AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Metoprolol
Study Code	D4022L00008
Edition Number	1.0
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A randomised, open label, parallel group, multicentre, phase IV study on the effect of 8 weeks Succinate Metoprolol ZOK (95 – 190 mg) on heart rate in the Stable angina patients

Study dates:	First subject enrolled: 29 Oct 2010
	Last subject last visit: 8 Nov 2011
Phase of development:	Therapeutic use (IV)

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

Study centre(s)

The study was conducted at 15 sites in China.

Publications

It is planned that the study will be published in a domestic core periodical (e.g. Chinese Journal of Cardiology 中华心血管病杂志) in Q3 2013.

Objectives and criteria for evaluation

Table S1 Objectives and outcome variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description**
Primary	*Efficacy*	To investigate the impact on 24-hr average heart rate between two groups (metoprolol succinate 95mg vs. 190mg) after 8 weeks treatment in the study.	Difference of the 24-hr average heart rate between two groups after 8 weeks treatment.
Secondary	*Efficacy*	To investigate the impact on 24-hr average heart rate from baseline within groups after 8 weeks treatment in the study.	Difference of the 24-hr average heart rate within groups from baseline after 8 weeks treatment.
	Efficacy	To investigate the different impact on 24-hr average heart rate between two groups after 2 weeks treatment in the study	Difference of the 24-hr average heart rate between two groups after 2 weeks of treatment.
	Efficacy	To investigate the impact on 24-hr average heart rate from baseline within groups after 2 weeks treatment in the study.	Difference of the 24-hr average heart rate within groups from baseline after 2 weeks treatment.
	Efficacy	To investigate the proportion of patients with resting heart rate controlled to ≤60bpm after 2 and 8 weeks treatment.	Difference in proportions of patients who had resting heart rate controlled to ≤60 bpm after 2 weeks and 8 weeks treatment between groups
	Efficacy	To evaluate the difference of change from baseline in TIB between groups after 2 and 8 weeks treatment.	Difference in change from baseline in TIB between two groups after 2 weeks and 8 weeks treatment.
	Efficacy	To evaluate the difference of change from baseline in angina frequency between groups after 2 and 8 weeks treatment.	Difference in change from baseline of angina pectoris frequency between two groups after 2 weeks and 8 weeks treatment.
	Safety	To observe the numbers of DAEs and SAEs.	Difference of the numbers of DAEs and SAEs between groups.
	Safety	To explore the change from baseline in FPG, TC, and TG	Difference of change from baseline in FPG, TC, and TG after 8 weeks treatment between groups.

Study design

This study aimed to investigate the different effect of metoprolol succinate between different doses (95 *vs.* 190mg) on heart rate control in Stable angina patients. The tolerability of the

investigated doses was also observed in the study.

The study actually enrolled 251 randomized subjects and the design was specified three sequential periods:

- A run-in period of one week started from the date of metoprolol succinate 47.5mg/day run-in visit (visit 1, week 0) to the date of randomization (visit 2, week 1).

- An open-label treatment period of 2 weeks started from the date of randomization to the date of the Week 3. Two groups were on 47.5mg and 95mg respectively for two weeks.

- An open-label parallel group treatment period of 6 weeks started from the first date of week 3 to the end of the week 9. Two groups titrated to 95mg and 190mg respectively for six weeks.

During the initial 1 week run-in period, all the subjects were treated with 47.5mg metoprolol succinate. After that, the subjects were randomized into two groups. One group continued treatment with 47.5mg for two weeks then titrated to 95mg, if the patient could tolerate the dosage without bradycardia symptoms, SBP<100mmHg and heart rate < 45bpm according to 12-lead ECG at week 3 and week 9. The other group was with 95mg for two weeks then titrated to 190mg, if the patien could tolerate the dosage without bradycardia symptoms, SBP<100mmHg and heart rate < 45 bpm according to 12-lead ECG at week 3 and week 9. The heart rate control and anti-ischemia effects were evaluated between and within the groups.

After the treatment period, the investigational drug was provided for another 2 weeks to ensure the subjects' well being and benefit. The study duration was 9 weeks in total. The time window for each visit during treatment period was ±3 days. There were five scheduled visits at week 0, 1, 3, 4 and 9 during run-in and treatment periods. Any unscheduled visits were to be guided by the perceived clinical need. At each study centre, the investigator dedicated a back-up physician who was fully informed on the procedures for unscheduled visits.

