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Subject: Briefing Document for Arthritis Advisory Committee
Etanercept (Enbrel®) and Congestive Heart Failure

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Background

Etanercept, recombinant human TNF receptor (rhu TNFR:Fc), is a fusion protein dimer consisting of 2 identical molecules of the extracellular portion of the (p75) TNF receptor fused to the Fc portion of IgG1. The product binds to and inactivates the pro-inflammatory cytokine TNF-α; neutralization of TNF-α is the anticipated mode of action of the agent.

Several lines of experimental evidence support a potential role of TNF-α in the pathogenesis of congestive heart failure (CHF). Elevated circulating levels of TNF-α have been associated with advanced CHF, and TNF-α has been immunolocalized in cardiac myocytes of explanted hearts from patients with dilated cardiomyopathy and ischemic heart disease. TNF-α is also negatively inotropic *in vivo*, and can produce cardiomyopathy and pulmonary edema in animal models. It has been hypothesized that expression of cytokines such as TNF-α constitutes an adaptive response to myocardial injury, and that TNF-α overexpression may lead to deleterious cardiac remodeling with progressive left ventricular (LV) dysfunction.

Two phase 2/3 studies were conducted concurrently: A North American study: Randomized Etanercept North American Strategy to Study Antagonism of Cytokines ("RENAISSANCE"), protocol 1600.21, conducted by Immunex Corporation, and a similar study conducted by Wyeth in Europe, Australia, and New Zealand: Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of the Efficacy and Safety of Soluble Recombinant Human Tumor Necrosis Factor Receptor Fc Fusion Protein in Patients with Congestive Heart Failure (class 2-4), "RECOVER," study 0881A2-200-EU. Combined analyses of all-cause mortality and CHF hospitalizations were provided in "RENEWAL."

The two studies share similarities in their objectives, designs and patient populations, and are described together in this briefing document. Where appropriate, similarities and differences between the studies are discussed.

Protocol 1600.21 – "RENAISSANCE"

Title:	Multicenter, Double-Blind, Randomized, Placebo-controlled, Phase 2/3 Study of the Efficacy and Safety of Recombinant Human Tumor Necrosis Factor Receptor (p75) Fc Fusion Protein (TNFR:Fc) (etanercept) in Patients with Chronic Heart Failure (Class II-IV). Randomized Etanercept North American Strategy to Study Antagonism of Cytokines "RENAISSANCE"
Study Period:	March 18, 1999 – June 21, 2001
Funding:	Immunex Corporation
Centers:	105 sites in the US and Canada

Protocol 0881A2-200-EU/AU/NZ – "RECOVER"

Title:	A Phase 2/3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial of the Efficacy and Safety of Soluble Recombinant Human Tumor Necrosis Factor Receptor Fc Fusion Protein (etanercept/TNR-001) in Patients with Congestive Heart Failure (class II-IV). Research into Etanercept: Cytokine Antagonism in Ventricular Dysfunction Trial "RECOVER"
Study Period:	July, 1999 – June, 2001
Funding:	Wyeth-Ayerst Research
Centers:	194 sites in the European Union (EU), Australia, and New Zealand

Objectives

Each study had two primary objectives. The first primary objective of each study was to compare the effect of Etanercept and placebo as measured by a clinical composite score at 24 weeks. The clinical composite score was to classify subjects as improved, unchanged, or worsened, based on vital status, hospitalizations for worsening CHF, New York Heart Association (NYHA) Functional Class (FC), and patient global assessment of heart failure. For each study, the second primary objective was a combined analysis of all-cause mortality and hospitalizations for CHF across both studies.

Study Design

RENAISSANCE was a double-blind, randomized, placebo-controlled, multicenter trial. Subjects were randomized to three (3) treatment groups:

a) etanercept 25 mg SC BIW and placebo QW
b) etanercept 25 mg SC TIW
c) placebo SC TIW

An overall sample size of 900 was planned, with 300 subjects for each treatment group (1:1:1 randomization). There was a 24 week study period, during which treatment was maintained, followed by a blinded maintenance period with safety evaluations every 12 weeks. Subjects were to continue study agent until all subjects across both studies had completed 24 weeks of follow-up. Accrual of 900 subjects over 12 months at ≈100 sites (average ≈ 9 subjects/ site) was planned.

Treatment assignment followed a 2 to 4-week screening period. Randomization was blocked within study sites, and stratified based on baseline beta-blocker use and NYHA functional classification. A centralized interactive randomization system was used to randomize subjects once consent was signed, and randomization was irreversible.

RECOVER followed the same basic study design, with the exception of the dosing regimens:

a) etanercept 25 mg SC QW and placebo QW
b) etanercept 25 mg SC BIW
c) placebo SC BIW

An n of 300 subjects was planned for each treatment group.

