AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Not Applicable
Study Code	D2452L00010
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A randomised, parallel group, single blind, multicentre, 9-month, phase IV study in a primary care setting, comparing treatment guided by clinical symptoms and signs and NT-proBNP vs treatment guided by clinical symptoms and signs alone, in patients with heart failure and left ventricular systolic dysfunction.

Study dates: First patient enrolled: 3 October 2006
Last patient completed: 16 January 2009

Phase of development: IV

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

Study centre(s)

This study was conducted in Sweden with 45 centres.

Publications

The results of this study was presented in an abstract June 1st 2009.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To evaluate if 9 months of heart failure treatment guided by clinical symptoms, signs and NT-proBNP values was more effective at reducing the combination of CV death, CV hospitalisation and heart failure symptoms, than treatment guided by clinical symptoms and signs alone, in patients with chronic heart failure	A composite endpoint of days alive, days out of hospital and the symptom score subset (questions 3, 5, 7, 9) of the KCCQ. Only CV deaths and days spent in hospital for CV reasons contributed to the endpoint	Efficacy
Secondary	**Secondary**	
To study if 9 months of treatment guided by clinical symptoms, signs and NT-proBNP values compared with treatment guided by clinical symptoms and signs alone, were more effective to		
- reduce CV death	Number of CV deaths	Efficacy
- decrease the number of days in hospital for CV reasons	Number of days in hospital for CV reasons	Efficacy
- reduce heart failure symptoms	Changes in the symptom score subset (questions 3, 5, 7, 9) of KCCQ	Patient reported outcome (PRO)
To study the change in NT-proBNP values over time in all patients	Changes in NT-proBNP values over time in all patients	Efficacy
To study the change in NT-proBNP values over time related to different medications used	Changes in NT-proBNP values over time divided into different medications	Efficacy
To study the change in health-related quality of life in the two treatment groups	Changes in the overall score of KCCQ	PRO
To study the correlation between NYHA class and NT-proBNP values	NYHA class, NT-proBNP values and changes in these	Efficacy
To study the correlation between KCCQ and NT-proBNP values	KCCQ, NT-proBNP values and changes in these	PRO
Changes in vital signs, laboratory values and heart failure status in the two treatment groups	Difference in change in vital signs, laboratory values, heart failure status between the treatment groups	Safety

Objectives	Outcome variables	Type
The level of titration and intensified treatment according to the Swedish guidelines as outlined by the Swedish Medical Product Agency (MPA, Läkemedelsverket 2006). This objective was added in CSP Amendment 2	Levels of titration, levels of intensified treatment and the reasons stated by the investigators why not target doses and/or not all medications in MPA guidelines were used	Efficacy
To compare the incidence of Serious Adverse Events (SAE) in the two treatment groups, and the proportion of patients who discontinued the study due to adverse events (AE)	Number of SAEs and proportion of patients who discontinue due to AEs	Safety

Study design

This was a randomised, parallel group, single blind, multicentre, 9-month study in chronic heart failure in patients with NYHA class II-IV, left ventricular systolic dysfunction and elevated NT-proBNP levels in the primary care setting.

Target subject population and sample size

Male or female patients aged 18 years and above, with a diagnosis of heart failure with previously verified left ventricular systolic dysfunction, at least moderately impaired (equivalent to ejection fraction (EF) <40%), as judged by the investigator. Plasma NT-proBNP at enrolment were to be >800 ng/L (males) and >1000 ng/L (females).

The numbers of patients to be evaluated in the study should be at least 106 in each treatment group. The sample size had 80% power to detect a probability of 0.389 (38.9%) that an observation in one treatment group was less than an observation in a second treatment group using a Wilcoxon (Mann-Whitney) rank-sum test with a 0.050 two-sided significance level. Since a drop-out rate of 15% was expected, it was calculated that 250 patients needed to be randomised into the study to enable 212 evaluable patients. A total of 237 randomised patients completed the study: 119 in treatment group guided by NT-proBNP and 118 in treatment group not guided by NT-proBNP.

