Clinical Study Report Synopsis

Drug Substance	zolmitriptan
Study Code	D1220C00005
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An Open Label, Positron Emission Tomography (PET) Study with [^{11}C]AZ10419369 to Determine Central 5-HT$_{1B}$ Receptor Occupancy of ZOMIG® Rapimelt (zolmitriptan) in Healthy Male Volunteers

Study dates: First subject enrolled: 26 May 2010
Last subject last visit: 11 October 2010

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)

The study was conducted at a single centre: Quintiles AB, Global Phase I Services, PO Box 1543, SE-751 45 Uppsala, Sweden.

PET measurements were performed at Karolinska Institute, Solna, Sweden.

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**	
To determine by PET that zolmitriptan and/or its active metabolite 183C91, at therapeutic Zomig® Rapimelt doses, crosses the blood–brain barrier and binds to 5-HT_{1B} receptors in the living human brain.	BP_{ND}	PD
Exploratory	**Exploratory**	
To describe the relation between:	$C_{max, PET}$, $t_{max, PET}$, AUC_{PET}, $C_{av, PET}$	PK
(a) Zomig® Rapimelt dose and 5-HT_{1B} receptor occupancy	BP_{ND}, receptor occupancy	PD
(b) plasma concentrations of zolmitriptan and 183C91 and 5-HT_{1B} receptor occupancy	receptor occupancy versus $C_{av,PET}$	PK/PD

AUC_{PET}: the area under the plasma concentration-time curve during the time period of the PET measurement, BP_{ND}: non-displaceable binding potential, $C_{av, PET}$: the average plasma concentration during the time period of the PET measurement, $C_{max, PET}$: the maximum plasma concentration during the time period of the PET measurement, PD: pharmacodynamics, PK: pharmacokinetics, t_{max}, PET: time to $C_{max, PET}$

Study design

This was an open, non-randomised, repeated dose, single-centre, exploratory positron emission tomography (PET) study in male healthy volunteers in which the central 5-HT_{1B} receptor occupancy by zolmitriptan and/or its active metabolite 183C91 was studied by PET measurements and the radioligand [^{11}C]AZ10419369.

The study comprised 3 cohorts with 3 healthy volunteers in each of the first 2 cohorts and 2 healthy volunteers in the third cohort. One or 2 baseline PET measurements and 2 to 3 PET measurements following administration of therapeutic doses of Zomig® Rapimelt (5 or 10 mg) were performed for each healthy volunteer.

Target subject population and sample size

The main inclusion criteria were male healthy volunteers aged ≥20 to ≤45 years and with a body mass indix (BMI) of ≥19 to ≤30 kg/m^2. The healthy volunteers had to have a normal magnetic resonance image (MRI) scan at Visit 2.

The study used a standard design for PET receptor occupancy studies and the healthy volunteers served as their own controls. The study comprised 3 cohorts and the number of healthy volunteers in each cohort (n=3 in Cohorts 1 and 2 and n=2 in Cohort 3) was based on experience from drug occupancy studies using PET measurements.

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

Table S2 Details of investigational product and other study treatments

Investigational product	Dosage form, strength, and route of administration	Manufacturer	Batch number
Zomig® Rapimelt	Orodispersible tablet, 5 mg	AstraZeneca	GJ391 and GB116
[^{11}C]AZ10419369	Solution for iv injection	PET Centre, Karolinska Institute	Not applicable

Each dose of Zomig® Rapimelt was administered approximately 2 hours post a standardised breakfast or lunch and the [^{11}C]AZ10419369 radioligand was injected approximately 2 hours post dose of Zomig® Rapimelt. Each healthy volunteer received 2 or 3 doses of Zomig® Rapimelt (2x10 mg [n=6] or 2x10 mg and 1x5 mg [n=2]).

Duration of treatment

Two or 3 single doses of Zomig® Rapimelt were administered to healthy volunteers in 2 to 3 treatment periods. Each dose was separated by a wash-out period of 7 to 16 days.

Statistical methods

The data were summarised using descriptive statistics.

Subject population

A total of 8 male healthy volunteers, aged 20 to 29, were included in the study at 1 study site. All but 1 healthy volunteer (E0001004) completed the study. E0001004 was discontinued from investigational product (IP) due to low receptor occupancy after administration of 2x10 mg doses of Zomig® Rapimelt at Visit 3 and 4. The PK, PD and safety analysis sets included all included healthy volunteers, ie, 8. .

Summary of pharmacokinetic results

The plasma concentrations of zolmitriptan and its active metabolite 183C91 were in general relatively constant during the PET measurements, hence $C_{av, PET}$ (10 mg: geometric mean of 7470 pg/mL for zolmitriptan and 4820 pg/mL for 183C91 [n=16], 5 mg: 3150 to 5810 pg/mL for zolmitriptan and 2960 to 3950 pg/mL for 183C91 [n=2]), was close to the $C_{max, PET}$

(10 mg: geometric mean of 8230 pg/mL for zolmitriptan and 5290 pg/mL for 183C91, 5 mg: 3300 to 6989 pg/mL for zolmitriptan and 3060 to 4590 pg/mL for 183C91). The range for $t_{max, PET}$ following 5 and 10 mg Zomig® Rapimelt was 0.00 to 0.53 hours for zolmitriptan and 0.00 to 1.08 for 183C91. However, the relatively constant plasma levels suggest that the PET measurements were performed close to C_{max} of zolmitriptan and 183C91.