In this study, the dose of metoprolol succinate could be titrated up to 190mg at most. If a patient couldn't tolerate and be confirmed by the investigator at any visits, the dose should be reduced to a lower level and patients should continue the lower level treatment till the end of the study when current dose was >47.5mg. If the current dose was 47.5mg,the subjects should be discontinued.

Current dose	**Discontinuation or dose reduction**
47.5 mg	Discontinuation
95 mg	Dose is to be decreased to 47.5 mg
190 mg	Dose is to be decreased to 142.5 mg*

* If patient still couldn't tolerate 142.5mg，the investigator should discuss with AstraZeneca Study physician on how to handle this situation. 24-hour ambulatory ECGs were recorded from the morning on the day right before randomization and the visit day at week1, week3, week4 and week 9, for the variables of heart rate and total ischemic burden.

Target subject population and sample size

For inclusion in the study subjects around China should fulfil the following criteria:

1. Male or female Chinese patients aged 18-75 years;

2. Heart rate ≥ 65bpm;

3. Diagnosed as Stable angina for at least 1 month and with stable angina pectoris symptoms within 2 weeks previous to enrolment(Please find the diagnose criteria of Stable angina on Appendix C)

4. With LVEF ≥ 50% according to ultrasound cardiogram;

5. On beta-blockers for at least 4 weeks*, on the dose equivalent to metoprolol succinate 23.75-47.5mg/day.

There were 231 patients in ITT population and 274 in Safety population. There were 115 patients in metoprolol succinate 190 mg regimen and 116 in metoprolol succinate 95 mg regimen in ITT population. There were 112 and 162 patients in metoprolol succinate 190 mg and 95 mg regimen respectively in Safety population.

A sample size of 101 in each group had 80% power to detect a difference in means of-4.2 (the difference between metoprolol succinate 190mg mean of 59.8 and metoprolol succinate 95mg mean of 64.0) assuming that the metoprolol succinate 190mg standard deviation was 11.1 and the metoprolol succinate 95mg standard deviation was 10.0 (based on study D4026C00001) using a two group Satterthwaite t-test with a 0.050 two-sided significance level.

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

Investigational product	Dosage form and strength	Manufacturer
Metoprolol succinate	95 mg, tablets	Astrazeneca AB, Sweden

The study drug will be supplied to the investigator by AstraZeneca.

Metoprolol succinate tablet is a white or off-white film-coated tablet. It is white after removing the film-coating. Metoprolol succinate tablets are administrated orally once daily, preferably in the morning. The sustained-release tablets can be divided, but must not be chewed or crushed. The tablets should be swallowed together with least half a glass of liquid. Concomitant intake of food does not influence the bioavailability.

Duration of treatment

The investigational product, metoprolol succinate, was taken orally, once a day during this study.

In the run-in period, all subjects started to take the first dose of metoprolol succinate 47.5mg after the visit 1 (week 0), and continued for one week till the visit 2 (week 1).

After the visit 2 (week 1), the subjects were randomised to low and high dose groups.

Subjects in low dose group continued on 47.5mg for 2 weeks, till the visit 3 (Week 3). Subjects in high dose group started to take 95mg after the visit 2 (week 1), and maintained the dose for 2 weeks, till the visit 3 (Week 3).

The dose was titrated to 95mg and 190mg respectively at visit 3 (Week 3). The subjects continued on this dose (95mg and 190mg) for 6 weeks, till the end of the study. For the subjects who couldn't be tolerated and confirmed by the investigators dose should be decreased to a lower level.

Current dose	**Discontinuation or dose reduction**
47.5mg	Discontinuation
95mg	Dose is to be decreased to 47.5 mg
190mg	Dose is to be decreased to 142.5 mg*

* If patient still compliant couldn't tolerate 142.5mg, the investigator should discuss with AstraZeneca Study physician on how to handle this situation.

Statistical methods

To determine the effect of treatment on 24-hr average heart rate in two treatment groups after 8 weeks treatment, a mixed model repeated measures (MMRM) analysis was performed on change from baseline in the 24-hr average heart rate (OC, Observed Case). This approach assumed that missing observations were missing at random and utilizes all available data. The model included treatment, centre and baseline 24-hr average heart rate, visit and treatment by visit interaction as explanatory variables. Centre was treated as a random effect while all other explanatory variables was treated as fixed effects. To model the covariance structure an unstructured covariance matrix (UN) was used. If the algorithm did not converge for the change from baseline data set, first-order autoregressive covariance structure was used. The primary contrasts of interest were the treatment differences between metoprolol succinate 95mg and metoprolol succinate 190mg at week 9.

