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STUDY TITLE:	A randomised, open-label, 4-way crossover study in healthy subjects to explore the performance of IntelliCap® by comparing pharmacokinetic profiles of a probe drug
STUDY NUMBER:	RD 267/25619
EUDRACT NUMBER:	2013-004734-16
MEDICAL DEVICE:	IntelliCap® system (CE Ref. No. 2139618CE01)
INVESTIGATIONAL MEDICINAL PRODUCT (PROBE DRUG):	Metoprolol (50 mg): Gastroenteral solution 233 mg/mL (as metoprolol tartrate 298 mg/mL) Oral solution 1 mg/mL (as metoprolol tartrate 1.28 mg/mL)
STUDY INITIATION (first visit):	6 January 2014
STUDY COMPLETION (last visit):	7 March 2014
CHIEF INVESTIGATOR:	
REPORT AUTHOR:	
STUDY SPONSOR:	AstraZeneca AB 151 85 Södertälje Sweden
ISSUE DATE:	17 November 2014
VERSION:	Final

This study was performed in compliance with the International Conference on Harmonisation (ICH), Harmonised Tripartite Guideline for Good Clinical Practice (GCP).

2 SYNOPSIS

NAME OF COMPANY: AstraZeneca AB	Publication (reference)	*For National Authority Use only)*
NAME OF MEDICAL DEVICE: IntelliCap® system (CE Ref. No. 2139618CE01)		
NAME OF IMP (PROBE DRUG): Metoprolol		
TITLE OF STUDY: A randomised, open-label, 4-way crossover study in healthy subjects to explore the performance of IntelliCap® by comparing pharmacokinetic profiles of a probe drug.		
CHIEF INVESTIGATOR:		
STUDY CENTRE:		
STUDY START (First Visit): 6 January 2014 **STUDY COMPLETED (Last Visit):** 7 March 2014		**CLINICAL PHASE:** I

OBJECTIVES:

Primary objective:

- To assess the *in vivo* performance of the IntelliCap® system by characterizing the plasma concentration time profiles of a single dose of probe drug, released from the IntelliCap® capsule with three different release profiles, and a reference probe drug solution following a single oral dose, as a basis for establishing a correlation with *in vitro* release profiles. The *in vitro in vivo* correlation (IVIVC) work, based on the data generated, will be reported outside of the clinical study report (CSR).

Secondary objectives:

- To determine the pharmacokinetic (PK) parameters, within the studied population, of a probe drug released from the IntelliCap® capsule with three different release profiles and a reference probe drug solution following a single oral dose, by assessment of area under the concentration-time curve (AUC) from the time of dosing to the time of the last observed concentration (AUC_{0-t}) and extrapolated to infinity (AUC_{0-inf}), maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), terminal elimination half-life ($t_{½}$) and volume of distribution (Vz/F). C_{max} and t_{max} for both peaks following pulsatile probe drug release were assessed.
- To assess the safety and tolerability of the IntelliCap® system.

METHODOLOGY: This was an open-label, randomised, 4-way crossover study in 12 healthy male volunteers.

The study characterised the performance of IntelliCap® system by evaluating the plasma concentration and PK profile of a probe drug (metoprolol) released from the IntelliCap® capsule (as a gastroenteral solution with 3 different release profiles - treatment A, B and C (Table S1)), and after a single dose of an oral solution (treatment D), in order to establish a relationship between the *in vitro* release profiles and *in vivo* absorption profiles (IVIVC work).

The study comprised a Screening Visit (Screening), 4 Treatment Periods and a Post-Study Follow-up Visit.

Screening: Pre-study assessments were carried out in the 28 day period before dosing in order to assess eligibility for the study. Eligible subjects were invited to return for Treatment Period 1.

Study Periods 1-4: Eligible subjects randomly received treatment A, B, C and D (Table S1) over 4 Treatment Periods (1 treatment/period). Final confirmation of eligibility was made prior to dosing during Treatment Period 1. Confirmation of ongoing eligibility was made prior to dosing during Treatment Period 2, 3 and 4.

Table S1: Treatments Administered

	Treatment
A[a]	IntelliCap® capsule release profile 1: 50 mg metoprolol gastroenteral solution **c**onstant release rate over 6 h.
B[a]	IntelliCap® capsule release profile 2: 50 mg metoprolol gastroenteral solution constant release rate over 14 h.
C[b]	IntelliCap® capsule release profile 3: 50 mg metoprolol gastroenteral solution two-pulse release at 1 h and 6 h, each pulse releasing 25 mg metoprolol.
D	50 mg metoprolol oral solution (1 mg/mL).

