Synopsis

Clinical Report Synopsis for Protocol 156-03-236

Name of Company: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Product: Tolvaptan (OPC-41061)

Trial Title: Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Long Term Efficacy and Safety of Oral Tolvaptan Tablets in Subjects Hospitalized with Worsening Congestive Heart Failure

Investigator(s) and Trial Center(s): Multicenter (432 centers in Argentina, Belgium, Brazil, Bulgaria, Canada, the Czech Republic, France, Germany, Italy, Lithuania, the Netherlands, Norway, Poland, Romania, the Russian Federation, Spain, Sweden, Switzerland, the United Kingdom, and the United States)

Publications:

- Konstam MA, Gheorghiade M, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA 2007;297:1319-31.
- Gheorghiade M, Konstam MA, Burnett JC Jr, Grinfeld L, Maggioni AP, Swedberg K, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Short-term clinical effects of tolvaptan, an oral vasopressin antagonist, in patients hospitalized for heart failure: the EVEREST Clinical Status Trials. JAMA 2007;297:1332-43.
- Yancy CW. Climbing the mountain of acute decompensated heart failure: the EVEREST Trials. JAMA 2007;297:1374-6.
- Gheorghiade M, Orlandi C, Burnett JC, Demets D, Grinfeld L, Maggioni A, et al. Rationale and design of the multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy of vasopressin antagonism in heart failure: outcome study with tolvaptan (EVEREST). J Card Fail 2005;11:260-9.
- Orlandi C, Zimmer CA, Gheorghiade M. Role of vasopressin antagonists in the management of acute decompensated heart failure. Curr Heart Fail Rep 2005;2:131-9.
- Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, et al, for the EVEREST Investigators and Committee Members. Effects of vasopressin receptor antagonism with tolvaptan on clinical status, morbidity and mortality in patients hospitalized with acute decompensated heart failure: results of the EVEREST trial. Paper presented at: 56th Annual Scientific Session of the American College of Cardiology; 25 Mar 2007, New Orleans, LA.

- Konstam MA, Gheorghiade M, Burnett JC, Grinfeld L, Maggioni AP, Swedberg K, et al, for the EVEREST Investigators and Committee Members. Effects of vasopressin receptor antagonism with tolvaptan on clinical status, morbidity, and mortality in patients hospitalized with acute decompensated heart failure: results of the EVEREST trial. Paper presented at: Heart Failure Congress 2007, 11 Jun 2007, Hamburg, Germany.
- Wang NC, Konstam MA, Gheorghiade M, Bechhofer R, Burnett JC, Grinfeld L, et al, and the EVEREST Investigators. Regional comparison of baseline therapy in patients hospitalized for acute heart failure with systolic dysfunction. Poster to be presented at: 11th Annual Scientific Meeting of the Heart Failure Society of America 16-19 Sep 2007, Washington, DC.
- Wang NC, Konstam MA, Bechhofer R, Gheorghiade M, Burnett JC, Grinfeld L, et al, and the EVEREST Investigators. Regional differences in baseline characteristics and outcomes in patients hospitalized with worsening heart failure and systolic dysfunction. To be presented at: 11th Annual Scientific Meeting of the Heart Failure Society of America 16-19 Sep 2007, Washington, DC.

Studied Period:

Date of first signed informed consent: 07 Oct 2003
Trial Termination Date: 17 Apr 2006
Date of last trial observation: 05 Jul 2006

Clinical Phase: 3

Protocol Overview: This was a multicenter, randomized, double-blind, placebo-controlled protocol to evaluate the long-term efficacy and safety of tolvaptan in subjects hospitalized with worsening CHF. This trial was a 3-in-1 design: a Primary Outcome Trial (referred to as the Long-term Outcome Trial) and 2 distinct embedded trials (referred to as Short-term Clinical Status Trials A and B). The protocol also included an optional substudy, designed to explore the effect of tolvaptan on the serum concentrations of proinflammatory, remodeling, and necrosis markers, as well as the relationship(s) between the markers. This protocol was designed to serve as the pivotal trial to support global marketing applications. Because of the complexity of the trial design (3-in-1 design) and multiple endpoints being analyzed, this synopsis has been organized to report the results of each in its own separate section.

Diagnosis and Main Criteria for Inclusion: The same inclusion criteria applied to the Long-term Outcome Trial, the Short-term Clinical Status Trials, and the optional substudy: male and female subjects, 18 years of age or older, hospitalized with worsening of CHF were enrolled. Subjects had an ejection fraction less than or equal to 40% and were in New York Heart Association (NYHA) Class III or IV heart failure at the time of hospitalization. Subjects also had signs of extracellular volume expansion, defined as 2 or more of the following: a) jugular venous distension (JVD), b) pedal

edema (≥ 1+), or c) dyspnea. Baseline and demographic characteristics were similar in the Long-term Outcome Trial and in the Short-term Clinical Status Trials and were comparable in the 2 treatment groups. Approximately 60% of subjects were NYHA Class III and 40% were Class IV, and mean ejection fraction was 27% in the Long-term Outcome Trial.

Test Product, Dose, Mode of Administration, Batch or Lot No(s): Subjects received daily oral doses of trial drug, tolvaptan 30 mg QD or placebo, for the duration of treatment according to the group to which they were randomized. The tolvaptan tablets were from lot numbers 03C88A030A, 03C88A030B, 03C88A030C, 03L73A030A, 03L73A030B, 03L73A030C, 03L73A030D, 04C77A030B, 04C77A030C, 04J88A030A, 04J88A030B, 04J88A030C, 04J88A030D, 04J88A030E, 05D73A030A, 05D73A030B, 05D73A030C, 05I84A030A, and 05I84A030B. The matching placebo tablets were from lot numbers 03C88P000A, 03C88P000B, 03C88P000C, 03K81P000A, 03K81P000E, 03K81P000B, 03K81P000C, 03K81P000D, 04A95P000C, 04A95P000D, 04H00P000A, 04H00P000B, 04H00P000C, 04H00P000D, 04H00P000E, 05D73P000A, 05D73P000B, 05D73P000C, 05I84P000A, and 05I84P000B.

The tolvaptan and placebo tablets used in this trial were manufactured by Otsuka Pharmaceutical Co., Ltd. (Japan).

Reference Product, Dose, Mode of Administration, Batch or Lot No(s): No comparators were studied in this trial.

Long-term Outcome Trial

Objectives, Long-term Outcome Trial: The primary objectives of the Long-term Outcome Trial were to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the time to all-cause mortality in subjects hospitalized with worsening congestive heart failure (CHF) and to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the time to first occurrence of cardiovascular (CV) mortality or hospitalization for heart failure. The secondary efficacy objectives were to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the secondary and tertiary efficacy variables, including time to first occurrence of CV mortality/morbidity; incidence of CV mortality/morbidity; incidence of clinical worsening of heart failure; dyspnea status at Inpatient Day 1 for those with dyspnea at baseline; change from baseline in body weight (Inpatient Day 1, Inpatient Day 7 or discharge if earlier, and Outpatient Weeks 4 and 8), serum sodium for those with serum sodium < 134 mEq/L at baseline (Inpatient Day 1, Inpatient Day 7 or discharge if earlier, and Outpatient Weeks 4 and 8), edema score (Inpatient Day 7 or discharge if earlier for those with edema at baseline), Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (Outpatient Weeks 1 and 24, and End of Treatment Visit), KCCQ domains and KCCQ functional status and KCCQ clinical summary score (Outpatient Weeks 1 and 24, and End of Treatment Visit), and EuroQol 5D summary index (Outpatient Weeks 1 and 24, and End of Treatment Visit); and number of days alive out of the hospital. Additional secondary objectives were to assess the safety of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy by comparing adverse events (AEs), vital signs, clinical laboratory tests, and 12-lead electrocardiograms (ECGs); and to obtain blood samples for a population pharmacokinetic analysis to be reported separately.

Objectives, Substudy: The primary objectives of the optional substudy were to determine the serum concentrations of extracellular matrix (ECM), proinflammatory, and necrosis markers in subjects hospitalized with worsening heart failure and to determine whether treatment (tolvaptan versus placebo) affected these markers. The secondary objectives were to determine whether serum concentrations of ECM, proinflammatory, or necrosis markers were related to etiology, clinical disease severity, and outcome; and to determine whether serum concentrations of proinflammatory, necrosis, and remodeling markers were related to each other.

Methodology, Long-term Outcome Trial: The Long-term Outcome Trial was expected to be 20 months in length, with an 18-month enrollment period and an additional 2 months of treatment. The duration of the trial and the length of subject exposure were event driven. It was projected that the target number of events (1065 deaths) could be observed with 3600 enrolled subjects. The trial was terminated (ie, the Trial Termination Date) when the prespecified number of events (1065 deaths) and a minimum of 60 days of treatment for all active subjects was reached.

Subjects underwent screening procedures, then participated in an in-hospital period of up to 10 days followed by an outpatient period. Screening lasted up to 48 hours post hospitalization. After screening, eligible subjects were randomized and received either 30 mg tolvaptan or matching placebo in a double-blind fashion on Inpatient Day 0. Subjects were instructed to continue to take trial drug by mouth once daily (QD) upon awakening. Outpatient assessments occurred at Weeks 1, 4, and 8 and every 8 weeks thereafter. A follow-up visit occurred 7 days after the last dose of trial drug for all subjects allowing for adjustments in concomitant diuretic therapy and assessment of safety. Subjects were contacted by telephone 14 days after the last dose of trial drug to collect safety information. Subjects terminating the trial early were contacted every 3 months until the Trial Termination Date to collect safety information; the first call occurred 3 months after the 14-day follow-up call. An End of Treatment Visit, performed within 4 weeks after the Trial Termination Date, was scheduled for each subject who was still in the trial as of the Trial Termination Date.

Efficacy assessments included all-cause mortality, heart failure morbidity and CV mortality events, adjudicated by a Clinical Events Committee (CEC) which was blinded to treatment assignment; body weight; serum sodium concentrations; cardiovascular assessments including pedal edema; patient-assessed dyspnea status; the KCCQ; and the EuroQol 5D.

