Ascending single-dose study with ACT-280778, a non-dihydropyridine, dual L- and T-type calcium channel blocker: safety, tolerability, pharmacokinetics, and effect of food in healthy male subjects

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Introduction

- ACT-280778 is a non-dihydropyridine, dual L- and T-type calcium channel blocker. In animal models, ACT-280778 potently increases coronary blood flow, has anti-ischemic properties, and does not reduce myocardial contractility. Data from non-clinical studies (Actelion Pharmaceuticals Ltd, data on file) show that ACT-280778 is a potent anti-hypertensive agent with a long duration of action. It appears to have a low risk of inducing reflex tachycardia and shows no indication of increased effect over time or tachyphylaxis. Overall, the non-clinical profile of ACT-280778 warranted further investigation of this compound in human subjects.

Objectives

- The objectives of this study were to evaluate the safety and tolerability of ascending single oral doses of ACT-280778 in healthy male subjects and to investigate the single oral dose pharmacokinetics (PK) of ACT-280778, the effect of food on the single oral dose PK of ACT-280778, and the dose proportionality of PK parameters over a range of doses of ACT-280778.

Methods

Study design

- This study was a prospective, single-center, double-blind, placebo-controlled, randomized, single ascending dose, Phase 1 study in healthy male subjects based on study-specific inclusion and exclusion criteria.
- Each subject participated in one treatment period (fasted) with the exception of subjects in the food effect group who participated in two treatment periods (fasted and fed) at the 5 mg dose level. These subjects were given a second oral dose after a wash-out period of 7–10 days and within 10 min after completing a standardized high-fat/high-calorie breakfast.

Safety and tolerability evaluation

- Safety and tolerability were evaluated throughout the study at protocol-specified time points by monitoring adverse events (AEs), clinical laboratory variables, vital signs (blood pressure and heart rate [HR], both supine and standing), standard 12-lead electrocardiograms (ECGs), 24-h 12-lead Holter ECGs, 5-lead ECG telemetry, and physical examination.

Modeling and simulation

- A model-based adaptive design[1] with alterations (use of a maximum effect (E_{max}) model instead of a logistic regression model) was employed to quantify the PK and the safety of ACT-280778 to support the decision on the dose for the next group.
- The doses for the first two groups were fixed (2 and 5 mg) and the decision to proceed with 5 mg was supported by safety and tolerability data only. Subsequent doses were determined by employing a model-based approach. In addition, a modeling approach was set up to select the optimal dose as a trade-off for the tested pharmacodynamic parameters following Thall and Cook 2004.[2] The dose level for the next dose group was defined as the minimum of the model-estimated lowest maximum tolerated dose (MTD) across all safety endpoints but not exceeding 3 times the highest dose administered so far.

Table 1 *Summary of AEs (n [%]) following a single administration of ACT-280778.*

Treatment	ACT-280778 dose						
	Placebo	2 mg	5 mg	5 mg (food effect)		15 mg	40 mg
N	8	6	6	6		6	2
				Fasted	Fed		
Cardiac disorders							
Accelerated idioventricular rhythm	0	0	0	0	0	0	1 (50.0%)
Sinus arrhythmia	0	0	0	0	0	0	1 (50.0%)
Supraventricular extrasystoles	0	0	0	0	0	0	1 (50.0%)
Respiratory, thoracic, and mediastinal disorders							
Epistaxis	0	0	0	0	1 (16.7%)	0	0
Gastrointestinal disorders							
Abdominal pain	0	0	0	0	2 (33.3%)	0	0
Mouth ulceration	0	0	0	0	0	1 (16.7%)	0
Musculoskeletal and connective tissue disorders							
Myalgia	1 (12.5%)	0	0	0	0	0	0

AEs are categorized by system organ class, preferred term, and treatment. The table presents the number of AEs (and the percentage of subjects with at least one AE based on the number of subjects in each treatment group). The dose of 5 mg in fed and fasted state was administered to the same subjects (food effect group).