Duration of treatment

The investigators prescribed heart failure treatment in accordance with the national guidelines. The patient's heart failure status was evaluated at every study visit, to determine whether an intensification of treatment was needed. The patients' symptoms and signs guided the investigator in making the decision to intensify the treatment. For patients in the NT-proBNP guided arm, the level of NT-proBNP was compared to the enrolment level. Treatment was intensified, as tolerated by the patient, until a reduction of at least a 50% in NT-proBNP was achieved, even if not indicated by the clinical symptoms and signs. If a 50% reduction in NT-proBNP value was seen and the patient had persistent heart failure symptoms, the investigator was to further intensify the treatment if tolerated.

Statistical methods

The primary efficacy variable, the composite score including days alive, fraction of days out of hospital and KCCQ symptom score was analysed by a Wilcoxon test. The secondary variable, death, was analysed by descriptive statistics, since no difference between the treatment groups was expected. The fraction of days out of hospital, fraction of days alive, change in KCCQ symptom score, change in KCCQ overall score, change in NT-proBNP values were analysed by an analysis of variance (ANOVA) with treatment as factor and baseline NYHA-class as a covariate.

The safety variables were analysed by descriptive methods. The safety variables included SAEs, development of any abnormality in heart failure status, blood pressure and heart rate and abnormal laboratory data, throughout the treatment period.

All tests were two-sided with a significance level of 5%.

Subject population

Patient disposition is presented in Table S1 and baseline patient characteristics in Table S2. The randomised study population comprised 252 patients. 124 patients were randomised to treatment guided by clinical symptoms and signs and NT-proBNP and 126 patients were randomised to treatment guided by symptoms and signs alone. All 376 enrolled patients were included in the safety population and 250 patients in the ITT-population.

A total of 237 randomised patients completed the study: 119 in treatment group guided by clinical symptoms and signs and NT-proBNP and 118 in treatment guided by symptoms and signs alone. The overall number of discontinuations, and the number of patients who discontinued the study due to Adverse Events (AEs), were similar in the two treatment groups. Overall, the treatment groups were well matched with respect to demographic and baseline characteristics.

43 patients had protocol deviations considered serious enough to warrant exclusion of data from the PP-analysis. 209 patients were included in the PP-analysis.

Table S2 Patient disposition

	Guided by NT-proBNP (N=127)	Not guided by NT-proBNP (N=125)	Total (N=252)
Number of patients enrolled			376
Number of patients randomised	127	125	252
Number of patients in Full Analysis Set (FAS)	126	124	250
Number of patients in Per Protocol Analysis (PP1)	107	102	209
Number (%) of patients who completed the study[a]	119 (93.7%)	118 (94.4%)	237 (94%)
Number (%) of patients who discontinued during the study[a]	8 (6.3%)	7 (5.6%)	15 (6%)

[a] Percent of randomised patients

Table S3 Patient characteristics baseline, Full Analysis Set

	Guided by NT-proBNP (N=126)	Not guided by NT-proBNP (N=124)	Total (N=250)
Sex (n and % of patients), Male	96 (76.2%)	82 (66.1%)	178 (71.2%)
Age (years), Mean (SD)	78 (7)	77 (8)	78 (8)
SBP (mm Hg)			
Mean (SD)	133 (21)	135 (22)	134 (21)
DBP (mm Hg)			
Mean (SD)	73 (11)	75 (12)	74 (11)
Pulse (beats/min)			
Mean (SD)	71 (14)	72 (14)	72 (14)
Electrocardiogram (ECG)			
Abnormal	115 (92%)	113 (91.1%)	228 (91.6%)
Echocardiography (UCG) Left ventricular EF (%)			
Mean (SD)	31 (9)	33 (7)	32 (8)
Range	10 , 50	15 , 50	10 , 50
NYHA-class			
I	0 (0%)	0 (0%)	0 (0%)
II	78 (61.9%)	76 (61.3%)	154 (61.6%)
III	48 (38.1%)	48 (38.7%)	96 (38.4%)
IV	0 (0%)	0 (0%)	0 (0%)

Summary of efficacy results

The primary variable, a composite endpoint of days alive, days out of hospital and the symptom score subset (questions 3, 5, 7, 9) of the KCCQ, showed no statistically significant differences between the groups (p=0.2824).