Adverse events were recorded from Screening/Inpatient Day 0 and throughout the trial. A complete medical history was taken at the Screening/Inpatient Day 0 visit. Physical examinations were performed at Screening/Inpatient Day 0; Inpatient Days 1 and 7; Discharge; Outpatient Weeks 1, 4, 8, and every 8 weeks thereafter; End of Treatment (or Early Termination); and 7-day follow-up. Vital signs were measured at Screening/Inpatient Day 0; each inpatient day; Outpatient Weeks 1, 4, 8, and every 8 weeks thereafter; End of Treatment (or Early Termination); and 7-day follow-up. Twelve-lead ECGs were performed at Screening/Inpatient Day 0; Inpatient Days 1, 3, 6, 8, and 10; Discharge (if prior to Inpatient Day 10); and Outpatient Weeks 4, 16, 24, 48, and 96. Nonfasting samples for laboratory tests (including hematology, serum chemistry, serum/plasma osmolality, urinalysis) were collected at Screening/Inpatient Day 0; Inpatient Days 1 and 7; Discharge; Outpatient Weeks 1, 4, 8, and every 8 weeks thereafter; End of Treatment (or Early Termination); and the 7-day follow-up. Blood samples for brain natriuretic peptide (BNP) or pro-BNP, arginine vasopressin (AVP), and aldosterone were also collected at these times except at the 7-day follow-up, and only AVP was collected at Inpatient Day 1. A urine pregnancy test was performed for women of childbearing potential at Screening/Inpatient Day 0 (prior to randomization); Outpatient Weeks 1, 4, 8, and every 8 weeks thereafter; End of Treatment (or Early Termination), and the 7-day follow-up.

Subjects continued to receive their conventional therapy during the trial, which may have included diuretics, digoxin, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers, hydralazine, nitrates, and beta blockers. Adjustments to the conventional therapy were permitted at the discretion of the investigator.

Periodic interim analyses of efficacy and safety data were conducted by an independent statistician and were reviewed by an independent data monitoring committee, which exercised its option to become unblinded during the course of the study.

Methodology, Substudy: Participation in the substudy was offered to all sites but was optional. For subjects participating in the substudy, blood samples were collected to test for serum carboxyl-terminal telopeptide of collagen type I (ICTP), High Sensitivity C-reactive protein (HS-CRP), and cardiac troponin I (c-TnI) (Screening/Inpatient Day 0, Inpatient Day 7 or Discharge if earlier, and Outpatient Week 4).

Number of Subjects, Long-term Outcome Trial: A total of 4133 subjects were randomized: 2072 to the tolvaptan group and 2061 to the placebo group. All randomized subjects qualified for the intent-to-treat (ITT) population and were analyzed for efficacy in the Long-term Outcome Trial. Nine subjects randomized to the tolvaptan group and 6 subjects randomized to the placebo group did not receive trial drug (ie, were not treated); these subjects were included in the ITT population. All treated subjects (2063 in the tolvaptan 30 mg group and 2055 in the placebo group) were analyzed for safety.

Number of Subjects, Substudy: A total of 251 subjects participated in the optional substudy (126 tolvaptan 30 mg; 125 placebo).

Criteria for Evaluation, Long-term Outcome Trial:
Efficacy Variables

The primary efficacy endpoints for the Long-term Outcome Trial were as follows:

1) Time to all-cause mortality (superiority, noninferiority).
2) Time to first occurrence of CV mortality or heart failure hospitalization.

The secondary efficacy endpoints for the Long-term Outcome Trial were as follows:

1) Time to first occurrence of CV mortality/morbidity (morbidity included hospitalization for heart failure, acute myocardial infarction, stroke, arrhythmia, and other CV morbidity such as unstable angina, pulmonary embolism, etc).
2) Incidence of CV mortality, including sudden cardiac death, heart failure, acute myocardial infarction, stroke, and other CV mortality (eg, ruptured aortic aneurysm, cardiac tamponade, etc).
3) Incidence of clinical worsening of heart failure defined as any of the following:
    a) Hospitalization for heart failure
    b) Unscheduled visit for heart failure to an emergency department, outpatient clinic, or observation unit associated with need for intravenous therapy for heart failure
    c) Death due to heart failure.
4) Change from baseline in body weight at Inpatient Day 1.

5) Change from baseline in serum sodium concentration at Inpatient Day 7 or Discharge if earlier in subjects with a serum sodium concentration less than 134 mEq/L at baseline.
6) Change from baseline in edema score at Inpatient Day 7 or Discharge if earlier for those with edema at baseline.
7) Patient-assessed dyspnea status at Inpatient Day 1, for those with physician-assessed dyspnea at baseline.
8) Change from baseline in KCCQ overall summary score at Outpatient Week 1.

The tertiary efficacy endpoints for the Long-term Outcome Trial were as follows:

1) Incidence of CV morbidity leading to hospitalization, including heart failure, acute myocardial infarction, stroke, arrhythmia, and other CV morbidity (eg, unstable angina, pulmonary embolism, etc).
2) Change from baseline in body weight at Inpatient Day 7 or Discharge if earlier Outpatient Week 4, and Outpatient Week 8.
3) Change from baseline in serum sodium concentration at Inpatient Day 1, Outpatient Week 4, and Outpatient Week 8 in subjects with a serum sodium concentration less than 134 mEq/L at baseline.
4) Number of days alive out of the hospital.
5) Change from baseline in KCCQ overall summary score at Outpatient Week 24 and at End of Treatment Visit.
6) Changes from baseline in KCCQ domains, KCCQ functional status score, and KCCQ clinical summary score at Outpatient Week 1, Outpatient Week 24, and at End of Treatment Visit.
7) Change from baseline in EuroQol 5D summary index at Outpatient Week 1, Outpatient Week 24, and at End of Treatment Visit.

The CEC adjudicated the mortality and morbidity endpoints.

Pharmacokinetic Variables

Pharmacokinetic endpoints were plasma concentrations of tolvaptan and its metabolite DM-4103.

Safety Variables

Safety was monitored via AEs, clinical laboratory tests, physical examinations, vital signs, and 12-lead ECGs.

Criteria for Evaluation, Substudy: Endpoints for the optional substudy were change from baseline in serum concentrations of the markers (ICTP, HS-CRP, and c-TnI); correlations of marker concentrations with etiology, clinical disease severity, and outcome; and correlations of marker concentrations with each other.

Statistical Methods, Long-term Outcome Trial: The efficacy analyses were performed on the ITT dataset, which included data from all randomized subjects. The safety analyses included all subjects who consumed at least one dose of trial drug.

Primary Efficacy Analysis

The primary analysis of time to all-cause mortality was performed using the Peto-Peto-Wilcoxon log-rank test, using both the dataset determined by the investigators and the adjudicated dataset. As supportive analyses, the stratified Peto-Peto-Wilcoxon log-rank test and the (unweighted) log-rank test were performed using 3 strata based on country's mortality rate in the first 2 months since the subjects' enrollment (< 5%, ≥ 5% but < 10%, or ≥ 10%). An estimate of the hazard ratio (HR) and its 95.98% confidence interval (CI) were provided using the Cox proportional hazards model with a term for treatment in the model. The endpoint was tested for both superiority and noninferiority. If the null hypothesis for the test of superiority was not rejected at a significance level of 0.0402 (2-sided), then the test of noninferiority was to be conducted.

The primary endpoint of time to first occurrence of CV mortality or heart failure hospitalization was analyzed using events adjudicated by the CEC. As a supportive analysis, the stratified Peto-Peto-Wilcoxon log-rank test (using the strata specified for all-cause mortality) and the (unweighted) log-rank test were performed, and estimate of the HR and its CI were provided by the Cox proportional hazards model with treatment as the independent variable. The 2 components of this endpoint, and events as determined by the investigators, were also analyzed using the same procedures.

Secondary Efficacy Analyses

Standard error (SE) of the mean was calculated for use in some figures. For endpoint 1 (time to first occurrence of CV mortality or CV morbidity adjudicated by the CEC), the Peto-Peto-Wilcoxon log-rank test was used for the comparison. As a supportive analysis, the stratified Peto-Peto-Wilcoxon log-rank test (using the strata specified for all-cause mortality) and the (unweighted) log-rank test were performed, and an estimate of the HR and its CI were provided by the Cox proportional hazards model with treatment as the independent variable.

For endpoint 2 (incidence of CV mortality adjudicated by the CEC), the Cochran-Mantel-Haenszel (CMH) test was used for treatment comparison, with geographic region (containing one or more countries) serving as stratification factor.

For endpoint 3 (incidence of worsening of heart failure), events were based on adjudications by the CEC. The CMH test stratified by geographic region was used to compare treatments. Analyses on secondary endpoints 1 to 3 were also conducted using data collected on the case report form determined by investigators, using the same procedures.

For endpoint 4 (change from baseline in body weight at Inpatient Day 1), the analysis was performed using an analysis of covariance (ANCOVA) model with terms of treatment and (pooled) center, and baseline body weight as a covariate. Type III sum of squares from SAS was used for treatment comparison.

For endpoint 5 (change from baseline in serum sodium concentration at Inpatient Day 7 or Discharge), the same analysis given for change in body weight was applied, with baseline serum sodium concentration as the covariate, and including only subjects with baseline serum sodium concentration < 134 mEq/L; however, the ANCOVA model did not include the term (pooled) center.

For endpoint 6 (change from baseline in edema score for subjects who had edema at baseline), treatment comparison employed the CMH test with modified ridit scores (van Elteren test), stratified by (pooled) center. For both endpoints 5 and 6, the last observation carried forward (LOCF) dataset was used, and the observed case (OC) dataset was used as a supportive analysis.

For endpoint 7 (patient-assessed dyspnea status), treatment comparison employed the CMH test with modified ridit scores (van Elteren test) stratified by (pooled) center, for subjects with dyspnea at baseline as assessed by the investigator.

For endpoint 8 (KCCQ overall summary score), an ANCOVA model with terms of treatment and (pooled) center, and baseline score as a covariate was used. Type III sum of squares from SAS was used for the treatment comparison. The KCCQ scoring was performed using the originally specified instructions (as described in J Amer Coll Cardiol 2000;35:1245-55) and also in post hoc analyses using more recent instructions. The results using the more recent instructions are presented in this report.

Tertiary Efficacy Analyses

All the tertiary efficacy endpoints were tested at significance level of 0.05. For endpoint 1 (incidence of CV morbidity adjudicated by the CEC), the CMH test stratified by geographic region was used for treatment comparison. For endpoint 2 (change from baseline in body weight at various time points), the analysis at each visit was the same as the one provided for secondary endpoint 4 of the Long-term Outcome Trial. The LOCF dataset was used, and results based on OC analyses were also provided.

For endpoint 3 (change from baseline in serum sodium concentration at various time points), the analysis at each visit was the same as the one provided for secondary endpoint 5 of the Long-term Outcome Trial. The LOCF dataset for subjects with a serum sodium concentration less than 134 mEq/L at baseline was used, and results based the OC dataset were also provided. For endpoint 4 (number of days alive out of hospital), an analysis of variance (ANOVA) model with terms of treatment and center were used for the analysis, using Type III sum of squares from SAS for the treatment comparison.

