AstraZeneca

Clinical Study Report Synopsis

Drug Substance	ICI176,334-1
Study Code	D6874L00025
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Bioequivalence Study of ICI176,334-1 in Japanese Healthy Male Subjects - Evaluation of Bioequivalence of ICI176,334-1 and Casodex 80 mg Tablet -

Study dates: First volunteer enrolled: 21 July 2011
Last volunteer last visit: 22 December 2011

Phase of development: Clinical pharmacology (I)

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

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 bioequivalence (BE) between ICI176,334-1 (oral disintegrating tablet of Caosodex 80 mg tablet) and Casodex 80 mg tablet after a single oral dose of ICI176,334-1 and Casodex 80 mg tablet in Japanese healthy male volunteers	Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve from zero to the time of the last measurable concentration (AUC_t) of R-bicalutamide for primary endpoint for BE Area under the plasma concentration-time curve from zero to infinity (AUC_∞) and from zero to 72 hours ($AUC_{0\text{-}72h}$), time to C_{max} (t_{max}), mean residence time (MRT), elimination rate constant (k_{el}) and elimination terminal half-life ($t_{½}$) of R-bicalutamide for secondary endpoint for BE	Pharmaco kinetics
Secondary	**Secondary**	
The secondary objective was to investigate the safety after a single oral dose of ICI176,334-1 and Casodex 80 mg tablet in Japanese healthy male volunteers	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 study was a two-way cross-over study for two different formulations of ICI176,334-1 (test tablet) and Casodex 80 mg tablet (standard tablet) with the following administration conditions.

Administration condition 1 (with water):
Casodex 80 mg tablet (standard tablet): administered one tablet with 150 mL water
ICI176,334-1 (test tablet): administered one tablet with 150 mL water
Administration condition 2 (without water)
Casodex 80 mg tablet (standard tablet): administered one tablet with 150 mL water
ICI176,334-1 (test tablet): administered one tablet in the oral cavity, disintegrated on the tongue and swallowed with saliva.

Administration condition	Group	Number of volunteers	Treatment period 1	Wash-out period	Treatment period 2
1	A	12	Casodex 80 mg tablet	≥35 days	ICI176,334-1

			(with water)		(with water)
	B	12	ICI176,334-1 (with water)		Casodex 80 mg tablet (with water)
2	C	12	Casodex 80 mg tablet (with water)	≥35 days	ICI176,334-1 (without water)
	D	12	ICI176,334-1 (without water)		Casodex 80 mg tablet (with 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:
Test tablet: ICI176,334-1 (oral disintegrating tablet including 80 mg bicalutamide in a tablet)
Standard tablet: Casodex 80 mg tablet (film-coat tablet including 80 mg bicalutamide in a tablet)
Dosage and mode of administration:
Dosage:
In each administration condition, one tablet of each Casodex 80 mg tablet (standard tablet) or ICI176,334-1 (test tablet) (80 mg as bicalutamide) was administered at Treatment period 1. One tablet of the other was administered at Treatment period 2.
Mode of administration
At each period in each administration condition, the investigation product (IP) was administered after over 10 hours fasting. Subjects received the specified IP in accordance with the administration condition in each group randomised. Water was restricted for 1 hour after the administration of IP, but a moderate amount of water was allowed from 1 hour after dosing. Meal was served 4 hours after the administration of IP.

Administration condition 1 (with water):
Casodex 80 mg tablet (standard tablet): administered one tablet with 150 mL water
ICI176,334-1 (test tablet): administered one tablet with 150 mL water
Administration condition 2 (without water):
Casodex 80 mg tablet (standard tablet): administered one tablet with 150 mL water
ICI176,334-1 (test tablet): administered one tablet in the oral cavity, disintegrated on the tongue and swallowed with saliva.
Disintegration in the oral cavity was defined as that the IP was putted on the tongue and swallowed after the IP was infiltrated with saliva and lightly broken down with tongue.