Summary of pharmacodynamic results (PET measurements)

At baseline, radioligand uptake showed a regional distribution corresponding to the anatomical distribution of 5-HT_{1B} receptors. After treatment with single 5 mg or 10 mg doses of Zomig® Rapimelt, a decreased uptake of the radioligand was observed in majority of the measurements. The cortical region was used for the evaluation of drug effect, chosen as the region with largest volume and, thus, most accurate image statistics.

A summary of radioligand [^{11}C]AZ10419369 binding at baseline and after treatment with a single dose of zolmitriptan is shown in Table S3. Mean baseline BP_{ND} values were used for receptor occupancy calculations in the cases where two baselines (n=5) were available. The mean receptor occupancy at 10 mg zolmitriptan dose (16 measurements in total) was 8%.

Table S3 Summary of binding potential at baseline and after administration of zolmitriptan and occupancy (%) at 5-HT_{1B} receptors by regions of interest, ROI (PD analysis set)

ROI	Parameter (unit)	Treatment	n	Mean	SD	Min	Median	Max
Cortex	BP_{ND}	PET Baseline 1	8	1.21	0.14	0.98	1.25	1.35
		PET Baseline 2	5	1.30	0.17	1.03	1.35	1.46
		Difference (%)[a]	5	-11.55	11.91	-32.14	-8.24	-2.06
		PET Baseline 1&2	13	1.25	0.15	0.98	1.26	1.46
		Zomig® Rapimelt 5 mg	2	1.32	0.11	1.24	1.32	1.39
		Zomig® Rapimelt 10 mg	16	1.15	0.10	0.88	1.17	1.29
	Occupancy (%)	Zomig® Rapimelt 5 mg	2	-2	13	-11	-2	7
		Zomig® Rapimelt 10 mg	16	8	6	-3	10	19

[a] Difference (%) = ([PET Baseline 1 - PET Baseline 2]/PET Baseline 1)*100.
BP_{ND}: binding potential (non-displaceable), n: number of observations
Only results from PET model SRTM have been presented.

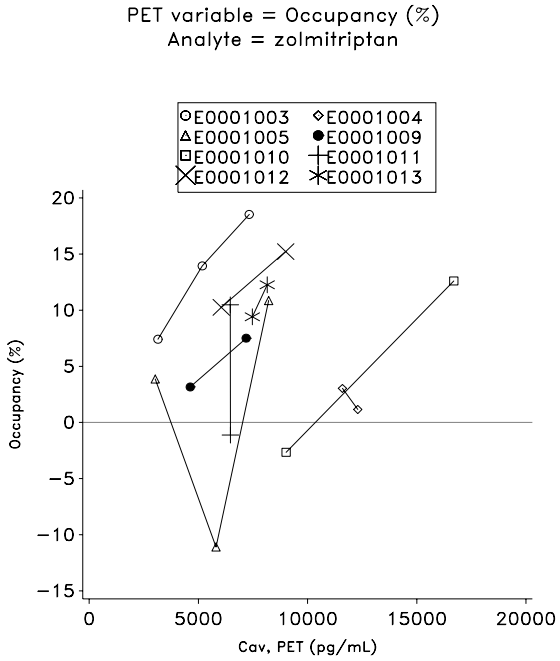
Summary of pharmacokinetic/pharmacodynamic relationships

In general, there was a plasma concentration-dependent reduction of the radioligand binding potential after administration of therapeutic doses of Zomig® Rapimelt. Consequently, receptor occupancy was increasing with increasing plasma exposure of zolmitriptan and

183C91. This relationship was evident for both analytes in 5 out of 8 healthy volunteers (Figure S1).

Due to the low receptor occupancy, modelling of the data was not considered clinically relevant. An estimation of $K_{i,plasma}$ would require zolmitriptan doses above the therapeutic range.

Figure S1 Individual values of occupancy versus $C_{av, PET}$ in cortex (PK/PD analysis set)



Summary of safety results

There were no deaths, other serious adverse events (SAEs), discontinuations of IP due to adverse events, or any other significant adverse events in the study. A total of 31 AEs were reported by 8 healthy volunteers. Thirteen of these AEs, of which 10 were mild and 3 were moderate in intensity, started within 0 to 24 hours after administration of Zomig® Rapimelt and were reported by 6 healthy volunteers. The most common AEs reported within 24 h after dose of Zomig® Rapimelt were injection site haematoma (associated with the arterial catheter) and arthralgia. None of these events were assessed as causally related to treatment with Zomig® Rapimelt by the investigator. There were no clinically significant abnormalities in any laboratory variables, vital signs, ECG or physical examination during the study.