For endpoint 5 (KCCQ overall summary score), an ANCOVA model with terms of treatment and (pooled) center, and baseline score as a covariate for each visit was used. Type III sum of squares from SAS was used for the treatment comparison. For endpoint 6 (KCCQ domains, KCCQ functional status, and clinical summary score), an ANCOVA model with terms of treatment and (pooled) center, and baseline score as a covariate for each visit and variable was used. Type III sum of squares from SAS were used for the treatment comparison. For endpoint 7 (EuroQol 5D summary index), the analysis was performed using an ANCOVA model with terms of treatment and (pooled) center, and baseline index as a covariate. Type III sum of squares from SAS was used for the treatment comparison. The EuroQol 5D summary index was derived using the US time trade-off valuation set. For endpoints 5, 6, and 7, both OC and LOCF analyses were applied.

Planned Exploratory Analyses

Analysis of time to all-cause mortality was applied to all the subjects with baseline serum sodium concentrations < 135 mEq/L, using the procedure described above for the primary analysis (except using an alpha of 0.05, and ignoring the stratified Peto-Peto-Wilcoxon log rank test). Similar analyses were also conducted for the endpoint of time to first occurrence of CV mortality or heart failure hospitalization, primarily using adjudicated data, and supported by the investigator-determined data.

Subgroup Analyses

Subgroup analyses (by demographic variables, comorbidities, selected baseline CV assessments, chemistry and neurohormones, and baseline concomitant therapy) were applied to the primary and secondary efficacy endpoints of the Long-term Outcome Trial.

Safety Analyses

In general, summary statistics of changes from baseline were provided for safety variables based on all available data. No inferential statistical testing was planned for the safety parameters. All AEs were coded by Medical Dictionary of Regulatory Activities (MedDRA, version 9.0) system organ class and preferred term. The incidences of treatment-emergent AEs (TEAEs), potentially drug-related TEAEs, serious AEs (SAEs), AEs leading to discontinuation of trial drug, and deaths due to TEAEs were summarized by treatment. For clinical laboratory tests and vital signs, descriptive statistics were provided by treatment group for absolute values and change from baseline, and the incidence of potentially clinically significant results were summarized by treatment group. Shift tables were also produced for clinical laboratory tests, assessing changes from baseline relative to the normal range (low-normal-high at baseline to low-normal-high at a postbaseline visit). Summary statistics for average changes from baseline in ECG intervals were provided by treatment, and categorical changes were summarized.

Pharmacokinetic Methods, Long-term Outcome Trial: Blood samples were obtained prior to the first dose of tolvaptan, at Inpatient Day 7, Discharge, and Outpatient Weeks 1, 4 and 8. Samples could be taken at any time postdose. Plasma concentrations of tolvaptan and DM-4103 (metabolite) were simultaneously measured by a validated liquid

chromatography with tandem mass spectrometry method. The tolvaptan concentration data will be used for future population pharmacokinetic analyses, to be reported separately.

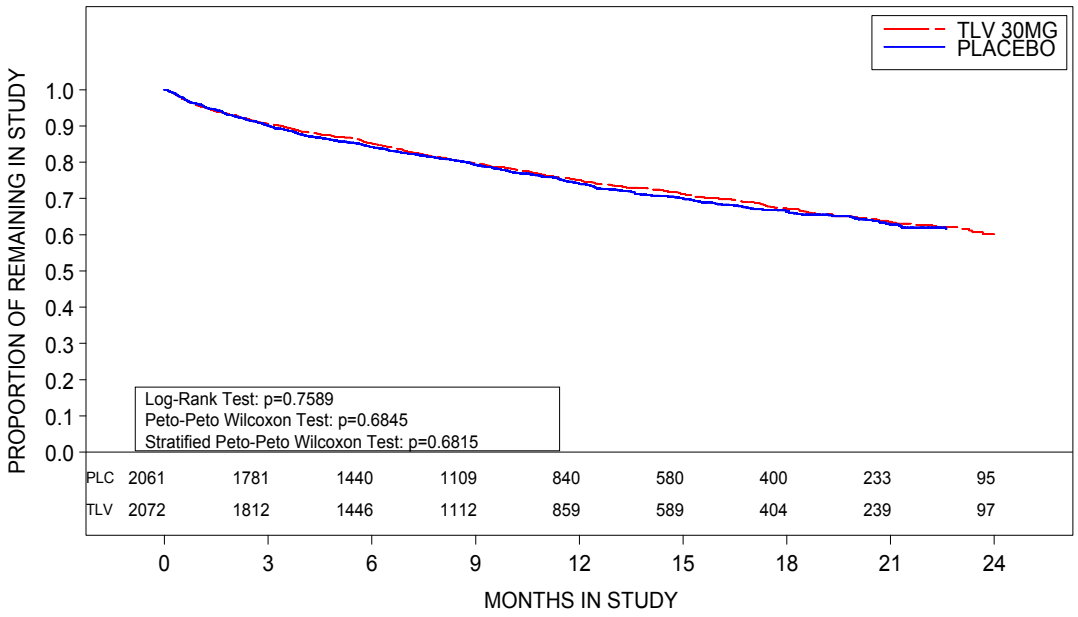
Efficacy Results, Long-term Outcome Trial: Results for the primary and secondary morbidity and mortality efficacy endpoints for the Long-term Outcome Trial are summarized in Synopsis Table 1. During a mean follow-up of 0.9 years, 537 subjects (25.9%) in the tolvaptan 30 mg group and 543 (26.4%) in the placebo group died (HR = 0.981, 95% CI = 0.866 to 1.112, p = 0.6845) (Synopsis Figure 1). The upper limit of the CI for the mortality difference was within the prespecified noninferiority margin of 1.25. During a mean follow-up of 0.7 years, the composite of first occurrence of CV mortality or hospitalization for heart failure occurred in 871 tolvaptan 30 mg group subjects (42.0%) and 829 placebo group subjects (40.2%, HR = 1.040, 95% CI = 0.946 to 1.144, p = 0.5451) (Synopsis Figure 2). Secondary endpoints of time to first occurrence of CV mortality/morbidity, incidence of CV mortality, and incidence of clinical worsening heart failure were also not different in the 2 treatment groups.

Synopsis Table 1 Summary of Primary and Secondary Morbidity and Mortality Efficacy Endpoints for the Long-term Outcome Trial

Endpoint	Subjects with events (%)		HR (CI)	P-value
	Tolvaptan 30 mg N = 2072	Placebo N = 2061		
Primary				
Survival Analysis - Time to all-cause mortality	537 (25.92)	543 (26.35)	0.981 (0.866, 1.112)	0.6845[a]
Survival Analysis - Time to CV mortality or heart failure hospitalization	871 (42.04)	829 (40.22)	1.040 (0.946, 1.144)	0.5451[a]
Secondary				
Survival Analysis - Time to CV mortality/ morbidity	1006 (48.55)	958 (46.48)	1.041 (0.953, 1.138)	0.5257[a]
Incidence of CV mortality	421 (20.32)	408 (19.80)	--	0.6673[b]
Incidence of clinical worsening of heart failure	757 (36.53)	739 (35.86)	--	0.6194[b]

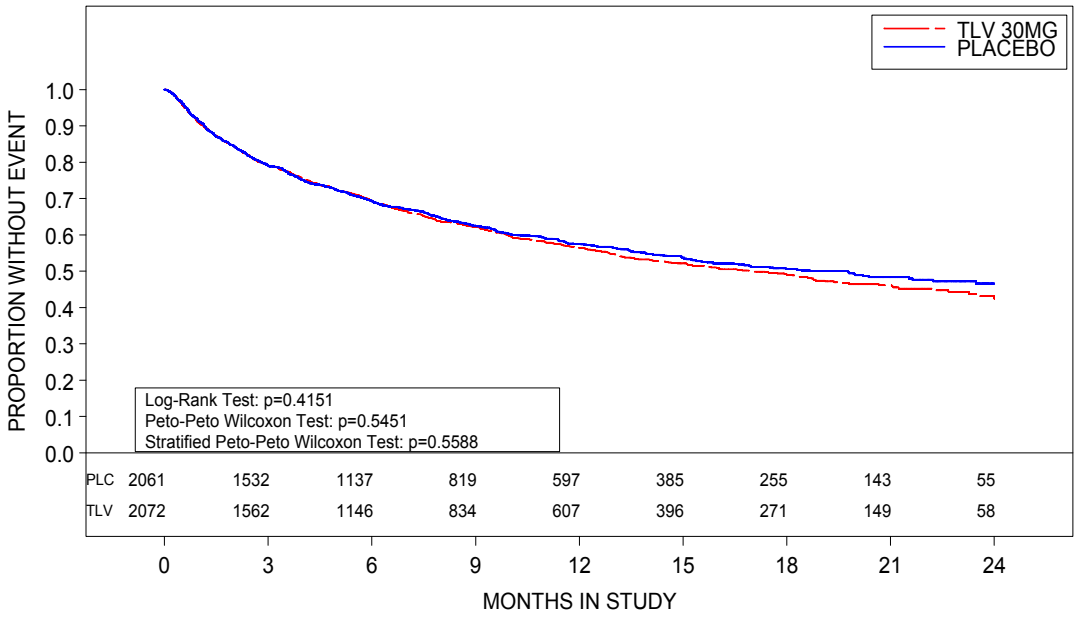
[a]Based on Peto-Peto-Wilcoxon test.

[b]Derived by using CMH test, stratified by geographic regions.



Synopsis Figure 1 Time to All-Cause Mortality (Determined by the Investigators) - Long-term Outcome Trial

PLC = placebo; TLV = tolvaptan 30 mg.
Note: Number of subjects at risk are shown at each time point.



Synopsis Figure 2 Time to First Occurrence of Cardiovascular Mortality or Hospitalization for Heart Failure (Adjudicated) - Long-term Outcome Trial

PLC = placebo; TLV = tolvaptan 30 mg.
Note: Number of subjects at risk are shown at each time point.

Signs, symptoms, and quality of life secondary efficacy endpoints relating to change from baseline in body weight, serum sodium concentration, patient-assessed dyspnea status, pedal edema, and the KCCQ Overall Summary Score are summarized in Synopsis Table 2. Tolvaptan 30 mg significantly improved secondary endpoints of patient-assessed dyspnea at Inpatient Day 1 (for subjects with physician-assessed dyspnea at baseline), body weight at Inpatient Day 1, and pedal edema at Inpatient Day 7 (for subjects with baseline pedal edema) relative to placebo. In subjects with hyponatremia (baseline serum sodium < 134 mEq/L), serum sodium concentrations significantly increased in the tolvaptan 30 mg group compared with the placebo group. In the tolvaptan 30 mg group, 74.3% of subjects with dyspnea at baseline compared with 68.0% of placebo subjects felt they had improvement in patient-assessed dyspnea status at Inpatient Day 1 ($p < 0.0001$, 95% CI = 0.525 to 0.559 for distribution across 7 categories of improvement, worsening, or no change) (Synopsis Figure 3). The mean (standard deviation [SD]) change from baseline in body weight was −1.76 (1.91) kg in the tolvaptan 30 mg group compared with −0.97 (1.84) kg in placebo group at Inpatient Day 1 ($p < 0.0001$, 95% CI = −0.89 to −0.66). In the tolvaptan 30 mg group, 73.8% of subjects had improvement of at least 2 points in pedal edema compared with 70.5% of placebo subjects at Inpatient Day 7 ($p = 0.0032$, 95% CI = 0.507 to 0.543 for distribution across 6 categories of improvement, worsening, or no change). The mean (SD) change in serum sodium concentration at Inpatient Day 7 or Discharge if earlier was 5.4 (5.7) mEq/L in the tolvaptan 30 mg group compared with 1.8 (5.0) mEq/L in the placebo group ($p < 0.0001$, 95% CI = 2.22 to 5.48). Improvement in the KCCQ Overall Summary Score at Outpatient Week 1 was not different in the 2 treatment groups ($p = 0.2844$, 95% CI = −0.81 to 2.75), but body weight and serum sodium effects persisted long after discharge (refer to the results for tertiary endpoints, below).