Table 2 *Summary of mean PR interval (standard deviation) and HR (standard deviation) changes from baseline to post-dose time points following single-dose administration of ACT-280778.*

Treatment		ACT-280778 dose													
		Placebo		2 mg		5 mg		5 mg (food effect)				15 mg		40 mg	
N		8		6		6		6				6		2	
								Fasted		Fed					
	Time (hours)	PR	HR	PR	HR	PR	HR	PR	HR	PR	HR	PR	HR	PR	HR
Day 1	1	3.1 (3.9)	3.4 (4.7)	–2.0 (–)	5.0 (–)	–0.4 (7.9)	–1.4 (3.5)	2.0 (2.3)	–4.0 (7.4)	–6.0 (4.2)	7.2 (2.3)	4.0 (5.5)	1.0 (3.7)	8.0 (–)	1.0 (–)
	2	1.3 (5.9)	1.4 (5.0)	0.0 (–)	–3.0 (–)	6.0 (6.9)	–1.3 (8.4)	–0.7 (11.1)	–4.0 (5.1)	1.5 (7.2)	10.0 (2.3)	8.0 (7.9)	0.2 (2.4)	21.0 (9.9)	–4.0 (2.8)
	4	0.9 (6.1)	1.2 (5.1)	5.2 (5.2)	–3.2 (2.4)	7.6 (4.6)	–1.0 (2.6)	10.8 (8.8)	–2.0 (6.3)	–5.6 (7.8)	3.8 (2.9)	13.7 (7.3)	–0.8 (5.1)	26.0 (–)	–7.0 (–)
	8	4.2 (4.1)	0.6 (9.4)	4.7 (6.4)	0.7 (2.5)	2.8 (9.0)	0.4 (1.5)	7.7 (5.7)	–1.3 (2.7)	1.0 (8.4)	–1.0 (3.7)	20.0 (6.9)	–3.7 (5.5)	20.0 (–)	–1.0 (–)
	24	3.5 (5.2)	1.5 (3.9)	–6.7 (6.1)	8.0 (2.0)	–1.0 (8.7)	–1.8 (2.8)	1.0 (3.0)	–4.2 (5.5)	3.0 (2.8)	–0.2 (3.5)	3.0 (2.0)	–0.8 (3.3)	11.0 (7.1)	–3.0 (0.0)

Mean PR interval changes are provided in ms and mean HR changes are provided as beat per minute. Both represent changes from study baseline to post-dose time points after study drug administration (Day 1) as assessed by standard 12-lead ECG. The dose of 5 mg in fed and fasted state was administered to the same subjects (food effect group).

Results

Subject disposition

- Thirty-four healthy male subjects were enrolled and all completed the study according to the protocol. Overall, subjects had a mean age (range) of 25.7 (19–36) years and a mean body mass index (range) of 24.6 (20.3–29.5) kg/m^2. Demographics were balanced between the treatment groups.
- A total of 8 subjects received placebo and 6 subjects each received 2, 5, or 15 mg of ACT-280778 in fasted state. In the food effect group, 6 subjects received a first dose of 5 mg in fasted state and, after a wash-out period, a second dose of 5 mg in fed condition. In the 40 mg group, only the first 2 subjects of the sentinel group received 40 mg ACT-280778 because the criteria for dosing of the remaining subjects were not met.