[a]The drug release profiles were actuated post-gastric emptying of the IntelliCap® capsule. For PK assessments time 0 was the time at which the actuator was employed.

[b] The drug release profiles were actuated one hour post-gastric emptying of the IntelliCap® capsule. For PK assessments time 0 was the time at which the actuator was employed.

During each Treatment Period, subjects were admitted to the Clinical Unit on the day before dosing (Day -1) and following a 10 hour (h) overnight fast received the IntelliCap® capsule or metoprolol oral solution in the morning of Day 1 as per Table 9.5.1. Subjects were allowed to leave the Unit on the afternoon of Day 2 (i.e. 32 h post gastric emptying of the IntelliCap® capsule or dosing of the oral metoprolol solution) after completion of all scheduled assessments. Gastric emptying of the IntelliCap® capsule was determined in real-time by monitoring gastric pH and temperature data transmitted from the device *in situ*.

Subjects wore a carrying strap with a data recorder and relay unit (portable unit) to track the movement of the IntelliCap® capsule from the time it was administered until excretion. Subjects were asked to collect their stools in a container and to retrieve the IntelliCap® capsule once excreted. The excreted IntelliCap® capsule was returned together with the portable unit to the Clinical Unit at the next scheduled visit.

There was at least 7 days washout (between each dose).

Post-study Follow-up Visit: The post-study follow-up was carried out 7-10 days after Day 2 of Study Period 4.

Safety and PK assessments were conducted at specified time-points throughout the duration of the study.

NUMBER OF SUBJECTS: Twelve (12) subjects were randomised, of whom 11 completed the study and 1 (subject 002) requested early discontinuation.

MAIN INCLUSION CRITERIA:

- Healthy males aged between 18 and 50 years, with a body weight of 50 - 100 kg and a body mass index (BMI) of 18 - 30 kg/m^2, with no history of severe allergy/hypersensitivity or on-going clinically important allergy/hypersensitivity as judged by the Investigator or known hypersensitivity to metoprolol (including other beta (β) blockers) or any other component of the product.

IDENTITY OF INVESTIGATIONAL MEDICINAL PRODUCTS (PROBE DRUG):

Table S2: Identity Of Investigational Medicinal Products (Probe Drug)

IMP (Probe Drug)	Strength	Presentation	Route	Batch No.	Expiry
Metoprolol	233 mg/mL[a]	Gastroenteral Solution (*contained within the IntelliCap® capsule*)	Oral	13-002444AZ	04.2014
	1 mg/mL[b]	Oral Solution	Oral	13-002442AZ	04.2014

[a] Equivalent to 298 mg/mL metoprolol tartrate. [b] equivalent to 1.28 mg/mL metoprolol tartrate. **Data Source:** Pharmacy File

The IntelliCap® capsules (containing metoprolol gastroenteral solution) were administered with 240 mL water in the standing position. The drug release profiles were actuated as per Table S1 post-gastric emptying of the IntelliCap® capsule. Subjects refrained from reclining or lying down post-IntelliCap® dose to actuation. Subjects were fully recumbent or reclined with the head of the bed elevated to 45 degrees from actuation until 4 h post-actuation.

The metoprolol oral solution was administered as a 50 mL solution, followed by 3 x10 mL rinses and a further 160 mL of water to give a total fluid intake of 240 mL. Subjects were fully recumbent or reclined with the head of the bed elevated to 45 degrees for 4 h post-dose.

STUDY END-POINTS:

PK: C_{max}, t_{max}, elimination rate constant (λ_z), $t_{½}$, AUC_{0-t}, AUC_{0-inf}, residual area ($AUC_{\%Ex}$), clearance (CL/F) and Vz/F. The first and second C_{max} and t_{max} (corresponding to first and second releases) were reported for treatment C.

Safety: Adverse events (AEs), laboratory safety (biochemistry, haematology and urinalysis), vital signs (supine systolic/diastolic blood pressure and pulse), 12-lead ECG (heart rate, PR, QRS, QT and QT interval corrected using Bazett's (QTcB) and Fridericia's (QTcF) formula) and telemetry.

STATISTICAL METHODS:

PK:

Plasma Concentration Data: Individual plasma metoprolol concentration-time data are listed by treatment. Individual and mean concentration-time data are also plotted by treatment on both linear and semi-logarithmic scales.

Derived PK: PK end-points were derived from plasma metoprolol concentration-time data using WinNonlin Phoenix 32. For the calculation of derived PK end-points, concentrations below the limit of quantification (BLQ) were assigned a value of zero. The actual time of sample collection was used in the calculations.