Synopsis Table 2 Summary of Other Secondary Efficacy Endpoints for the Long-term Outcome Trial

Endpoint	Tolvaptan 30 mg N = 2072	Placebo N = 2061	P-value (95% CI)
Change in body weight (kg) at Inpatient Day 1, mean (SD) [No.]	−1.76 (1.91) [1999]	−0.97 (1.84) [1999]	< 0.0001[a] (−0.89, −0.66)
Change in serum sodium[b] (mEq/L) at Inpatient Day 7[c], mean (SD) [No.]	5.43 (5.73) [166]	1.80 (5.04) [166]	< 0.0001[a] (2.22, 5.48)
Change in pedal edema[d] at Inpatient Day 7[c], n (%) showing improvement ≥ 2 points [No.]	1180 (73.8%) [1600]	1125 (70.5%) [1595]	0.0032[e] (0.507, 0.543)
Patient-assessed dyspnea status[d] at Inpatient Day 1, n (%) showing improvement [No.]	1364 (74.3%) [1835]	1243 (68.0%) [1829]	< 0.0001[e] (0.525, 0.559)

Synopsis Table 2	**Summary of Other Secondary Efficacy Endpoints for the Long-term Outcome Trial**		
Endpoint	**Tolvaptan 30 mg N = 2072**	**Placebo N = 2061**	**P-value (95% CI)**
KCCQ Overall Summary Score at Outpatient Week 1, mean (SD) [No.]	21.50 (20.58) [833]	20.18 (20.79) [837]	0.2844[a] (−0.81, 2.75)

No. = number of subjects.

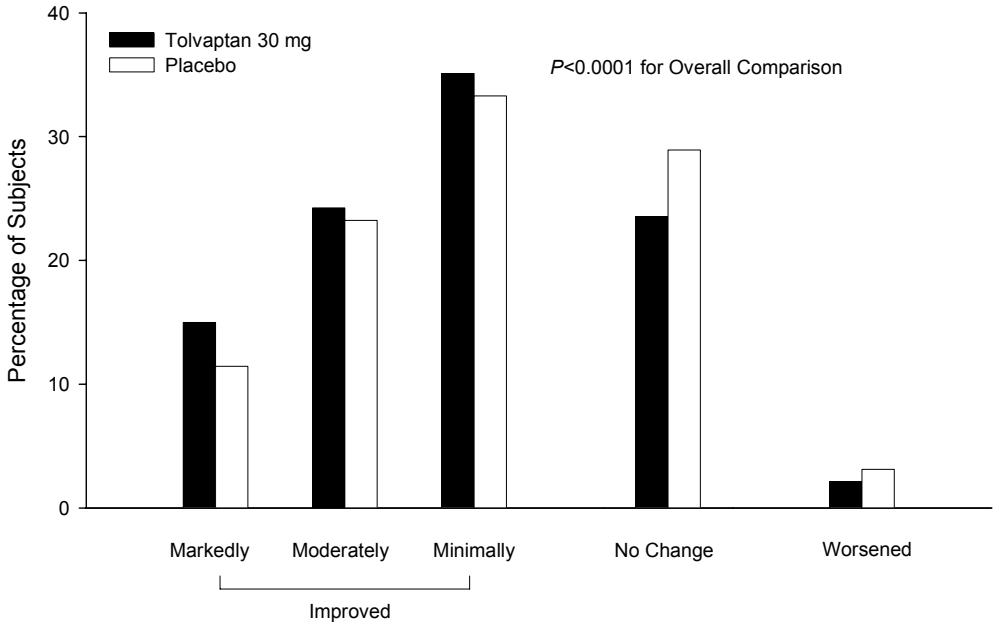
[a]P-values for analyses of body weight and KCCQ were derived from ANCOVA model with treatment and (pooled) clinical center as factors and baseline value as a covariate. P-value for serum sodium concentration was derived from ANCOVA model with treatment as a factor and baseline value as a covariate.

[b]Subjects with serum sodium concentration less than 134 mEq/L at baseline.

[c]Assessed at Discharge if before Inpatient Day 7.

[d]Subjects with symptoms (as assessed by the physician) at baseline.

[e]P-value was derived from CMH mean score test with modified ridit scores (van Elteren test) stratified by (pooled) center, for distribution across 7 categories of improvement, worsening, and no change.

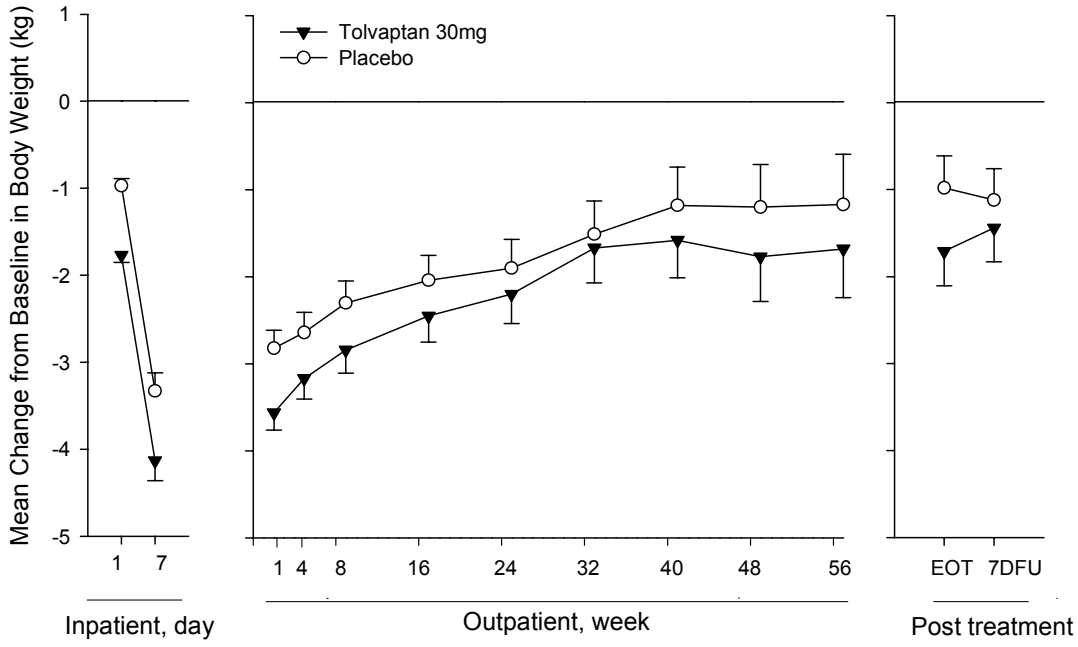


Synopsis Figure 3 Patient-assessed Dyspnea Status at Inpatient Day 1 in Subjects With Frequent or Continuous Physician-assessed Dyspnea at Baseline - Long-term Outcome Trial

Note: Subjects were asked "Compared to how much difficulty you were having with your breathing just before trial drug was started, how is your breathing now?"

Note: Worsened includes minimally worse, moderately worse, and markedly worse.

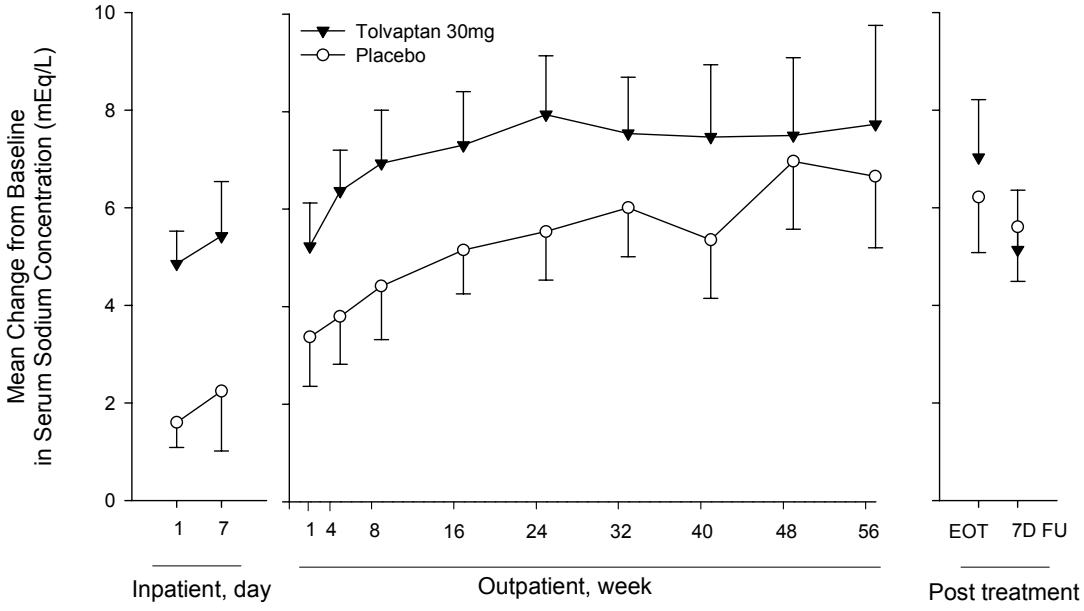
The analysis of the tertiary efficacy endpoints, in combination with analyses by visit using LOCF, showed statistically significant treatment group differences favoring tolvaptan 30 mg at each visit through Outpatient Week 128 in mean change from baseline in body weight and in mean change from baseline in serum sodium concentration (for subjects with hyponatremia). Using OC, there were significant differences, favoring tolvaptan 30 mg, at Inpatient Day 1 through Outpatient Week 8 for change in body weight (Synopsis Figure 4) and at Inpatient Day 1, Inpatient Day 7, and Outpatient Weeks 1, 4, 8, 16, 24, and 40 for change in serum sodium concentrations (Synopsis Figure 5). Post hoc analyses were conducted to evaluate the change in body weight and the change in serum sodium concentration 7 days after discontinuation of trial drug (OC). Approximately 7 days after discontinuation, the placebo treatment group continued to show a mean decrease in body weight while a mean increase was observed in the tolvaptan 30 mg group, and serum sodium concentrations in the tolvaptan 30 mg group declined to values not statistically significantly different from those in the placebo group.



