ml) Cmax (ng/ml) Tmax (hr) T1/2 (hr) CL/F (L/hr) Vz/F (L)	11100 ± 3770 11100 ± 3760 1320 ± 912 2 [1;4] 13.7 ± 5.89 39.0 ± 12.0 838 ± 541
Total radioactivity in plasma	AUCinf (ng*hr/ml) AUClast (ng*hr/ml) Cmax (ng/ml) Tmax (hr) T1/2 (hr)	18500 ± 6050 17000 ± 7230 1890 ± 1280 2 [1.5;4] 18.0 ± 10.7
Total radioactivity in blood	AUCinf (ng*hr/ml) AUClast (ng*hr/ml) Cmax (ng/ml) Tmax (hr) T1/2 (hr)	23000 ± 6800 20800 ± 7390 2320 ± 1400 2 [2;3] 11.1 ± 7.48
Fraction of total radioactivity in plasma over 24hr	Fp (%)	41.1 ± 3.90
AUC ratio (BYL719/total radioactivity in plasma) AUCinf		0.600 ± 0.040
^{14}C-BYL719 in plasma	% of 14C-plasma radioactivity (AUC0-12hr)	67.9 ± 3.39 %
^{14}C-BZG791 in plasma	% of 14C-plasma radioactivity (AUC0-12hr)	26.7 ± 1.96
Total mass balance	% of dose	92.6 - 95.8
Excretion of radioactivity in urine (0-72 hr)	% of dose	13.1 ± 3.98
Excretion of radioactivity in feces (0-144hr)	% of dose	79.8 ± 3.76
BYL719 excreted unchanged in urine	% of dose	2.01 ± 0.192
BYL719 excreted unchanged in feces	% of dose	36.2 ± 7.45

Secondary Outcome Result(s)

Refer to Safety Result section for secondary outcome results.

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Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class, preferred term Safety Set

Primary System Organ Class Preferred Term	All Subjects (N=4) n (%)
-Any primary system organ class	
-Total	1 (25.0)
Infections And Infestations	
-Total	1 (25.0)
Urethritis	1 (25.0)

- Primary system organ classes are presented alphabetically; Preferred terms are sorted within primary system organ class by descending order of frequencies.
- A subject with multiple occurrences of an AE is counted only once in the AE category.
- A subject with multiple adverse events within a primary system organ class is counted only once in the total row.

Serious Adverse Events by System Organ Class

No deaths, other SAEs, or other significant AEs were reported during this study.

Conclusion:

Efficacy results: Not applicable

Safety results: All the subjects were dosed as per protocol and completed the study. No deaths, SAEs or significant AEs were reported. In total 1 subject (25%) reported 1 TEAE of grade 1 urethritis. The relationship to the study drug was considered not suspected by the PI. No subject discontinued the study due to adverse event. No concomitant medication was used. For none of the safety assessments (vital signs, ECG, hematology, blood chemistry including cardiac enzymes, and urinalysis) any clinically significant abnormalities were reported. No trends were observed in any of the safety variables.

Date of Clinical Trial Report

28-Mar-2014

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Swiss Authorization date and authorization number

Swissmedic Approval Number: 67359

Swissmedic Approval Date 24.03.2020

Novartis Study Code

CBYL719X2107

EudraCT Number

Not applicable

Planned and Actual Number of Patients

Planned: 5
Actual: 4

Batch Numbers

(RSU6099-5 PL1- 131112-A)

Information on comparators drug dosage, route of administration, batch numbers

Not applicable

Publication(s)

James A, Blumenstein L, Glaenzel U, et al. Absorption, distribution, metabolism, and excretion of [14C]BYL719 (alpelisib) in healthy male volunteers. Cancer chemotherapy and pharmacology. 2015;76:751–760.

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Investigators & Information on Study Centers

Investigator	**Facility Name** **Address** **Country**
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