Subject population

The study was conducted at 15 sites in China.

Disposition	***Betaloc 190 mg***	***Betaloc 95 mg***	***Overall***
Patients enrolled *			317
Patients included in safety population	112	162	274
Patients excluded from safety population			43
Patients failed to receive any dose of investigational product			43
Patients randomized	126(100.0%)	125(100.0%)	251(100.0%)
Patients included in safety population but not randomized			23
Voluntary Discontinuation by Subject			16
Incorrect Enrolment			3
Heart Rate<45 bpm or SBP<100 mmHg during visit			1
Adverse Event			2

Disposition	*Betaloc 190 mg*	*Betaloc 95 mg*	*Overall*
Other			1
Patients randomized as high-dose group but were included in low-dose group			17
Patients randomized as low-dose group but were included in high-dose group			3
Patients included in ITT population	115(91.3%)	116(92.8%)	231(92.0%)
Patients excluded from ITT population	11 (8.7%)	9 (7.2%)	20 (8.0%)
Patients who randomized but didn't take any dose of investigational product	0	0	0
Patients who randomized but didn't have baseline 24-hr average heart rate	3 (2.4%)	1 (0.8%)	4 (1.6%)
Patients who randomized but didn't have any post randomization 24-hr average heart rate	8 (6.3%)	8 (6.4%)	16 (6.4%)
Patients included in PP population	89 (70.6%)	102(81.6%)	191(76.1%)
Patients excluded from PP population	26 (20.6%)	14 (11.2%)	40 (15.9%)
Treatment compliance is <75%	16 (12.7%)	5 (4.0%)	21 (8.4%)
Did not meet inclusion criteria No. 3 (Heart rate ≥65bpm).	11 (8.7%)	7 (5.6%)	18 (7.2%)
Wrong treatment arm.	1 (0.8%)	2 (1.6%)	3 (1.2%)
Prohibited medications	1 (0.8%)	0	1 (0.4%)
Met exclusion criteria No. 6 (PQ >0.24s at enrolment).	1 (0.8%)	0	1 (0.4%)

* Informed consent received.
Note: Safety population was defined as all patients who received at least one dose of investigational product. The patient will be high-dose group if the highest dose ever used is above 95mg; otherwise
(if the highest dose ever used is equal to or lower than 95 mg) he/she will be low-dose group.
Note: ITT population was defined as all randomized patients who have taken at least one dose of trial treatment, who have baseline 24-hr average heart rate and at least one post randomization 24-hr
average heart rate in the treatment period.
Note: PP population was defined as all ITT subjects without important protocol deviations.
Percentages were calculated based on the number of randomized subjects.
For subject data listing refer to Appendix 12.2.3.1-12.2.3.4.
Source Table: Table 11.1.3

Summary of efficacy results

The 24-hr average heart rate (Mean (Std)) between two groups after 8 weeks of treatment were 70.9 (8.71)bpm and 68.6 (8.40)bpm in the metoprolol succinate 95mg and metoprolol succinate 190mg groups respectively after 8 weeks of treatment. The LSmeans of treatment difference was 2.3615bpm (95% CI:0.63, 4.09) between metoprolol succinate 95mg and metoprolol succinate 190mg groups. There was statistical significant difference (P=0.0077) in 24-hr average heart rate between metoprolol succinate 95mg and metoprolol succinate 190mg groups after 8 weeks of treatment. because no similar studies were ever found, the setting of the primary endpoint was creative, which might be contributed to the formulation of guidelines on management of coronary heart disease in China.

The present study also showed that the proportion of patients with resting heart rate controlled to ≤60bpm were 24.1% (95% CI:16.35%, 31.93%) and 40.0% (95% CI:31.05%, 48.95%) in the metoprolol succinate 95mg and metoprolol succinate 190mg groups respectively after 8 weeks of treatment. There was statistical significant difference (odds ratio=2.838, 95% CI:

1.470, 5.477, P=0.0019) between the groups, which is similar with the findings from Cordero A (Cordero A et al 2011). In his study, Beta-blocker treatment was independently associated with RHR control (odds ratio [OR]: 2.42, 95% CI: 2.05-2.87; P<0.01), especially for metoprolol treatment (OR: 1.29, 95% CI: 1.04-1618; P = 0.04).