Synopsis Figure 4 Mean (SE) Change From Baseline or End of Treatment in Body Weight by Visit (OC) - Long-term Outcome Trial

7D FU = 7-day follow-up; EOT = End of Treatment.

Note: For tolvaptan 30 mg versus placebo, mean change from baseline, $p < 0.0001$ Days 1 and 7; $p < 0.003$ Weeks 1, 4, and 8; $p = 0.0092$ EOT; no other statistically significant differences; and mean change from EOT to 7DFU, $p < 0.0001$.



Synopsis Figure 5 Mean (95% CI) Change From Baseline or End of Treatment in Serum Sodium Concentration by Visit in Subjects With a Serum Sodium Concentration Less Than 134 mEq/L at Baseline (OC) - Long-term Outcome Trial

7D FU = 7-day follow-up; EOT = End of Treatment.
Note: For tolvaptan 30 mg versus placebo, mean change from baseline $p < 0.0001$ Days 1 and 7; $p = 0.0004$ Week 1; $p < 0.0001$ Week 4; $p = 0.0006$ Week 8; $p < 0.05$ Weeks 16, 24, 40; no other statistically significant differences.

For the remaining tertiary efficacy endpoints, there were statistically significant differences in the KCCQ assessments (using revised scoring instructions), favoring tolvaptan 30 mg over placebo, for the for the Overall Summary Score at End of Treatment (LOCF and OC), the Social Limitation Score at the End of Treatment Visit (OC), and for the Quality of Life Score at Outpatient Week 24 (LOCF) and the End of Treatment Visit (LOCF and OC). Mean KCCQ scores for other domains were generally higher for tolvaptan 30 mg compared with the placebo group at most time points, although the treatment group differences were not statistically significant. There were no statistically significant differences between the treatment groups with respect to the EuroQol 5D, the number of days alive outside of the hospital, or the total incidence of CV morbidity. CV morbidity was limited to hospitalization for CV reasons, which included heart failure, acute myocardial infarction, stroke, arrhythmia, and other CV morbidity (such as unstable angina, pulmonary embolism, etc). The most common type of CV morbidity leading to hospitalization was heart failure (approximately 31% in both treatment groups). A larger number of CV hospitalizations were adjudicated as due to myocardial infarction in the placebo group (42 [2.0%]) than in the tolvaptan group (25 [1.2%]; $p = 0.0350$), and a

larger number were adjudicated as due to stroke in the tolvaptan group (45 [2.2%]) than in the placebo group (24 [1.2%]; p = 0.0116).

Post hoc analyses of change from baseline in physician-assessed CV assessments were performed by visit using LOCF. The analyses were performed for subjects with the symptom of interest at baseline, as well as for all subjects regardless of their baseline symptoms. Among subjects with CV symptoms at baseline, statistically significantly more subjects receiving tolvaptan 30 mg than placebo exhibited improvements in dyspnea and rales over the first 4 inpatient days, and improvements in orthopnea and JVD over the first 3 inpatient days. In addition, the number of tolvaptan 30 mg subjects with improvement in fatigue was significantly greater than placebo over Inpatient Days 3 through 6, and in pedal edema over Inpatient Days 1 through 7. In the outpatient period, significant improvements in the tolvaptan 30 mg group compared with the placebo group were observed at Outpatient Weeks 1 and 4 for pedal edema and at Outpatient Weeks 4, 8, and 16 for rales. Post hoc by-visit responder analyses for the physician-assessed CV assessments were similar to the change from baseline analyses for each CV assessment.

With respect to the analyses by prespecified subgroups, the results were similar to those for all subjects in most subgroups. The differences between the treatment groups were not statistically significant for the mortality and morbidity endpoints in nearly all subgroups, including those based on age, gender, race, or region. The differences between the treatment groups were statistically significant, favoring tolvaptan 30 mg, in most subgroups for the change from baseline in body weight at Inpatient Day 1, change from baseline in serum sodium concentration (for subjects with baseline serum sodium concentration less than 134 mEq/L) at Inpatient Day 7 or Discharge if earlier, and patient-assessed dyspnea at Inpatient Day 1 (for subjects with physician-assessed dyspnea at baseline). For the other efficacy endpoints, the differences between the treatment groups were not statistically significant in the majority of subgroups.

Pharmacokinetic Results, Long-term Outcome Trial: Concentration data and calculated time postdose were reviewed for correctness; errors and discrepancies were noted and, if possible, corrections were noted. The population pharmacokinetic analysis will be reported separately.

Safety Results, Long-term Outcome Trial: Safety data for the Long-term Outcome Trial were analyzed for the overall trial period, as well as for the short-term period (through Inpatient Day 7 or Discharge, whichever came first). The overall incidence of treatment-emergent adverse events (TEAEs) for the overall trial period was higher for tolvaptan compared with placebo (89.0% versus 86.1%). Over the long-term period, the incidences of deaths due to TEAEs (22.0% versus 22.7%), of serious AEs (SAEs) (58.1% versus 58.2%), and of discontinuations due to TEAEs (6.5% versus 5.5%) were similar for tolvaptan and placebo, respectively. The most commonly reported potentially drug-related TEAEs (ie, ≥ 2% in the tolvaptan group and also ≥ 1% higher than placebo) were dry mouth (7.6% tolvaptan, 1.7% placebo), thirst (14.8% tolvaptan, 1.8% placebo), and polyuria (2.6% tolvaptan, 0.5% placebo). No meaningful age- or sex-related differences

in TEAEs were observed for tolvaptan. Caucasians had notably higher incidences of dry mouth (9.6% Caucasians, 1.7% non-Caucasians) and thirst (17.4% Caucasians, 8.0% non-Caucasians). Similar results were observed for the short-term period for the entire safety population (ie, the overall incidence of TEAEs was higher for tolvaptan compared with placebo, and the incidences of deaths, SAEs, and discontinuations due to TEAEs were similar for tolvaptan and placebo).

Slightly greater mean increases in serum sodium concentrations (all subjects regardless of baseline serum sodium concentration) from Inpatient Day 1 through Outpatient Week 96 were observed for tolvaptan 30 mg (ranging from 1.3 to 3.3 mEq/L) compared with placebo (ranging from −1.2 to 1.9 mEq/L). Greater mean increases in serum osmolality from Inpatient Day 1 through Outpatient Week 4 were observed for tolvaptan 30 mg (ranging from 2.7 to 6.7 mOsm/kg) compared with placebo (ranging from −0.2 to 1.3 mOsm/kg). Slightly greater mean increases in serum chloride from Inpatient Day 1 through Outpatient Week 96 were observed for tolvaptan 30 mg (ranging from 1.2 to 2.4 mEq/L) compared with placebo (ranging from −1.0 to 1.5 mEq/L). Although the magnitude of the mean changes in blood urea nitrogen (BUN) was small for both treatment groups, small mean decreases were seen at several time points for the tolvaptan 30 mg group (up to −2.1 mg/dL), whereas small mean increases (up to 3.3 mg/dL) were primarily seen for the placebo group. The mean changes and shifts for the other serum chemistry parameters were similar for both treatment groups during the treatment period through Outpatient Week 96, beyond which the sample sizes were too small to allow for a meaningful comparison. Although differences between the tolvaptan 30 mg and placebo groups were revealed in the post hoc analyses of mean change from baseline in BUN, serum creatinine, uric acid, potassium, magnesium, and sodium (analyzed for normonatraemic subjects only) the magnitude of the estimated treatment difference for tolvaptan was small.

The mean changes and shifts for each of the hematology parameters were similar for both treatment groups during the treatment period through Outpatient Week 96, beyond which the sample sizes were too small to allow for a meaningful comparison. The mean changes and shifts for urine pH were similar for both treatment groups; however, notable mean decreases in urine specific gravity were observed for tolvaptan 30 mg (ranging from −0.0023 to −0.0052) compared with placebo (ranging from 0.0004 to 0.0021) during the treatment period through Outpatient Week 96, beyond which the samples sizes were too small to allow for a meaningful comparison.

The mean changes in serum aldosterone were generally similar for both treatment groups; however, slightly greater mean increases in AVP concentrations were observed for tolvaptan 30 mg (ranging from 1.3 to 4.4 pg/mL) compared with placebo (ranging from −0.6 to 1.0 pg/mL) during the treatment period through Outpatient Week 96, beyond which the sample sizes were too small to allow for a meaningful comparison.

The results observed in the short-term period for the entire safety population in the analyses of mean change and shifts from baseline in serum chemistry, urinalysis, and

other laboratory parameters were consistent with those observed for the overall trial period (ie, greater mean increases in serum sodium, serum osmolality, serum chloride, and AVP, and greater mean decreases in urine specific gravity for tolvaptan compared with placebo), with the exception of BUN which was not noticeably different between treatment groups in the short-term period.

The mean changes for supine blood pressure, supine heart rate, respiration rate, and oral temperature were similar for both treatment groups during the treatment period. The mean changes for each ECG parameter were similar for both treatment groups during the treatment period and no notable differences were observed. Similar results were observed for the short-term period (through Day 7 or Discharge, whichever came first) for the entire safety population (ie, no notable differences were observed between tolvaptan and placebo for these parameters).

Results and Conclusions, Substudy: Treatment with tolvaptan 30 mg had no effect on the concentration of any of the 3 biomarkers. Relative to baseline, the ICTP concentration (tolvaptan and placebo subjects) was significantly increased at Inpatient Day 7 or Discharge if earlier. Baseline ICTP and HS-CRP concentrations were strongly correlated with each other, and the baseline ICTP concentration was associated with disease severity and trial outcome (ie, morbidity and mortality). Neither HS-CRP or c-TnI baseline concentrations were correlated with disease severity or trial outcome.

Conclusions, Long-term Outcome Trial: In adult subjects hospitalized with worsening heart failure and signs of congestion, once daily administration of oral tolvaptan 30 mg initiated within 48 hours after hospitalization and continued long term after discharge, in addition to continued conventional therapy including diuretics, demonstrated the following in comparison with placebo:

- No effect on survival or in the combined endpoint of time to CV mortality or heart failure hospitalization.
- Early and sustained weight reduction.
- Improvement in patient-assessed dyspnea (Inpatient Day 1) and pedal edema (Inpatient Day 7 or Discharge if earlier).
- Normalization of serum sodium in subjects with hyponatremia.
- A well-defined and acceptable short-term and long-term safety profile.

