AstraZeneca

Clinical Study Report

Drug substance:	Metoprolol Succinate
Document No.:	
Edition No.:	1
Study code:	D4025L00006
Date:	*Jul.14th, 2006*

An open-label, non-comparative, multi-centre study to evaluate the Efficacy and safety of Metoprolol Succinate prolonged-release tablet (Betaloc Zok) in patients with mild to moderate essential hypertension

Study dates:	First subject enrolled: 17-Oct-2005 Last subject enrolled: 06-Jan-2006
Phase of development:	Phase IV
International Co-ordinating Investigator:	Prof. Liu Lisheng Institute of Beijing Hypertension Union
Sponsor's Responsible Medical Officer:	<<>>

This study was performed in compliance with Good Clinical Practice.

Drug product:	Betaloc ZOK	**SYNOPSIS**	
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An open-label, non-comparative, multi-centre study to evaluate the Efficacy and safety of Metoprolol Succinate prolonged-release tablet (Betaloc Zok) in patients with mild to moderate essential hypertension

International co-ordinating investigator

Prof. Liu Lisheng

Institute of Beijing Hypertension Union

Study centre(s)

Totally 14 centres were involved in the study

Study dates		**Phase of development**
First subject enrolled	17-Oct-2005	Therapeutic use (IV)
Last subject completed	07-Apr-2006	

Objectives

The primary objective of the study was to estimate the hypertensive control rate and BP reduction in responders (defined as < 140 / 90 mmHg) at 8 weeks of a regimen that started with metoprolol succinate sustained-release tablet (Betaloc Zok) 47.5mg and allowed for dose escalation to 95mg at 4 weeks in patients with mild to moderate essential hypertension.

The secondary objective of the study was to

1. estimate the hypertensive control rate at 4 weeks and BP reduction in responders (defined as < 140 / 90 mmHg) and all subjects;

2. estimate the BP reduction in all subjects at 8 weeks;

3. estimate the hypertensive control rate at 12 weeks that also allows for the addition of felodipine sustained release tablet (Plendil) 5mg at week 8 and BP reduction in responders (defined as < 140 / 90 mmHg) and all subjects;

4. evaluate the safety of metoprolol succinate sustained-release tablet (Betaloc Zok) 47.5mg, 95mg and combined treatment in patients with mild to moderate essential hypertension.

Study design

This was an open-label, non-comparative, multi-centre clinical study.

Target subject population and sample size

Male and female subjects aged between 18 and 70 years old with mild to moderate essential hypertension who were newly diagnosed and had not received anti-hypertension treatment , or who without antihypertensive medication in two weeks before screening.

Investigational product, dosage, mode of administration and batch number

Metoprolol succinate prolonged-release 47.5mg tablet, once daily, orally.

Metoprolol succinate prolonged-release 95mg tablet, once daily, orally.

Felodipine sustained release tablet (Plendil) 5mg, once daily, orally.

Comparator, dosage, mode of administration and batch number

None

Duration of treatment

Eligible subject would first take metoprolol succinate prolonged release tablet 47.5mg, once daily orally for 4 weeks.

If blood pressure was controlled after 4 weeks, then the subject would continue the treatment until 12 weeks' treatment period finishes.

If blood pressure was not controlled after 4 weeks, then the subject would take metoprolol succinate prolonged release tablet 95mg, once daily orally for 4 weeks.

If blood pressure was controlled after 8 weeks, then the subject would continue the treatment until 12 weeks' treatment period finishes.

If blood pressure was not controlled after 8 weeks, then the subject would take combined treatment: metoprolol succinate prolonged release tablet 95mg, once daily, orally, with felodipine sustained release tablet (Plendil) 5mg, once daily, orally for 4 weeks.

All subjects would finish the study after 12 weeks' treatment.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: the hypertensive control rate and BP reduction in responders (defined as < 140 / 90 mmHg) at 8 weeks
- Secondary variables:
  - the hypertensive control rate at 4 weeks and BP reduction in responders (defined as < 140 / 90 mmHg) and all subjects;
  - the BP reduction in all subjects at 8 weeks;
  - the hypertensive control rate at 12 weeks that also allows for the addition of felodipine sustained release tablet (Plendil) 5mg at week 8 and BP reduction in responders (defined as < 140 / 90 mmHg) and all subjects.

Safety

- Adverse events
- Laboratory variables:
  - Urinalysis
  - Clinical Chemistry: Fasting Glucose (FPG), Liver Function (ALT, AST, TBIL), Lipids (TC, LDL-C, TG, HDL-C), Renal Function (Cr, BUN), HbA1c (be measured in diagnosed diabetes mellitus subjects, and the subjects with increased FPG(>126mg/dl) which was newly diagnosed in this study)
- Other safety measurements:
  - Physical examination
  - Heart rate
  - ECG (Electrocardiogram)

Statistical methods

The ITT population was defined as all subjects who received at least one dose of study drug treatment and had blood pressure measurements at baseline and at least one blood pressure measurement after visit 2. Per protocol (PP) population was defined as all subjects in the ITT population who fulfilled the entrance criteria with no major protocol violations and deviations, and completed the 8-week trial treatment period. Safety population was defined as all subjects who had taken at least one dose of study drug treatment.

Analysis on efficacy endpoints would be performed in the ITT and PP population. Analysis on demographic would be performed in the ITT population.

Analysis on safety endpoints would be performed in the safety population.

The N, mean, standard deviation, median, maximum, minimum would be calculated for continuous variables, frequency counts and percentages would be calculated for categorical variables.