The 24-hr average heart rate change from baseline and after 8 weeks of treatment within groups were -2.9858bpm (95% CI:-4.23, -1.75) within metoprolol succinate 190mg group. The percentage of reduced 24-hr heart rate was 4.21% in the metoprolol succinate 190mg group. This finding is also similar with what Lücker P reported (Lücker P et al 1990). According to his conclusion, after 7 days of treatment, metoprolol succinate 100mg reduced 24-hr average heart rate 23.3% from baseline, while the reduction of that by metoprolol succinate 200mg was 26%. The subjects in his study were healthy voluntees, while in the present study the patients with stable angina were enrolled. Quoted from Heikki V. Huikuri (Heikki V. Huikuri et al 1994), the cardial autonomic nerve system was impaired in patients with CHD, which might explain why metoprolol succinate was less effective in the present study.

The 24-hr average heart rate change from baseline and after 2 and 8 weeks of treatment within groups were -0.4938bpm (95% CI: -1.40, 0.41) and -0.6244bpm (95% CI:-1.94, 0.69) within metoprolol succinate 95mg group respectively, which is no statistical significance. The reasons for that might consist of five points. First, the sample size was insufficient for the endpoint. Besides, the treatment prior to study did not correlate well with 47.5 mg metoprolol succinate, but with some higher dose. Also, the metoprolol succinate treatment resulted in a higher threshold for angina, allowing for elevated levels of activitites with corresponding higher heart rates. Morever, the dose-response relationship might have exponential relationship especially in metoprolol succinate, according to the MERIT-HF study (The MERIT-HF Study Group 1999), which might partly explain the lack of effect from the 95 mg dose in the current angina study. Last but not least, there existed poor compliance both in the metoprolol succinate 95mg and 190mg groups during the study, which might contribute to the insignificance.

As for the possible mechanism on the insignificant result about improvement of TIB between the groups, besides the small sample size, there were too many confounding factors, e.g. the calculation for TIB was on software in most of the centers, while it was by manual process in the other 6 sites.

Karl Werdan showed (Karl Werdan et al 2012) that compared with the baseline, the number of angina attacks was reduced by 1.4 ± 1.9 per week ($p < 0.0001$) and nitrate consumption by 1.9 ± 2.9 U per week ($p < 0.0001$) with heart rate reduced by 19.4 ± 11.4 to 65.6 ± 8.2 bpm ($p < 0.0001$). The similar trend was also showed in the present study. The difference of change from the baseline in weekly angina frequency (Mean (Std)) in the present study were -0.4 (2.10) and -0.4 (2.27) in the metoprolol succinate 95mg and metoprolol succinate 190mg groups respectively after 8 weeks of treatment. The LSmeans of treatment difference was 0.0523 (95% CI: -0.22, 0.33) between the groups.

Summary of safety results

Overall, treatment with metoprolol succinate 95mg-190mg were well tolerated over the 8-week treatment period in patients with stable angina. The tolerability of metoprolol succinate 95mg was comparable to metoprolol succinate 190mg during the treatment period, with low incidence of SAEs (1.2% in the metoprolol succinate 95mg group and 2.7% in the metoprolol succinate 190mg group) and DAEs (10 patients in the metoprolol succinate 95mg group and 5 patients in metoprolol succinate 190mg group).

No adverse events were classified as other significant adverse events in this study.

In the study, there were no clinical significant fast plasma glucose,total cholesterol or triglyceride changes related to the investigational product occurred at visit 1 and visit 5.

During the treatment period, there were 5 and 6 patients were observed urine protein at baseline and 8-week treatment respectively in the metoprolol succinate 190mg group. There were 4 and 9 patients were observed urine protein at baseline and 8-week treatment respectively, in the metoprolol succinate 95mg group.

The trend of decrease in SBP and DBP from baseline were observed.

During the treatment period, the numbers of patients with normal ECG at baseline but abnormal ECG after 8 weeks of treatment were 7 and 16 in the metoprolol succinate 95mg and metoprolol succinate 190mg groups.

During the treatment period, the numbers of patients with normal 24-hr ambulatory ECG at baseline but abnormal after 8 weeks of treatment were 9 both in the metoprolol succinate 95mg and metoprolol succinate 190mg groups.