Short-term Clinical Status Trials A and B

Objectives, Short-term Clinical Status Trials A and B: The primary objective of embedded Short-term Clinical Status Trials A and B was to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the composite of change from baseline in patient-assessed global clinical status at Inpatient Day 7 or Discharge if earlier, and change from baseline in body weight at Inpatient Day 7 or Discharge if earlier. The secondary objectives of Short-term Clinical Status Trials A and B were to compare the efficacy of tolvaptan or placebo in conjunction with optimal (as determined by the investigator) current therapy on the secondary efficacy variables including change from baseline in body weight (Inpatient Day 1 and Inpatient Day 7 or discharge if earlier), edema score (Inpatient Day 7 or discharge if earlier for those with edema at baseline), and patient-assessed global clinical status (Inpatient Day 7 or discharge if earlier); and dyspnea status at Inpatient Day 1 for those with dyspnea at baseline.

Methodology, Short-term Clinical Status Trials A and B: The purpose of the Short-term Clinical Status Trials was to assess the effect of tolvaptan during the in-hospital treatment period. All centers were assigned to one of the Short-term Clinical Status Trials at the end of the trial according to a prespecified algorithm. Trial conduct was as described for the Long-term Outcome Trial, except the observation period ended on Inpatient Day 7 or Discharge if earlier. In the Short-term Clinical Status Trials, efficacy assessments were body weight, patient-assessed global clinical status, pedal edema, and patient-assessed dyspnea. Safety assessments were as described for the Long-term Outcome Trial through Inpatient Day 7 or Discharge if earlier.

Number of Subjects, Short-term Clinical Status Trials A and B: In Short-term Clinical Status Trial A, 2048 subjects were analyzed for efficacy (1018 tolvaptan 30 mg; 1030 placebo) and 2042 subjects were analyzed for safety (1015 tolvaptan 30 mg; 1027 placebo). In Short-term Clinical Status Trial B, 2085 subjects were analyzed for efficacy (1054 tolvaptan 30 mg; 1031 placebo) and 2076 subjects were analyzed for safety (1048 tolvaptan 30 mg; 1028 placebo). Subjects who were randomized but did not receive trial drug were analyzed for efficacy but were not analyzed for safety.

Criteria for Evaluation, Short-term Clinical Status Trials A and B:
Efficacy Variables
The primary efficacy endpoint for the Short-term Clinical Status Trials was the composite of change from baseline in patient-assessed global clinical status and body weight at Inpatient Day 7 or Discharge if earlier (sum of the rank scores from 0 to 1, with 0 = the worst change and 1 = the best change).

The secondary efficacy endpoints for the Short-term Clinical Status Trials were as follows:

1) Change from baseline in patient-assessed global clinical status at Inpatient Day 7 or Discharge if earlier.

2) Change from baseline in body weight at Inpatient Day 7 or Discharge if earlier.
3) Change from baseline in body weight at Inpatient Day 1.
4) Change from baseline in edema score at Inpatient Day 7 or Discharge if earlier for those with edema at baseline.
5) Patient-assessed dyspnea status at Inpatient Day 1, for those with physician-assessed dyspnea at baseline.

Safety Variables
Safety was monitored as for the Long-term Outcome Trial.

Statistical Methods, Short-term Clinical Status Trials A and B:
The efficacy analyses were performed on the ITT dataset, which included data from all randomized subjects. The safety analyses included all subjects who consumed at least one dose of trial drug.

Primary Efficacy Analysis
The primary composite endpoint was combined using O'Brien's procedure, so that higher rank corresponded to better result for change in body weight. The primary test for this composite endpoint was based on an ANOVA using treatment as the only factor. This endpoint was required to reach a significance level of 0.04 in each of the 2 Short-term Clinical Status Trials.

Secondary Efficacy Analyses
Standard error of the mean was calculated for use in some figures as for the Long-term Outcome Trial. For endpoint 1 (change from baseline in patient-assessed global clinical status at Inpatient Day 7 or Discharge if earlier), the primary test was based on an ANCOVA using the baseline value as a covariate and treatment and (pooled) clinical center as factors. The analysis of endpoint 2 (change from baseline in body weight at Inpatient Day 7 or Discharge if earlier) was similar to the analysis of endpoint 1, except that LOCF was used if a subject had no observation in body weight at Inpatient Day 7 or Discharge if earlier.

For endpoint 3 (change from baseline in body weight at Inpatient Day 1), the analysis was the same as the one provided for secondary endpoint 4 of the Long-term Outcome Trial. For endpoint 4 (change from baseline in edema score at Inpatient Day 7 or Discharge if earlier for those with edema at baseline), the same statistical analysis for secondary endpoint 6 of the Long-term Outcome Trial was applied. For endpoint 5 (patient-assessed dyspnea at Inpatient Day 1, for those with physician-assessed dyspnea at baseline), a statistical analysis similar to the one provided for secondary endpoint 7 of the Long-term Outcome Trial was applied.

Planned Exploratory Analyses
Patient-assessed global clinical status was summarized by visit.

Subgroup Analyses
Subgroup analyses were performed as for the Long-term Outcome Trial.

Safety Analyses
Safety analyses were performed as for the Long-term Outcome Trial.

Efficacy Results, Short-term Clinical Status Trial A: The results of the efficacy analyses for Short-term Clinical Status Trial A are summarized in Synopsis Table 3. The primary efficacy endpoint was the composite of change from baseline in patient-assessed global clinical status and body weight at Inpatient Day 7 or Discharge if earlier. For Trial A, the mean composite for the tolvaptan 30 mg group was greater than the mean composite for the placebo group (p = 0.0005, 95% CI = 0.03 to 0.11). Mean (SD) body weight reduction was greater with tolvaptan 30 mg compared with placebo on Inpatient Day 7 or Discharge if earlier (–3.4 [3.3] kg versus −2.7 [3.3] kg; p < 0.0001, 95% CI = −0.89 to −0.36), whereas improvements in patient-assessed global clinical status were not different between the groups. Mean (SE) body weight reduction is graphically depicted in Synopsis Figure 6.

Synopsis Table 3 Summary of Efficacy Results for Short-term Clinical Status Trial A

	Tolvaptan 30 mg N = 1018	**Placebo N = 1030**	**P-value (95% CI)**
Composite primary endpoint at Inpatient Day 7[a], mean (SD) [No.]	1.06 (0.43) [893]	0.99 (0.44) [901]	0.0005[b] (0.03, 0.11)
Patient-assessed global clinical status at Inpatient Day 7[a], mean (SD) [No.]	18.25 (22.26) [903]	17.73 (22.47) [910]	0.5131[c] (−1.09, 2.18)
Change in body weight (kg) at Inpatient Day 7[a], mean (SD) [No.]	−3.35 (3.27) [997]	−2.73 (3.34) [1007]	< 0.0001[c] (−0.89, −0.36)
Change in body weight (kg) at Inpatient Day 1, mean (SD) [No.]	−1.71 (1.80) [978]	−0.99 (1.83) [997]	< 0.0001[c] (−0.87, −0.56)
Change in pedal edema at Inpatient Day 7[a], n (%) showing improvement ≥ 2 points [No.][d]	570 (73.8) [772]	555 (70.2) [790]	0.0653[e] (0.496, 0.547)
Patient-assessed dyspnea status at Inpatient Day 1, n (%) showing improvement [No.][d]	686 (76.7) [894]	646 (70.6) [915]	0.0004[e] (0.517, 0.565)

No. = number of subjects.

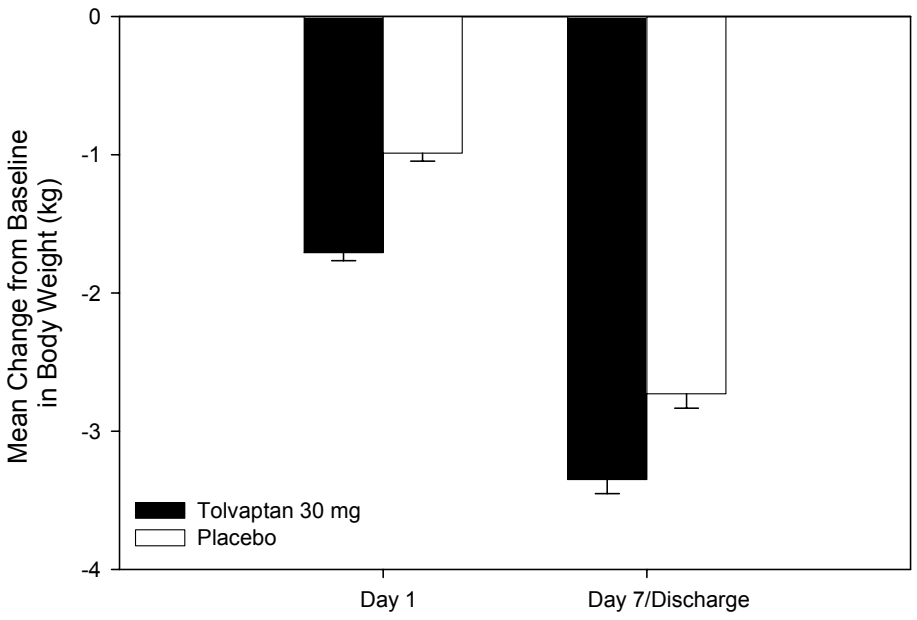
[a]Assessed at Discharge if before Inpatient Day 7.

[b]P-value was derived from an ANOVA model with treatment as a factor.

[c]P-value was derived from an ANCOVA model with treatment and (pooled) clinical center as factors and baseline value as covariate.

[d]Subjects with symptoms (as assessed by the physician) at baseline.

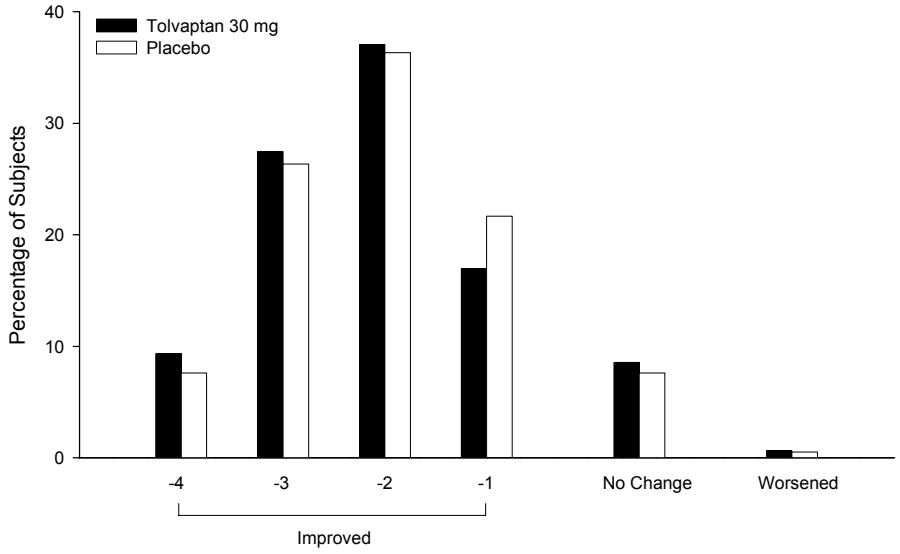
[e]P-value was derived from CMH mean score test with modified ridit scores (van Elteren test) stratified by (pooled) center, for distribution across 7 categories of improvement, worsening, and no change.