Derived PK end-points are listed and summarised by treatment. The descriptive statistics presented are number dosed (N), number of observations (n), arithmetic mean, arithmetic standard deviation (SD), coefficient of variation (CV%), minimum, median, maximum and geometric mean (with the exception of t_{max}). The results for t_{max} were reverted back to the nominal time.

Bioequivalence: Following logarithmic transformation, C_{max}, AUC_{0-t} and AUC_{0-inf} values were subjected to a mixed effects analysis of variance (ANOVA) including fixed effects for sequence, period and treatment and a random effect for subject nested within sequence. Point estimates and 90 % confidence intervals (CI) were constructed for the contrasts between each treatment with gastroenteral solution (Intellicap® capsule) versus treatment with oral solution using the residual mean square error obtained from the ANOVA. The point and interval estimates were then back-transformed to give estimates of the ratios of the geometric least square means (LSmeans) and corresponding 90 % CI. In addition, estimated geometric means were produced for each treatment group.

An assessment of t_{max} was performed by analysing each treatment with gastroenteral solution (Intellicap® capsule) versus treatment with oral solution using the Wilcoxon matched pairs test. In addition, a 95 % non-parametric CI was constructed for the median difference in the t_{max} values based on the method of Campbell and Gardner.

Safety:

AEs: All AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary, version 16.1.

All AEs, including those which occurred prior to the first administration of study drug, are listed. Only treatment-emergent AEs (TEAEs), i.e. existing conditions that worsened or events that occurred during the course of the study after administration of study drug, are included within the summary tables. AE summaries are presented by treatment and overall.

An overall summary of AEs has been produced including the number of TEAEs; the number and % of subjects reporting at least 1: TEAE, serious TEAEs, TEAEs leading to withdrawal from the study; the number and % of subjects reporting TEAEs by severity and relationship to study drug.

Adverse Device Effects: Adverse device effects are listed.

Laboratory Safety: Biochemistry, haematology and urinalysis parameters are listed with any out of normal range values flagged. Laboratory test results which were out of normal range are presented separately along with normal reference ranges.

Vital Signs and 12-lead ECG: Parameters are listed with any out of normal range values flagged.

Telemetry ECG: The start and stop times and physicians review of telemetry data are listed.

Demographics and Background Data:

Disposition: Subject disposition is listed with any withdrawals flagged. Frequencies (N, number and %) of the total number of subjects randomised, completed, and prematurely discontinued (including reason for discontinuation) from the study are summarised by treatment. Additionally the frequency of subjects within each analysis population (safety, PK) are summarised by treatment.

Demographics: Demographic data are listed. Descriptive statistics (N, n, mean, SD, minimum, median and maximum) are tabulated for the continuous variables age, height, weight and BMI and frequencies (n and %) for the categorical variable race.

RESULTS:

PK: The PK data demonstrate that the metoprolol gastroenteral solution (released from the Intellicap® capsule with a constant release rate over 6 h and 14 h post-gastric emptying or when released in 2 pulses at 1 h and 6 h post-gastric emptying) is not bioequivalent to the metoprolol oral solution at a 50 mg dose as reflected by a test/reference geometric LS mean ratio of < 100 for C_{max}, AUC_{0-t} and AUC_{0-inf} and 90 % CIs that are not contained within the 80 - 125 % lower and upper limits (Table S3). The rate of absorption (t_{max}) was also shown to be significantly slower for the metoprolol gastroenteral solution released from the Intellicap® capsule with a constant release rate over 6 h and 14 h post-gastric emptying when compared to the oral solution, although there was no difference in t_{max} between the oral solution and 2 - pulse release of the gastroenteral solution from the Intellicap® capsule (Table S3). The Vz/F tended to be higher for metoprolol following 2 - pulse release from the Intellicap® capsule (1124.85 L) than that observed for the metoprolol oral solution (686.37 L), indicating greater degree of distribution, however, the data was extremely variable as reflected by a large SD. The Vz/F was considered similar between the metoprolol gastroenteral solution released from the Intellicap® capsule with a constant release rate over 6 h (825.53 L) and 14 h (879.07 L) post-gastric emptying and the metoprolol oral solution (686.37 L).

There was little difference in the rate of elimination between the two formulations, as reflected by similar CL/F and $t_{1/2}$ between the metoprolol gastroenteral solution (released from the Intellicap® capsule with a constant release rate over 6 h (132.90 L/h and 5.13 h) and 14 h (156.83 L/h and 4.49 h) post-gastric emptying or when released in 2 pulses at 1 h and 6 h post-gastric emptying (159.11 L/h and 5.86 h)) and the metoprolol oral solution (117.43 L/h and 4.74 h).

Table S3: Summary of Statistical Analysis of Bioequivalence

	Treatment[1]				Treatment Comparisons		
Parameter	**A (N=11)**	**B (N=11)**	**C (N=11)**	**D (N=11)**	**A vs D**	**B vs D**	**C vs D**
	Geometric LSMean				Geometric LSMean Ratio (90 % C.I.)		
C_{max} (nmol/L)[a]	175.56	109.39	170.18	359.50	48.84 (41.62 – 57.30)	30.43 (25.93 - 35.71)	47.34 (40.34 - 55.55)
AUC_{0-t} (nmol.h/L)	1793.35	1727.67	1505.63	2095.42	85.58 (73.91 - 99.10)	82.45 (71.20 - 95.47)	71.85 (62.05 - 83.20)
AUC_{0-inf} (nmol.h/L)	1860.37	1797.57	1568.63	2127.40	87.45 (74.99 - 101.97)	84.50 (72.46 - 98.53)	73.73 (63.23 - 85.98)
	Median				Median Difference (95 % C.I.) (p-value[b])		
t_{max} (h)	6.0	12.0	1.5	1.0	4.00 (2.00 – 4.75) (0.0044)	8.50 (6.50 – 11.00) (0.0033)	0.00 (-0.25 – 0.75) (0.5633)

[1] Treatment A: IntelliCap® capsule Release Profile 1 (50 mg metoprolol gastroenteral solution, constant release rate over 6 h).
Treatment B: IntelliCap® capsule Release Profile 2 (50 mg metoprolol gastroenteral solution, constant release rate over 14 h).
Treatment C: IntelliCap® capsule Release Profile 3 (50 mg metoprolol gastroenteral solution, two-pulse release at 1 h and 6 h).
Treatment D: Metoprolol 50 mg oral solution.

NB. Results obtained using a mixed effects ANOVA with fixed effects of study period, sequence and treatment and a random effect of subject nested within (excl. t_{max}). t_{max} results obtained using the method of Campbell and Gardner and the [b] Wilcoxon Matched Pairs test.[a] Analysis performed using the highest C_{max}(and corresponding t_{max}), regardless of whether 1st or 2nd peak.

Data Source: Table 14.2.2

Safety: There were no adverse device effects or study drug (metoprolol) related AEs reported.

There were no TEAEs of note reported as a result of metoprolol release during the study and overall the incidence of TEAEs was low, with a total of 3 (25.0 %) subjects reporting 3 mild AEs (Table S4) (1 event each). One (1) (9.1 %) subject reported diarrhoea following metoprolol gastroenteral solution released from the Intellicap® capsule with a constant release rate over 6 h and 2 (16.7 %) subjects reported headache (Subject 004) or dizziness (Subject 009) following 2-pulse release of metoprolol gastroenteral solution from the Intellicap® capsule (at 1 h and 6 h). All reported events were considered not related to the study medication and the subjects completely recovered. There were

no TEAEs reported following metoprolol gastroenteral solution released from the Intellicap® capsule with a constant release rate over 14 h or the metoprolol oral solution (Table S4).

Table S4: Overall Summary of TEAEs

	Treatment [1]				
	A (N=11)	**B (N=11)**	**C (N=12)**	**D (N=11)**	**Overall (N=12)**
Number of TEAEs:	1	0	2	0	3
Number(%) of subjects reporting ≥ 1:					
TEAE	1 (9.1)	0	2 (16.7)	0	3 (25.0)
Serious TEAE	0	0	0	0	0
TEAE Leading to Withdrawal	0	0	0	0	0
Number(%) of subjects with TEAE by severity:					
Mild	1 (9.1)	0	2 (16.7)	0	3 (25.0)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
Number(%) of subjects with TEAE by relationship to study drug:					
Related	0	0	0	0	0
Not Related	1 (9.1)	0	2 (16.7)	0	3 (25.0)

[1]Treatment A: IntelliCap® capsule Release Profile 1 (50 mg metoprolol gastroenteral solution, constant release rate over 6 h).
Treatment B: IntelliCap® capsule Release Profile 2 (50 mg metoprolol gastroenteral solution, constant release rate over 14 h).
Treatment C: IntelliCap® capsule Release Profile 3 (50 mg metoprolol gastroenteral solution, 2-pulse release at 1 h and 6 h).
Treatment D: Metoprolol 50 mg oral solution.

NB. A subject with multiple occurrences of an AE is counted only once within each level of severity or relationship.

Data Source: Table 14.4.1

There were no severe or serious TEAEs or suspected unexpected serious adverse reaction (SUSARs) reported.

There were no clinically significant biochemistry, haematology, urinalysis, vital sign, 12-lead ECG or telemetry findings observed during the study.

CONCLUSIONS:

DATE OF REPORT: 17 November 2014