The sitting blood pressure values being measured at baseline and after 4, 8 and 12 weeks' treatment (i.e. visits 2, 3, 4 and 5) would be summarized by using the descriptive statistics.

After 4, 8, and 12 weeks' treatment, the subjects reaching the blood pressure target would be summarized as percentage and 95% confidence intervals. The magnitude of systolic blood pressure and diastolic blood pressure reduction from baseline for the subjects reaching the blood pressure target and all subjects would be summarized and its 95% confidence intervals would be presented.

The adverse events would be summarized using frequency counts, percentages and severity. The clinical significant changes in laboratory values would be summarized using frequency counts and percentages.

Subject population

Total 321 patients were on the screening but 310 cases with mild to moderate essential hypertension entered the study due to 11 cases with screening failure.

Table S1 Subject population and disposition

		Total	
Population		310	
Demographic characteristics			
Sex (n and % of subjects)	Male	170	(54.8%)
	Female	140	(45.2%)
Age (years)	Mean (SD)	51.1	(10.6)
	Range	19 to 76	
Race (n and % of subjects)	Oriental	310	(100%)
Baseline characteristics			
Mean (SD) SBP (mmHg)		148.6	11.4
Mean (SD) DBP (mmHg)		96.3	5.1

		Total	
Disposition			
N (%) of subjects who	Completed	281	(90.6%)
	discontinued*	29	(9.4%)
N analysed for safety[a]		308	
N analysed for efficacy (ITT)		297	
N analysed for efficacy (PP)		260	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number; PP=Per-protocol
* Including 2 cases who entered the study but without any study medication

Efficacy results

The primary variable:

The hypertensive control rate (defined as < 140 / 90 mmHg) was 69.0% in the intention-to treat sample(95% CI 63.6%to 74.3%) at 8 weeks of a regimen that started with metoprolol succinate sustained-release tablet (Betaloc Zok) 47.5mg and allowed for dose escalation to 95mg at 4 weeks in patients with mild to moderate essential hypertension. And 70.4% of the hypertensive control rate at 8 weeks was proven in the per-protocol analysis(95% CI 64.8% to 75.9%). The BP reduction in responders at 8 weeks was 17.5/13.8 mmHg(P<0.001) in ITT which was further proven in the per-protocol analysis (P<0.001).

Secondary variables:

The hypertensive control rate (defined as < 140 / 90 mmHg) was 50.8% in the intention-to treat sample(95% CI 45.2%to 56.5%) at 4 weeks of the treatment with metoprolol succinate sustained-release tablet (Betaloc Zok) 47.5mg. The BP reduction in responders and in all subjects at 4 weeks was 15.5/12.9mmHg(P<0.001) and 10.2/8.1mmHg(P<0.001) respectively which was further proven in the per-protocol analysis.

The BP reduction in all subjects was 14.2/10.9 mmHg(P<0.001) at 8 weeks which was further proven in the per-protocol analysis.

The hypertensive control rate (defined as < 140 / 90 mmHg) was 77.3% in the intention-to treat sample(95% CI 72.4% to 82.1%) at 12 weeks that also allowed for the addition of felodipine sustained release tablet (Plendil) 5mg at week 8. The BP reduction in responders and in all subjects at 12 weeks was 19.9/14.7 mmHg(P<0.001) and 17.5/12.6 mmHg (P<0.001) respectively which was further proven in the per-protocol analysis.

Safety results

- Incidence of AE was 22.1%(68/308). Total number of AE cases was 91， most were mild (85.7%), 12 moderate (13.2%), 1 severe (1.1%).

- AEs included Upper Respirtatory Infection (1.0%), discomfort (1.0%), fatigue (1.0%), asthenia (1.9%), hyperglycemia (1.3%), hypercholestolemia (1.0%), hypertriglycerides (1.6%), insomnia (1.0%), diarrhoea (1.0%), somnolence (1.6%), dizziness (2.6%), headache (3.6%).

- 13 DAEs

- The investigators judged that 2 SAEs were not related to investigatational drug.

- No death in this study.

Table S2 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set) (N=308) n (%)

Total number of AE	91
Number of subjects who had at least one AE in any category (a)	68 (22.1)
By severity	
Mild	60 (19.5)
Moderate	7 (2.3)
Severe	1 (0.3)
Drug related AE	35 (11.4)
Number of subjects who had at least one SAE	2 (0.6)
DAE	13 (4.2)
Death	0

(a)includes all AE after receiving investigational drugs. Subjects with multiple events in the same category are counted only once in that category，counted in the most severity one.

Table S3 Number (%) of subjects with the most commonly reporteda adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) (N=308)

Adverse event (WHO-ART preferred term) (c)	**Number (%) of subjects who had an adverse event n (%)**
headache	11 (3.6)
dizziness	8 (2.6)
asthenia	6 (1.9)
hypersomnia	5 (1.6)
hyperglycerides	5 (1.6)
hyperglycemia	4 (1.3)
upper respiratory infection	3 (1.0)
insomnia	3 (1.0)
diarrhoea	3 (1.0)
discomfort	3 (1.0)
fatigue	3 (1.0)

Table S3 Number (%) of subjects with the most commonly reporteda adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) (N=308)

Adverse event	**Number (%) of subjects who had an adverse event**
(WHO-ART preferred term) (c)	**n (%)**

[a]Events with a total frequency of ≥1% across all treatment groups are included in this table.

Date of the report

Jul.14th, 2006