Synopsis Figure 6 Mean (SE) Change From Baseline in Body Weight at Inpatient Day 1 and Inpatient Day 7 or Discharge if Earlier - Short-term Clinical Status Trial A

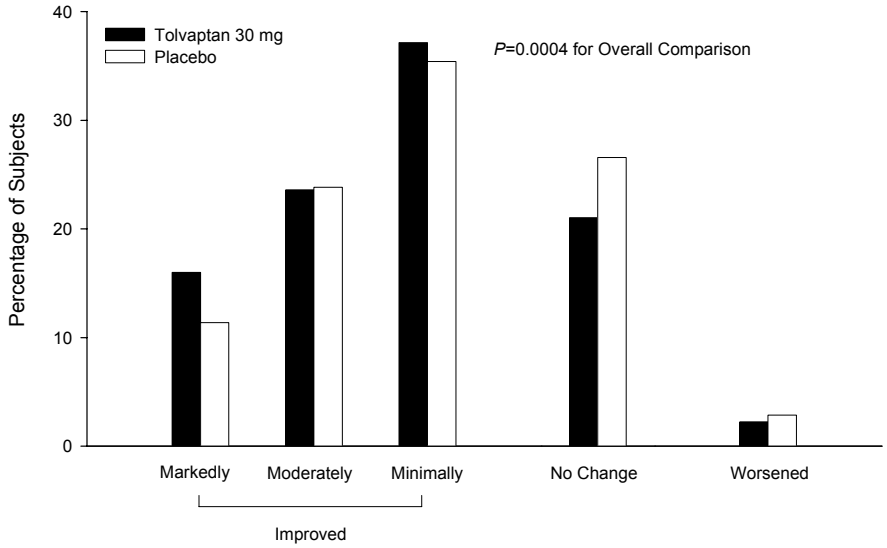
Note: $p < 0.0001$ on Inpatient Days 1 and 7 or Discharge if earlier for tolvaptan 30 mg versus placebo.

Additional secondary efficacy endpoints for Trial A demonstrated significant improvements in the tolvaptan 30 mg group over placebo. Mean (SD) body weight reduction was greater with tolvaptan 30 mg on Inpatient Day 1 (−1.7 [1.8] kg versus −1.0 [1.8] kg; $p < 0.0001$, 95% CI = −0.87 to −0.56), consistent with the Inpatient Day 7/Discharge findings (Synopsis Figure 6). Pedal edema (for subjects with pedal edema at baseline) at Inpatient Day 7 or Discharge if earlier improved by at least 2 points for more subjects receiving tolvaptan 30 mg compared with placebo, although the difference did not reach statistical significance (570 [73.8%] versus 555 [70.2%]; $p = 0.0653$, 95% CI = 0.496 to 0.547 for distribution of scores across 6 categories of improvement, worsening, or no change) (Synopsis Figure 7). More subjects receiving tolvaptan 30 mg (686 [76.7%]) versus subjects receiving placebo (646 [70.6%]) reported improvement in patient-assessed dyspnea at Inpatient Day 1 ($p = 0.0004$, 95% CI = 0.517 to 0.565 for distribution of scores across 7 categories of improvement, worsening, or no change) among those with dyspnea at baseline (Synopsis Figure 8).



Synopsis Figure 7 Change From Baseline in Pedal Edema Score at Inpatient Day 7 or Discharge if Earlier in Subjects Who Had Edema (1+, 2+, 3+) at Baseline - Short-term Clinical Status Trial A

Note: p = 0.0653 for distribution of scores across 7 categories (worsened includes change of +1 and +2) for tolvaptan 30 mg versus placebo.



Synopsis Figure 8 Patient-assessed Dyspnea Status at Inpatient Day 1, for Subjects With Frequent or Continuous Physician-assessed Dyspnea at Baseline - Short-term Clinical Status Trial A

Note: Subjects were asked "Compared to how much difficulty you were having with your breathing just before trial drug was started, how is your breathing now?"

Note: Worsened includes minimally worse, moderately worse, and markedly worse.

Post hoc analyses of change from baseline and change from baseline in the percentage of responders were performed by visit for selected physician-assessed CV assessments (for subjects in Trial A with the symptom of interest at baseline, and separately for all subjects in Trial A). The results of the analyses supported those described above for the Long-term Outcome Trial. In Trial A, greater improvement was observed in the tolvaptan 30 mg group compared with the placebo group at Inpatient Days 1 and/or 2 for dyspnea, orthopnea, JVD, and pedal edema. Results favoring tolvaptan 30 mg were also noted at Inpatient Day 6 (pedal edema). The results of the by-visit responder analyses were similar to those of the change from baseline analyses for each CV assessment.

Prespecified subgroups analyses of the primary and secondary endpoints in Trial A showed results consistent with those from the full Trial A population in most subgroups. In general, if the treatment group differences for an endpoint were statistically significant for the full population, then the same was true for most subgroups. Similarly, endpoints with no significant treatment groups differences in the full population were not significantly different in most subgroups.

Efficacy Results, Short-term Clinical Status Trial B: The results of the efficacy analyses for Short-term Clinical Status Trial B are summarized in Synopsis Table 4. The primary efficacy endpoint was the composite of change from baseline in patient-assessed global clinical status and body weight at Inpatient Day 7 or Discharge if earlier. For Trial B, the mean composite for the tolvaptan 30 mg group was greater than the mean composite for the placebo group ($p < 0.0001$, 95% CI = 0.06 to 0.13). Mean (SD) body weight reduction was greater with tolvaptan 30 mg compared with placebo on Inpatient Day 7 or Discharge if earlier (–3.8 [3.6] kg versus −2.8 [3.5] kg; $p < 0.0001$, 95% CI = −1.20 to −0.63), whereas improvements in patient-assessed global clinical status were not different between the groups. Mean (SE) body weight reduction is graphically depicted in Synopsis Figure 9.

Synopsis Table 4 Summary of Efficacy Results for Short-term Clinical Status Trial B

	Tolvaptan 30 mg N = 1054	**Placebo N = 1031**	**P-value (95% CI)**
Composite primary endpoint at Inpatient Day 7[a], mean (SD) [No.]	1.07 (0.42) [923]	0.97 (0.43) [892]	< 0.0001[b] (0.06, 0.13)
Patient-assessed global clinical status at Inpatient Day 7[a], mean (SD) [No.]	18.72 (21.71) [931]	18.28 (21.59) [900]	0.5188[c] (−1.05, 2.08)
Change in body weight (kg) at Inpatient Day 7[a], mean (SD) [No.]	−3.77 (3.59) [1031]	−2.79 (3.46) [1008]	< 0.0001[c] (−1.20, −0.63)
Change in body weight (kg) at Inpatient Day 1, mean (SD) [No.]	−1.82 (2.01) [1021]	−0.95 (1.85) [1002]	< 0.0001[c] (−1.00, −0.67)
Change in pedal edema at Inpatient Day 7[a], n (%) showing improvement ≥ 2 points [No.][d]	610 (73.7) [828]	570 (70.8) [805]	0.0202[e] (0.503, 0.553)

Synopsis Table 4	**Summary of Efficacy Results for Short-term Clinical Status Trial B**		
	Tolvaptan 30 mg N = 1054	**Placebo N = 1031**	**P-value (95% CI)**
Change in patient-assessed dyspnea at Inpatient Day 1, n (%) showing improvement [No.][d]	678 (72.1) [941]	597 (65.3) [914]	0.0002[e] (0.520, 0.566)

No. = number of subjects

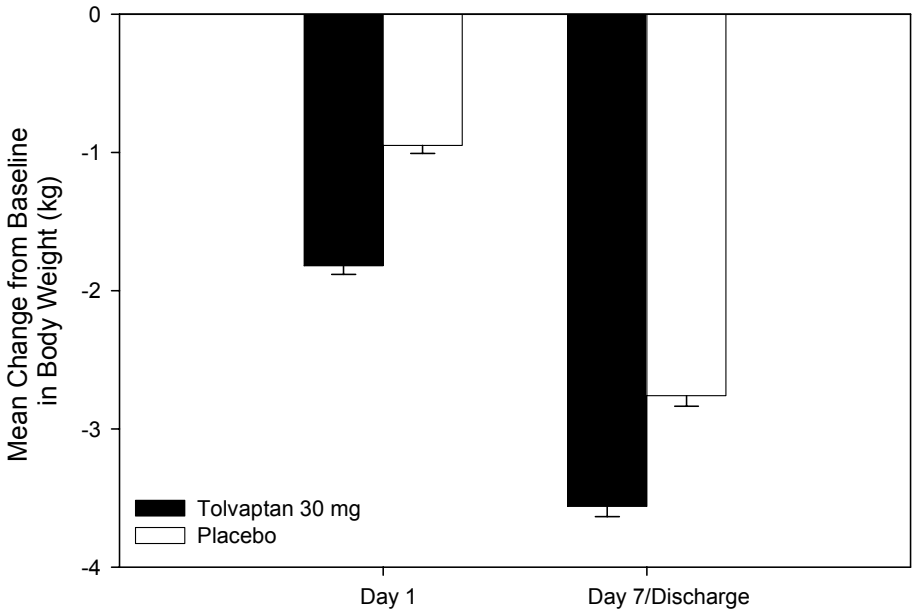
[a]P-value was derived from an ANOVA model with treatment as a factor.

[b]Assessed at Discharge if before Inpatient Day 7.

[c]P-value was derived from an ANCOVA model with treatment and (pooled) clinical center as factors and baseline value as covariate.

[d]Subjects with symptoms (as assessed by the physician) at baseline.

[e]P-value was derived from CMH mean score test with modified ridit scores (van Elteren test) stratified by (pooled) center, for distribution across 7 categories of improvement, worsening, and no change.