Tolerability and safety

- In total, 8 AEs were reported by 6 subjects, all of mild intensity and resolved without sequelae. No serious AEs were reported throughout the study. An overview is provided in Table 1.
- Following treatment with 40 mg of ACT-280778, one subject (ID 401) showed electrocardiographic signs of sinus arrhythmia (associated with junctional rhythm) and supraventricular extrasystoles with an onset approximately 1 h and 36 min after drug administration, lasting for approximately 24 and 15 h, respectively. Another subject (ID 402) showed electrocardiographic signs of accelerated idioventricular rhythm occurring at about 8.5 h after drug administration. This subject experienced a single, self-limiting episode of 11 beats of nodal or potentially supraventricular origin with a HR of 91 beat per minute (bpm), lasting for approximately 7 seconds.
- Both subjects had no relevant past medical or family history and were confirmed to have a structurally normal heart. They were clinically asymptomatic and hemodynamically stable during these events and during the entire study. No medical or pharmacological intervention was required and all associated morphological ECG changes resolved after 25 h. The abnormal ECG findings associated with single doses of 40 mg resulted in discontinuation of treatment of further subjects at the 40 mg dose level and cessation of further dose escalation.
- Overall, 4 different AEs were assessed by the investigator to be related to the study medication: sinus arrhythmia (associated with junctional rhythm) and supraventricular extrasystoles, and accelerated idioventricular rhythm within the 40 mg dose group and abdominal pain (2 subjects) in the 5 mg group under fed condition. Abdominal discomfort was experienced only in the fed group, which suggests that this may have been related to the high-fat/high-calorie breakfast. However, a relation to ACT-280778 could not be ruled out.
- No clinically relevant changes from baseline were observed in clinical laboratory, vital signs, or individual ECG variables in all dose groups up to and including 15 mg.
- A slight increase from baseline was observed for the PR interval within the 15 and 40 mg dose groups (Table 2).

Pharmacokinetics

- Plasma concentration–time profiles for the different dose levels are shown in Figure 1 and a summary of the PK parameters is provided in Table 3. A larger than dose-proportional increase of maximum plasma concentration observed (C_{max}) and area under the plasma concentration–time curve ($AUC_{0-\infty}$) occurred across doses. In the presence of food, time to reach maximum plasma concentration (t_{max}) (range) was 5.3 h (3.5–6.0) compared with 0.75 h (0.75–2.0) without food. Food increased $AUC_{0-\infty}$ by a factor of 2, but had only a small effect on C_{max}.
- A population PK model estimated that food reduced the absorption rate by 80% and increased the extent of absorption by 82%. PK parameters were characterized by high inter-subject variability.

Figure 1. *Arithmetic mean plasma and individual plasma concentration–time profiles of ACT-280778 after administration of single oral doses to healthy male subjects (a) after administration of 2, 5, or 15 mg ACT-280778 in fasted condition, (b) after administration of 40 mg ACT-280778 in fasted condition, and (c) after administration of 5 mg ACT-280778 in fed or fasted condition.*

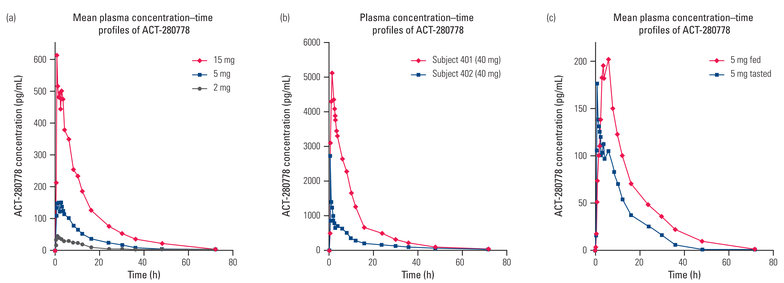
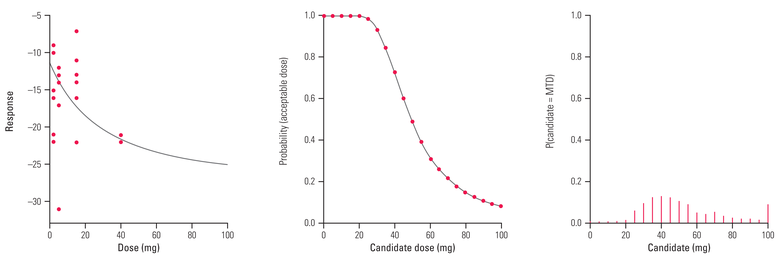