Batch number for IP (batch number for tablet):
Test tablet (ICI176,334-1): D6874L25-1 and D6874L25-2 (H05140)
Standard tablet (Casodex 80 mg tablet): 35390 (35390)

Duration of treatment

Each volunteer received a single dose of ICI176,334-1 (test tablet) or Casodex 80 mg tablet (standard tablet) on study Day 1 and discharged on study Day 4 of treatment period 1. The volunteer visited the study site on study Day 8, 15, 22 and 29 of treatment period 1 for PK sampling and safety evaluation. After equal to or more than 35 days wash-out period the volunteer visit the study site and started Treatment period 2. The volunteer then received a different table of treatment period 1 on Day 1 and discharged on study Day 4. The volunteer visited the study site on study Day 8, 15, 22 and 29 of Treatment period 2. Follow-up visit was conducted during the study Day 35 to 42 of Treatment period 2.

Statistical methods

Analysis of PK parameters and evaluation of BE
The AUC_t and C_{max} were calculated as primary parameters. The AUC_∞, $AUC_{0\text{-}72h}$, t_{max}, MRT , k_{el} and $t_{1/2}$ were calculated as secondary parameters. In principle, t_{max} with unconverted value and other parameters with logarithmically converted value were used for analysis. The ratio of test tablet versus standard tablet was calculated. Also the ratio of AUC_t versus AUC_∞ was calculated and validity of cut-off of sampling point was evaluated.
For the primary parameters, BE was evaluated by comparing the tablets in each administration condition (comparison of test tablet with water and standard tablet using the data of groups A and B, and comparison of test tablet without water and standard tablet using the data of groups C and D). In each comparison, the 90% confidence interval (CI) of ratio with the 90% CI of difference of the mean of logarithmically converted values of AUC_t and C_{max}. When the 90% CI of ratio was included in the range of 0.8 - 1.25 in each comparison, the test tablet and standard tablet was to be judged as bioequivalent. The secondary parameters were analysed as reference data.
As secondary analysis of the primary parameters, calculation was performed by using the linear mixed effect model with the AUC_t and C_{max} of 4 groups at the same time, and the 90% CI of ratio between test tablet and standard tablet for each administration condition was calculated by means of linear contrasts.
The analysis method was implemented in relation to the “Guideline for Bioequivalence Study” and details were provided in the statistical analysis plan.

Subject population

In total, 48 of volunteers were randomised into the groups and all volunteers received the investigational product.

One volunteer in group A (with water), two volunteers in group B (with water) and two volunteers in group C (without water) were discontinued from the study. There was no discontinuation in group D (without water). Finally, 43 of volunteers were completed the study (group A: 11, group B: 10, group C: 10, group D: 12). In randomised 48 volunteers, the data of all volunteers (48) were used for safety analysis set, and the data of 46 volunteers, excluding two volunteers of CSP deviation, was used for PK analysis set. Also the data of 42 volunteers, excluding the volunteers (6) of CSP deviation and discontinuation, was used for BE evaluation.

Summary of pharmacokinetic results

In the groups with water (groups A and B), the 90% CIs of ratios for the geometric means of AUC_t and C_{max}, which were subjected to BE assessment, between test tablet and standard tablet were calculated as 0.954 - 1.100 and 0.972 - 1.086, respectively. Therefore, since the 90% CIs of the differences of two formulations were included in the range between log (0.8) and log (1.25), it was concluded that both test tablet and standard tablet were bioequivalent.

In the groups without water (groups C and D), the 90% CsI of ratios for the geometric means of AUC_t and C_{max}, which were subjected to BE assessment, between test tablet and standard tablet were calculated as 1.002 - 1.168 and 0.988 - 1.110, respectively. Therefore, since the 90% CIs of the differences of two formulations were included in the range between log (0.8) and log (1.25), it was concluded that both test tablet and standard tablet were bioequivalent.

There was no volunteer who showed the value of AUC_t/AUC_∞ below 80 %.

Summary of safety results

No adverse event was reported in the groups with water (groups A and B).

In the groups without water (groups C and D), 1 of 22 volunteers (1 event) reported the adverse event (AE) of pharyngitis afterthe test tablet was administered. The AE was mild intensity and recovered with concomitant medicines, but it was considered unrelated to the investigational product by the investigator. One of 24 volunteers (1 event) reported the AE of nasopharyngitis after the standard tablet was administered. The AE was mild intensity and recovered without any treatment. It was considered unrelated to the investigational product by the investigator, but the volunteer was discontinued.

No clinically relevant observation and abnormality were noted in clinical laboratory and physiological tests in both groups with and without water.