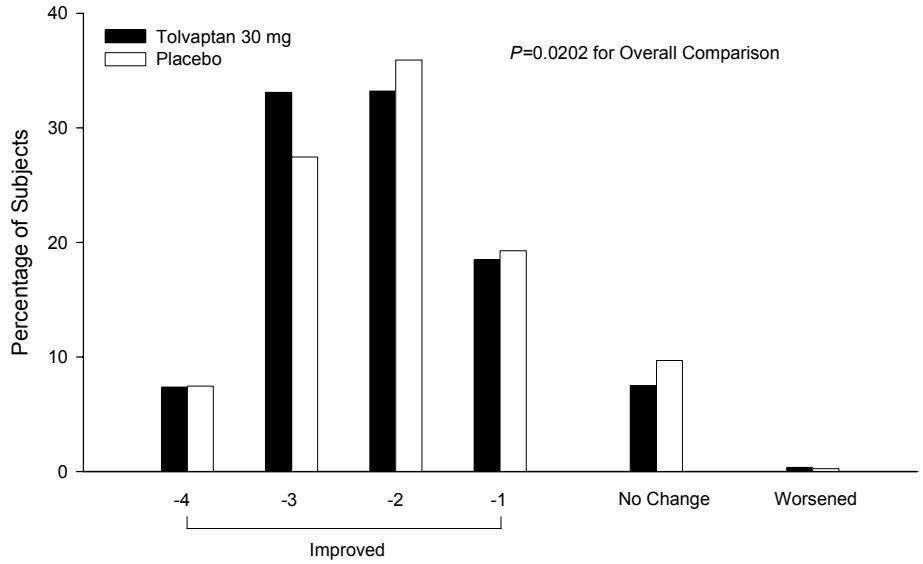


Synopsis Figure 9 **Mean (SE) Change From Baseline in Body Weight at Inpatient Day 1 and Inpatient Day 7 or Discharge if Earlier - Short-term Clinical Status Trial B**

Note: $p < 0.0001$ on Inpatient Days 1 and 7 or Discharge if earlier for tolvaptan 30 mg versus placebo.

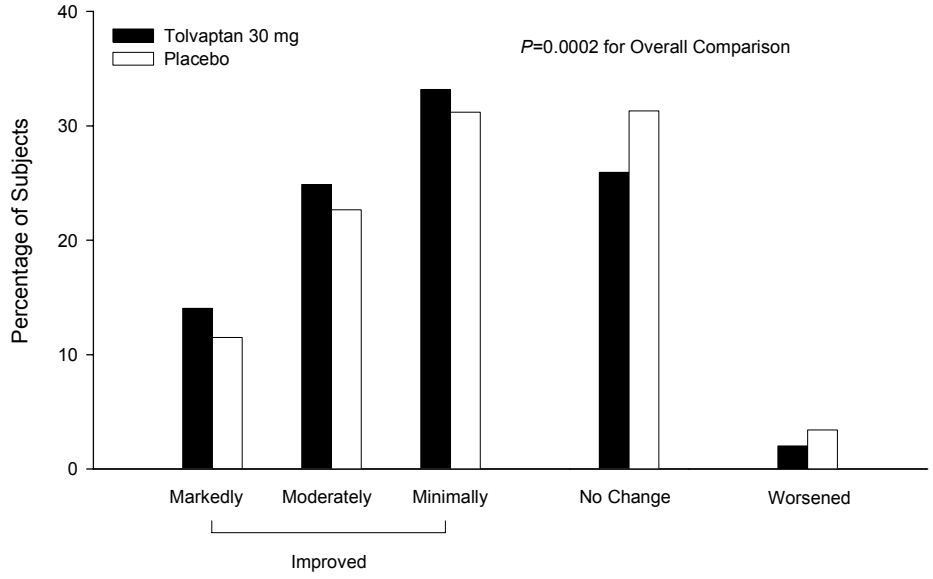
Additional secondary efficacy endpoints for Trial B demonstrated significant improvements in the tolvaptan 30 mg group over placebo. Mean (SD) body weight reduction was greater with tolvaptan 30 mg on Inpatient Day 1 (−1.8 [2.0] kg versus −1.0 [1.9] kg; $p < 0.0001$, 95% CI = −1.00 to −0.67), consistent with the Inpatient Day 7/Discharge findings (Synopsis Figure 9). Pedal edema (for subjects with pedal

edema at baseline) at Inpatient Day 7 or Discharge if earlier improved by at least 2 points for significantly more subjects receiving tolvaptan 30 mg compared with placebo (610 [73.7%] versus 570 [70.8%]; p = 0.0202, 95% CI = 0.503 to 0.553 for distribution of scores across 6 categories of improvement, worsening, or no change) (Synopsis Figure 10). More subjects receiving tolvaptan 30 mg (678 [72.1%]) versus subjects receiving placebo (597 [65.3%]) reported improvement in patient-assessed dyspnea at Inpatient Day 1 (p = 0.0002, 95% CI = 0.520 to 0.566 for distribution of scores across 7 categories of improvement, worsening, or no change) among those with dyspnea at baseline (Synopsis Figure 11).



Synopsis Figure 10 Change From Baseline in Pedal Edema Score at Inpatient Day 7 or Discharge if Earlier in Subjects Who Had Edema (1+, 2+, 3+) at Baseline- Short-term Clinical Status Trial B

Note: Worsened includes change of +1 and +2.



Synopsis Figure 11 Patient-assessed Dyspnea Status at Inpatient Day 1, for Subjects With Frequent or Continuous Physician-assessed Dyspnea at Baseline - Short-term Clinical Status Trial B

Note: Subjects were asked "Compared to how much difficulty you were having with your breathing just before trial drug was started, how is your breathing now?"
Note: Worsened includes minimally worse, moderately worse, and markedly worse.

Post hoc analyses of change from baseline and change from baseline in the percentage of responders were performed by visit for selected physician-assessed CV assessments (for subjects in Trial B with the symptom of interest at baseline, and separately for all subjects in Trial B). The results of these analyses supported those described above for the Long-term Outcome Trial. In the inpatient period in Trial B, greater improvement was observed in the tolvaptan 30 mg group compared with the placebo group throughout much of the first 7 days for dyspnea, pedal edema, and fatigue. Greater improvement for tolvaptan 30 mg was observed at Inpatient Day 3 for orthopnea and JVD and Inpatient Days 3 and 4 for rales. The results of the by-visit responder analyses were similar to those of the change from baseline analyses for each CV assessment.

Prespecified subgroups analyses of the primary and secondary endpoints in Trial B showed results consistent with those from the full Trial B population in most subgroups. In general, if the treatment group differences for an endpoint were statistically significant for the full population, then the same was true for most subgroups. Similarly, endpoints with no significant treatment group differences in the full population were not significantly different in most subgroups.

Safety Results, Short-term Clinical Status Trial A: The overall incidence of TEAEs in Trial A was higher for tolvaptan compared to placebo (49.1% versus 40.0%). The

incidences of deaths due to TEAEs (1.8% versus 1.3%), of SAEs (5.9% versus 4.8%), and of discontinuations due to TEAEs (1.0% versus 0.3%) were similar for tolvaptan and placebo, respectively. The most commonly reported potentially drug-related TEAEs occurring through Day 7 or Discharge if earlier (ie, ≥ 2% in the tolvaptan group and also ≥ 3% higher than placebo) were dry mouth (4.0% tolvaptan, 0.5% placebo) and thirst (7.6% tolvaptan, 0.4% placebo). No meaningful age- or sex-related differences in TEAEs were observed for tolvaptan. Caucasians had a notably higher incidence of thirst (8.5% Caucasians, 3.4% non-Caucasians). Non-Caucasians had a notably higher incidence of constipation (2.6% Caucasians, 8.2% non-Caucasians).

Slightly greater mean increases in serum sodium, serum osmolality, and serum chloride were observed for tolvaptan 30 mg compared with placebo, but differences between treatment groups for BUN were not observed. No notable differences between tolvaptan 30 mg and placebo in change from baseline results were observed for any hematology parameter in Trial A. Notable mean decreases in urine specific gravity were observed for tolvaptan 30 mg compared with placebo in Trial A. Slightly greater mean increases in AVP concentrations were observed for tolvaptan 30 mg compared with placebo. No differences between tolvaptan 30 mg and placebo were observed for serum aldosterone.

No differences between tolvaptan 30 mg and placebo were observed in Trial A for vital signs (supine blood pressure, supine heart rate, respiration rate, and oral temperature) or ECGs.

Safety Results, Short-term Clinical Status Trial B: The overall incidence of TEAEs in Trial B was higher for tolvaptan compared to placebo (55.9% versus 47.9%). The incidences of deaths due to TEAEs (1.2% versus 1.6%), of SAEs (4.3% versus 5.8%), and of discontinuations due to TEAEs (0.2% versus 0.1%) were similar for tolvaptan and placebo, respectively. The most commonly reported potentially drug-related TEAEs occurring through Day 7 or Discharge if earlier (ie, ≥ 2% in the tolvaptan group and also ≥ 3% higher than placebo) were dry mouth (5.3% tolvaptan, 0.7% placebo) and thirst (10.6% tolvaptan, 1.0% placebo). No meaningful age- or sex-related differences in TEAEs were observed for tolvaptan, but Caucasians had notably higher incidences of dry mouth (7.1% Caucasians, 0.0% non-Caucasians) and thirst (12.5% Caucasians, 3.9% non-Caucasians).

Slightly greater mean increases in serum sodium, serum osmolality, and serum chloride were observed for tolvaptan 30 mg compared with placebo, but differences between treatment groups for BUN were not observed. No notable differences between tolvaptan 30 mg and placebo in change from baseline results were observed for any hematology parameter in Trial B. Notable mean decreases in urine specific gravity were observed for tolvaptan 30 mg compared with placebo in Trial B. Slightly greater mean increases in AVP concentrations were observed for tolvaptan 30 mg compared with placebo. No differences between tolvaptan 30 mg and placebo were observed for serum aldosterone.

No differences between tolvaptan 30 mg and placebo were observed in Trial B for vital signs (supine blood pressure, supine heart rate, respiration rate, and oral temperature) or ECGs.

Conclusions, Short-term Clinical Status Trials A and B: In adult subjects hospitalized with worsening heart failure and signs of congestion, once daily administration of oral tolvaptan 30 mg initiated within 48 hours after hospitalization, in addition to continued conventional therapy including diuretics, demonstrated the following in comparison with placebo:

- Significant improvement in the primary endpoint of the composite of patient-assessed global clinical status and body weight at Inpatient Day 7 or Discharge if earlier.
- Significant weight reduction at Inpatient Day 1 and Inpatient Day 7 or Discharge if earlier, and consistent throughout the Inpatient Period.
- Significant improvement in patient-assessed dyspnea at Inpatient Day 1, and greater improvements in pedal edema at Inpatient Day 7 or Discharge if earlier (trend for improvement in Trial A and statistically significant improvement in Trial B).
- Significant improvements in pedal edema and other physician-assessed CV signs and symptoms (dyspnea, orthopnea, and JVD at one or more time points in Trial A, and dyspnea, orthopnea, JVD, rales, and fatigue at multiple time points in Trial B) in the Inpatient Period that were supportive of the findings at the prespecified time points.
- A well-defined and acceptable safety profile.

Otsuka Pharmaceutical Development & Commercialization, Inc.

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