Table 3 *Summary of PK variables of ACT-280778 determined after single doses of 2, 5, 15, and 40 mg ACT-280778 to healthy male subjects.*

ACT-280778 Dose	N	t_{max} (h)	C_{max} (pg/mL)	$AUC_{0-\infty}$ (pg-h/mL)	$t_{1/2}$ (h)
2 mg	6	0.98 (0.75, 3.0)	48.4 (29.1, 80.7)	498 (358, 695)	9.1 (7.1, 11.6)
5 mg	6	2.0 (0.8, 2.8)	160 (86.1, 298)	1719 (1028, 2873)	11.7 (9.5, 14.5)
5 mg (Fasted, Period 1)	6	0.75 (0.75, 2.0)	191 (117, 312)	1555 (716, 3377)	9.5 (6.8, 13.4)
5 mg (Fed, Period 2)		5.3 (3.5, 6.0)	212 (154, 292)	2925 (1656, 5165)	10.8 (8.8, 13.2)
15 mg	6	0.98 (0.75, 2.8)	668 (474, 940)	6461 (4528, 9221)	12.1 (10.2, 14.2)
40 mg (Subject 401)	1	1.5	5100	46,876	12.5
40 mg (Subject 402)	1	0.75	2720	13,263	16.4

Data are geometric means (and 95% CI) and, for t_{max}, median (range). The dose of 5 mg in fed and fasted state was administered to the same subjects (food effect group).
$AUC_{0-\infty}$: area under the plasma concentration–time curve from 0 to infinity; C_{max}: maximum plasma concentration observed; $t_{1/2}$: terminal half-life; t_{max}: time to reach C_{max}.

Figure 2. *Modeling and simulation results for maximum individual decrease in systolic blood pressure in supine position after administration of 40 mg. Figures show (a) observed maximum individual decrease versus dose administered and E_{max} regression fit, (b) probability estimate for candidate doses in 5 mg steps between 0 and 100 mg to be clinically acceptable (not more than 25% of subjects showing a maximum decrease of 20 mmHg or higher), and (c) estimated distribution of maximum tolerated dose for candidate doses.*



Modeling and Simulation

- Figure 2 shows as an example the estimated relationship between dose and maximum decrease from baseline in systolic blood pressure in standing position for all 4 dose groups in this study. Figure 2a shows the data and the fitted regression line. Figure 2b shows the estimated probabilities that a candidate dose (0 to 100 mg in 5 mg increments) is clinically acceptable. Figure 2c shows the distribution of the estimated MTD. A dose was defined as not acceptable if more than 25% of subjects show a maximum decrease in systolic blood pressure of 20 mmHg or more. For example, the 1000 simulations of an administration of 50 mg to 6 virtual subjects showed that 50 mg was not acceptable in 98 of 1000 simulations. Thus, the probability that 50 mg was a non-acceptable dose was estimated as 9.8%. In each simulation, the highest acceptable dose constituted the MTD. The 1000 simulated MTDs provided an estimation of the distribution of the MTD.

Summary and conclusions

- Single oral doses of ACT-280778 up to and including 15 mg were well tolerated. A single dose of 40 mg ACT-280778 was associated with abnormal ECG findings that prevented further dosing at this level and further dose escalation. Therefore, the single oral maximum tolerated dose was determined as 15 mg.
- Model-guided dose escalation proved to be helpful for the decision to select the next dose to be administered. The quantification of risk provided confidence in the decision-making based on estimated probabilities and adaptation of the dose escalation step size if indicated by the model.
- ACT-280778 was rapidly absorbed and the increase of C_{max} and AUC was more than dose-proportional. A population PK model estimated that food reduced the absorption rate by 80% and increased the extent of absorption by 82%, leading to approximately twice the exposure with food.
- The PK profile of ACT-280778 is consistent with a once-daily dosing regimen and further evaluation of ACT-280778 in patients with hypertension is warranted.

References

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Disclosures

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