AstraZeneca

SH-MET-0024

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Seloken ZOK / Toprol-XL™

ACTIVE INGREDIENT: Metoprolol Succinate

Trial title (number): Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure - MERIT-HF.

A Double-Blind, Placebo Controlled Survival Study with Metoprolol CR/XL in Patients with Decreased Ejection Fraction and Symptoms of Heart Failure..(SH-MET-0024)

Developmental phase: Therapeutic confirmatory
First subject recruited: 29 January 1997
Last subject completed: 6 April 1999
Approval date: 24 August 1999

OBJECTIVES

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The first primary objective was to determine whether metoprolol CR/XL od reduced total mortality. The second primary objective was to determine whether metoprolol CR/XL od reduced the combined endpoint of all cause mortality and all cause hospitalisation (time to first event).

STUDY SITE

Multicentre study with a total number of 313 sites (Belgium 15, Czech Republic 10, Denmark 14, Finland 8, Germany 53, Hungary 16, Iceland 2, The Netherlands 29, Norway 17, Poland 11, Sweden 9, Switzerland 5, UK 13, USA 111).

METHODS

STUDY DESIGN

This was a randomised, double-blind, placebo controlled, parallel group, international multicentre survival study.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Patients of either sex, aged 40-80 years, symptomatic heart failure (NYHA functional class II-IV), optimal standard therapy at enrolment (any combination of diuretics and an ACE inhibitor; if an ACE inhibitor was not tolerated, hydralazine/long-acting nitrate or an angiotensin II receptor antagonist could be used; digitalis could also be prescribed), a stable clinical condition during placebo run-in, left ventricular ejection fraction of 0.40 or less, and supine heart rate of 68 beats per minute or more. The exclusion criteria included acute myocardial infarction or unstable angina within 28 days before randomisation, indication or contra-indication for treatment with beta-blocking agents and use of heart rate reducing calcium antagonists such as diltiazem or verapamil.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Metoprolol CR/XL 12.5-200 mg od, oral.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Placebo tablets identical to corresponding strength of metoprolol CR/XL, oral.

DURATION OF TREATMENT

Treatment range (shortest and longest period on metoprolol CR/XL to date of study closure 31 October 1998; some patients were randomised, but never started on double-blind treatment): 0-622 days, with a mean follow-up time of approximately one year.

MAIN VARIABLES:

The two primary efficacy variables in order of importance were reduction of total mortality and reduction in the combined endpoint of all cause mortality and all cause hospitalisation (time to first event) (see Section 9.5.2.3).

STATISTICAL METHODS

For the main analyses (time to event) the log-rank test was used to compare the metoprolol CR/XL and placebo groups Cox's proportional hazards model was used to calculate relative risks with 95% confidence intervals. An adjusted p-value for total mortality accounting for the two performed predefined interim analyses was calculated.

RESULTS

PATIENTS

	Metoprolol CR/XL	**Placebo**	**Total**
No. planned (randomised)	1600	1600	3200
No. planned according to Amendment No. 3	1900	1900	3800
No. randomised	1990	2001	3991
Males/Females	1539/451	1554/447	3093/898
Mean age (range)	63.8 (40.1-80.7)	63.7 (40.1-81.0)	63.8 (40.1-81.0)
No. analysed for efficacy	1990	2001	3991
No. analysed for safety	1990	2001	3991
No. completed	1990	2001	3991

- **EFFICACY RESULTS**

Treatment with metoprolol CR/XL added to standard treatment with ACE inhibitors and diuretics in patients with decreased left ventricular ejection fraction and symptoms of heart failure (NYHA class II-IV) reduced:

- All cause mortality by 34%
- Combined endpoint of all cause mortality and all cause hospitalisation (time to first event) by 19%
- Combined endpoint of all cause mortality and hospitalisation due to worsening heart failure (time to first event) by 31%
- The combined endpoint of death and heart transplantation (time to first event) by 32%
- Cardiovascular mortality by 38%
- Sudden death by 41%
- Death from worsening heart failure by 49%
- The pooled incidence of cardiac death and non-fatal acute MI by 39%
- Combined endpoint of all cause mortality, hospitalisation due to worsening heart failure, and emergency room visit due to worsening heart failure (time to first event) by 32%

The group of patients with severe heart failure (NYHA functional class IV) was smaller, but the survival effect of metoprolol CR/XL was of the same magnitude as in the less severe forms of heart failure – NYHA functional class II and III (see below). Most of the patients were of Caucasian origin.

Metoprolol CR/XL improved symptoms according to the judgement of the investigators (NYHA functional class) and had a favourable overall treatment effect on Quality of Life as judged by the patients themselves (OTE questionnaire).

Metoprolol CR/XL was well tolerated and the withdrawal rate due to worsening heart failure was 25% lower than in the placebo group.

SAFETY RESULTS

The total number of patients with AEs as well as the number of fatal and non-fatal SAEs was consistently lower in the metoprolol CR/XL group compared to placebo. Also the number of patients who discontinued due to AEs were lower in the metoprolol CR/XL group.

The number of patients with SAEs leading to death was 145/1990 (7.3%) in the metoprolol CR/XL group and 217/2001 (10.8%) in the placebo group. The corresponding figures for non-fatal SAEs and discontinuations due to AEs were 664 (33.4%) and 751 (37.5%), 205 (10.3%) and 245 (12.2%) respectively.

Metoprolol CR/XL treatment was not associated with any increase in mortality risk in any of the pre-specified subgroups analysed for safety reasons defined on the basis of: left ventricular ejection fraction, heart rate, systolic blood pressure, diastolic blood pressure, age, previous hypertension, smoking, sex, race, diabetes mellitus, NYHA class (II/III), NYHA class IV, previous MI and aetiology (ischaemic / non-ischaemic)

Reference:

The International Steering Committee on Behalf of the MERIT-HF study group. Rationale, Design and Organization of the Metoprolol CR/XL Randomized Intervention Trial in Heart Failure (MERIT-HF). Am J Cardiol 1997;80(9B):54J-58J.

MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL randomised intervention trial in congestive heart failure (MERIT-HF). Lancet 1999; 353:2001-07.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Seloken ZOK / Toprol-XL™ (metoprolol CR/XL), Healthcare Professionals should view their specific country information.