There were 4 CV related deaths in the treatment group guided by NT-proBNP and 5 CV related deaths in treatment group not guided by NT-proBNP. A log-rank test of time to death showed no difference between the treatments (p=0.9267). Nor were there any differences in fraction of days spent in hospital or changes in NT-proBNP between the treatment groups. Only minor reductions in NT-proBNP were observed. No gender differences were seen although patients younger than 75 years of age achieved a lower NT-proBNP. No differences between the treatment groups regarding blood pressure, heart rate and weight but a decrease in systolic (p=<0.0001) and diastolic (p=<0.0003) blood pressure, heart rate (p=<0.0001) and weight at the end of the study compared with baseline were seen. Improvements were seen in symptoms assessed by heart and lung auscultation and in dyspnoea and oedema. Patient reported quality of life is clearly impaired at baseline but increase in both treatment groups at the end of study.

The analysis of secondary variables supports the conclusion from the primary analysis that there was no additional benefits of measuring NT-proBNP to guide heart failure treatment.

Summary of safety results

The number (%) of patients who had at least 1 adverse event in any category is summarised in Table S3. In general, the study therapy was safe and the overall incidence of serious adverse events (SAEs) was similar in both treatment groups. 14 deaths were reported in this study of which 9 were considered to be from cardiovascular causes.

Table S4 Number (%) of patients who had at least one AE/SAE in any category

	Guided by NT-proBNP (N=127)	Not guided by NT-proBNP (N=125)	Total (N=252)
No of patients with at least one Serious adverse event	46 (36.2%)	41 (32.8%)	87 (34.5%)
Total no of patients with a Serious adverse event leading to death	7 (5.5%)	7 (5.6%)	14 (5.6%)
Total no of patients with a Serious adverse event not leading to death	42 (33.1%)	39 (31.2%)	81 (32.1%)
Total number of serious adverse events	81	74	155
Discontinuation of treatment due to adverse events	8 (6.3%)	6 (4.8%)	14 (5.6%)

87 patients reported a SAE at least once. The most common SAE reported during the study was cardiac disorders (15.9%). The incidence of common SAE (occurring at an total incidence of >5%) is summarised in Table S4. None of the SAEs were considered related to the clinical trial procedure. 14 patients discontinued the study due to AE. Most of the DAEs were related to the underlying condition and the most common DAE was cardiac disorders.

There were no differences between the treatment groups regarding vital signs, ECGs or physical findings. There was a decrease in blood pressure (systolic and diastolic), heart rate and weight in both treatment groups. Positive changes in patients' symptoms and signs e.g. heart- and lung auscultations, oedema and dyspnoea were also seen in both groups.

Table S5 Number (%) of patients with the most commonly reported[a] serious adverse events, sorted by decreasing order of frequency (Safety analysis set)

	Guided by NT-proBNP (N=127)	Not guided by NT-proBNP (N=125)	Total (N=252)
Serious adverse events	46 (36.2%)	41 (32.8%)	87 (34.5%)
Cardiac disorders	18 (14.2%)	22 (17.6%)	40 (15.9%)
Infections and infestations	10 (7.9%)	7 (5.6%)	17 (6.7%)
Respiratory, thoracic and mediastinal disorders	4 (3.1%)	7 (5.6%)	11 (4.4%)
Nervous system disorders	5 (3.9%)	5 (4%)	10 (4%)
Vascular disorders	6 (4.7%)	3 (2.4%)	9 (3.6%)
General disorders and administration site conditions	6 (4.7%)	1 (0.8%)	7 (2.8%)
Gastrointestinal disorders	4 (3.1%)	3 (2.4%)	7 (2.8%)
Musculoskeletal and connective tissue disorders	2 (1.6%)	5 (4%)	7 (2.8%)
Injury, poisoning and procedural complications	4 (3.1%)	2 (1.6%)	6 (2.4%)
Metabolism and nutrition disorders	3 (2.4%)	2 (1.6%)	5 (2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (2.4%)	2 (1.6%)	5 (2%)

[a] This table uses a cut-off 5%