2 SYNOPSIS OF STUDY REPORT, No. D-11.236 (AC-SWE-001)

COMPANY:	TABULAR FORMAT REFERRING TO PART Enter Part OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Actelion Pharmaceuticals AB	Type … *(ONLY DRA)*	
NAME OF FINISHED PRODUCT:	Volume:	
Miglustat	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
OGT 918, ACT-149071	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	Determination of [^{11}C]-miglustat uptake in bone tissue and brain using positron emission tomography (PET)		
INDICATION	Gaucher's disease type 1		
INVESTIGATOR(S) / CENTER(S) AND COUNTRY(IES)	The study was conducted at one center in Sweden (Karolinska University Hospital, Stockholm, Sweden). [redacted]		
PERIOD OF TRIAL	10 Aug 2009 to 1 Oct 2009 (first subject visit to last subject follow-up visit)	CLINICAL PHASE	4
OBJECTIVES	To determine the biodistribution and time course of [^{11}C]-miglustat in bone tissue and brain at the therapeutic dose level of miglustat.		
STUDY DESIGN	Prospective, single-center, open-label exploratory Phase 4 biodistribution study. The study consisted of a screening visit (21 ± days before treatment), a 2-day treatment/measurement period, and a 28-day safety follow-up. Each of three treatment/measurement cycles consisted of a computed tomography (CT) scan followed by an intravenous (i.v.) injection of [^{11}C]-miglustat at the start of a 60-min PET scan of brain or bone (femur). On Day 1, the first treatment/measurement cycle (brain		

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	scan) was followed by a therapeutic oral dose of miglustat 100 mg given 240 ± 120 h before the second cycle (bone scan). On Day 2, a therapeutic oral dose of miglustat 100 mg was given 240 ± 120 h before the third cycle (brain scan). Blood samples were taken periodically during each PET scan.
NUMBER OF SUBJECTS	One or two subjects were planned, and one subject was enrolled.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female, ≥ 18 years of age with Gaucher's disease type 1 and typical bone manifestations diagnosed with radiological examinations (x-ray, magnetic resonance) and without severe renal impairment, defined as creatine clearance < 30 mL/min.
TRIAL DRUG / DOSE / ROUTE / REGIMEN / DURATION	[^{11}C]-miglustat freshly synthesized and diluted in saline, with about 250 MBq and 10 μg miglustat administered as a bolus i.v. injection at the start of each of the three PET scans Miglustat (OGT 918, ACT-149071) 100-mg capsules, taken orally once on Day 1, 240 ± 120 min prior to the second PET scan and once on Day 2, 240 ± 120 min prior to the third PET scan
REFERENCE DRUG	Not applicable.
CRITERIA FOR EVALUATION	
PHARMACOKINETICS:	Plasma miglustat concentration just prior to and immediately after each of the second and third PET scans following oral miglustat 100 mg Time course of [^{11}C]-miglustat in blood over the first 60 min after its i.v. administration Time-activity curves for [^{11}C]-miglustat uptake in bone (femur) and brain over the first 60 min after its i.v. administration as assessed by PET
SAFETY:	Occurrences of adverse events, serious adverse events, and discontinuation, and changes in vital signs and body weight
STATISTICAL METHODS:	
No hypothesis or sample size calculation was proposed for this exploratory study; one or two subjects were considered sufficient based on empirical considerations. All clinical data were presented as collected on the case report form. Miglustat concentrations and radioactivity in blood and/or plasma were presented by time point of measurement.	

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Radioactivity (from PET) was converted to standardized uptake values (SUV), with both radioactivity and SUV presented by time point of measurement (time-activity curves) for relevant tissues. SUV data were illustrated graphically. All results were evaluated by inspection.

SUBJECT DISPOSITION:

The single subject enrolled in the study was a 55-year-old, Caucasian, post-menopausal woman with type 1 Gaucher disease (N370S mutation, treatment naïve) who completed the study per protocol.

PHARMACOKINETIC RESULTS:

The miglustat concentration in plasma following oral administration was relatively stable over each 60-minute PET scan, but was higher after the second administration than the first (931 vs 791 ng/mL). When the subject was treatment naïve, standardized uptake of [^{11}C]-miglustat in whole blood following bolus i.v. infusion peaked at about 2 minutes (approximately 6 SUV with blood:plasma ratio 0.78) and decreased thereafter in a biphasic manner. After administration of oral miglustat, results were generally similar to those before administration of oral miglustat in one of the scans and a little different in the other scan.

Initial uptake of [^{11}C]-miglustat in femur following a therapeutic 100-mg dose of miglustat was rapid, and radioactivity decreased in a biphasic manner (to about 1 SUV) with kinetics similar to that in blood over the 60-minute monitoring period. No indication of [^{11}C]-miglustat uptake in brain was found during the 60-minute monitoring period, whether performed before (treatment naïve) or after oral administration of miglustat 100 mg. The high radioactivity seen in the urinary bladder confirmed urine as the primary route of excretion.

SAFETY RESULTS:

The subject had no adverse events or other clinically relevant change in safety variable during the study. No safety issues were indicated during treatment or follow-up.

CONCLUSIONS:

This first study to measure miglustat uptake in human tissues *in vivo* showed a rapid uptake in bone (femur) but no observable uptake in brain during the first 60 minutes following an i.v. injection of [^{11}C]-miglustat in a female subject with type 1 Gaucher's disease. No relevant safety or tolerability issues were seen in the study.

13 December 2011: