AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ICI176,334-1
Study Code	D6874L00026
Edition Number	1
Date	02 July 2012

Oral Mucosal Absorption of ICI176,334-1 in Japanese Healthy Male Subjects

Study dates:	First volunteer enrolled: 19 August 2011 Last volunteer last visit: 14 September 2011
Phase of development:	Clinical pharmacology (I)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at one centre in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective of this study was to investigate the presence or absence of oral mucosal absorption of ICI176,334-1 (oral disintegrating tablet of Caosodex 80 mg tablet) in Japanese healthy male volunteers	Plasma concentration, AUC_{0-72h} and C_{max} of R-bicalutamide.	Pharmaco kinetics
	Secondary	
	Recovery of bicalutamide in saliva	Pharmaco kinetics
Secondary	**Secondary**	
The secondary objective was to investigate the safety	Adverse events, vital signs (blood pressure and pulse rate), 12-lead paper ECG, physical examination, clinical chemistry, haematology and urine analysis	Safety

Study design

This was unblinded, a single dose study to investigate the oral mucosal absorption of bicalutamide from the ICI176,334-1 (oral disintegrating tablet of Casodex 80 mg tablet). Under the fasting condition the ICI76,334-1 was disintegrated on the tongue without swallowing and retained in the oral cavity for 2 minutes. The disintegrated tablet component was collected with saliva and rinsing water.
The presence or absence of oral mucosal absorption of bicalutamide was assessed by measuring the plasma concentration of R-bicalutamide and the recovery of bicalutamide (R- and S-form) in saliva and rinsing water.

Target subject population

Japanese healthy male volunteers aged 20 to 45 years.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product:
ICI176,334-1 (oral disintegrating tablet including 80 mg bicalutamide in a tablet)

Dosage and mode of administration:
Dosage: 80 mg as bicalutamide (1 tablet)

Mode of administration:
One tablet of ICI176,334-1 was set on the tongue without swallowing after over 10 hours fasting before administration. The ICI176,334-1 was infiltrated with saliva and lightly broken down with tongue. The ICI176,334-1 was retained in the oral cavity for 2 minutes after setting it on the tongue, and the disintegrated component was collected with saliva. After that oral cavity was immediately rinsed more than 3 times with totally 150 mL water, and all rinsing water was collected. It was instructed that the volunteer would not swallow the saliva before finishing the rinsing and when he swallowed the saliva and/or rising water, he would report it to the investigator.
Before application of ICI176,334-1 to the volunteer, oral cavity was rinsed more than 3 times with totally 150 mL water, and the rinse water was collected as blank sample of saliva.
Water was restricted for 1 hour after the administration of ICI176,334-1, but a moderate amount of water was allowed from 1 hour after the administration. Meal was served 4 hours after the administration of ICI176,334-1.

Batch number for IP (batch number for tablet):
D6874L26-1 (H05140)

Duration of treatment

Each volunteer received a single dose of ICI176,334-1 on study Day 1 and discharged on study Day 4. The volunteer visited the study site on study Day 8.Follow-up visit was conducted during study Day 14 to 21.

Statistical methods

Analysis of PK parameters:
The descriptive statistics of $AUC_{0\text{-}72h}$ and C_{max} of R-bicalutamide were calculated as primary parameters. The descriptive statistics of the recovery of bicalutamide (R- and S-form) in saliva were calculated as secondary parameters. It was defined that relative bioavailability based on the $AUC_{0\text{-}72h}$ and C_{max} of R-bicalutamide would be calculated in comparison with the mean data obtained from the bioequivalence study (D6874L00025), when the plasma concentration of R-bicalutamide over the lower limit of quantification (LLOQ) was detected.

Subject population

Eight (8) volunteers received the ICI176,334-1 and all volunteers (8) were completed the study without discontinuation.

Summary of pharmacokinetic results

Plasma concentration of R-bicalutamide over LLOQ was detected in one of 8 volunteers, but the concentration was around LLOQ at all those time points. Since the plasma concentration was below LLOQ at all sampling time points in other 7 volunteers, the descriptive statistics of $AUC_{0\text{-}72h}$ and C_{max} could not be calculated.
Mean recovery rate of bicalutamide in saliva was 94.02 ± 0.86% (n=8). There was no large difference of the recovery of bicalutamide in saliva between the volunteer whom the plasma concentration of R-bicalutamide was detected and other volunteers.

Since the plasma concentration of R-bicalutamide was detected in only 1 volunteer, evaluation of relative bioavailability based on the AUC_{0-72h} and C_{max} of R-bicalutamide was not performed according to the statistical analysis plan.

Summary of safety results

No adverse event was reported in this study. No clinically relevant observation and abnormality were noted in clinical laboratory and physiological tests.