Data Safety Monitoring Board (DSMB)

A DSMB monitored major clinical events (deaths and hospitalizations) and safety during the studies. The DSMB could recommend early study termination for persuasive evidence of harm, evidence of futility, or evidence of very considerable benefit.

Patient Population

Major Inclusion Criteria

- Adult subjects with CHF on ischemic or non-ischemic basis, NYHA FC II-IV, LV ejection fraction (EF) ≤ 30%

- Medications required: diuretic and angiotensin converting enzyme (ACE) inhibitor, unless intolerance or contraindication to ACE inhibitor
- Medications allowed: digoxin, angiotensin II antagonists (if intolerant to ACE inhibitors), beta-blockers, nitrates, hydralazine, amiodarone, and warfarin
- Ambulatory, able to traverse < 375 meters in a 6-minute walk test, or < 425 meters if hospitalized for CHF within 6 previous months

Major Exclusion Criteria

- inability to exercise; congenital heart disease; uncorrected valvular disease; hypertrophic or peripartum cardiomyopathy; constrictive pericarditis; primary pulmonary HTN or severe primary lung disease; sick sinus syndrome, advanced heart block (in the absence of a functioning pacemaker); systolic blood pressure (BPs) > 160 or < 80 mm Hg; diastolic blood pressure (BPd) $\geq$ 100 mm Hg; serum creatinine $\geq$ 3.0 mg/dL
- recent acute MI, coronary angioplasty; revascularization or valve surgery; hospitalization for unstable angina; ventricular tachycardia (VT), fibrillation (VF), or sudden cardiac death without implantable cardiac defibrillator; implantable cardiac defibrillator discharge; cerebrovascular accident; transient ischemic attack; active/severe infection

Randomization

For both studies, randomization was blocked by study site, NYHA FC, and use of beta-blockers at screening. Randomization was considered an irreversible event.

Primary Endpoint

Each study had two co-primary efficacy endpoints: 1) Clinical Composite Score at Week 24; and 2) all-cause mortality and CHF hospitalizations across both studies together. The Clinical Composite Score could take values of "improved," "unchanged," or "worse," based on vital status, hospitalizations for CHF, change in NYHA FC, and subject-self assessment.

The Clinical Composite Score was assigned a value of "worse" if the subject:

- died
- was hospitalized for CHF (hospitalized $\equiv$ admitted to a hospital for >24 hours and received IV diuretics, vasodilators, or positive inotropic agents for CHF)
- worsened in NYHA FC
- was categorized as having a "Global Assessment" of moderately or markedly worse

The Clinical Composite Score was assigned a value of "improved" if:

- the Clinical Composite Score was not worse AND
- NYHA FC is improved OR
- Global Assessment (judged by subject) is moderately or markedly improved

The Clinical Composite Score was assigned a value of "unchanged" if neither better nor worse.

The Clinical Composite Score was to take a value of worse if NYHA FC and Global Assessment were discordant.

A subject was considered to have had a CHF hospitalization if he/she was hospitalized for, or with, worsening CHF (involving an overnight stay defined as a change in dates) and received IV diuretics, vasodilators, or positive inotropic drugs for the treatment of CHF. A blinded Endpoint Committee was to make this determination.

For the co-primary endpoint across the two studies, a treatment failure was defined as death or at least one hospitalization for CHF.

Secondary Endpoints

Numerous secondary endpoints included: number of hospitalizations for CHF and emergency department visits for worsening CHF; changes in NYHA FC, patient global assessment, and Minnesota Living with Heart Failure (MLWHF) Scale (baseline to 24 weeks).

Statistical Analysis Plan

The Clinical Composite Score was analyzed using a proportional odds logistic regression model controlling for baseline NYHA FC and beta-blocker use. To control type I error across the two components of the 1° endpoint, an alpha of 0.04 was to be allocated to the Clinical Composite Score in both studies. The combined all-cause mortality and morbidity endpoint was allocated an alpha of 0.01, such that the overall 2-sided alpha for each study was 0.05. A true intention-to-treat approach was used, including all randomized subjects.

"RENEWAL" was the combined analysis across both studies. All-cause mortality and morbidity (CHF hospitalizations) were summarized using Kaplan-Meier curves in a time to first event analysis. Treatment comparisons were planned by log-rank test, stratified by study, baseline beta-blocker use, and NYHA FC. Subjects lost to follow-up were censored at the time of loss. The single primary outcome was the comparison between the combined placebo group and the combined BIW and TIW Etanercept groups. A Cox proportional hazards model was used to assess the importance of major covariates on the results.

Interim Analyses

An independent DSMB monitored unblinded safety and major clinical events in both trials. After a planned interim review of unblinded data from both RENAISSANCE and RECOVER, the DSMB recommended that both studies be halted because of futility.

Study Results

Patient Disposition

RENAISSANCE: A total of 925 subjects were randomized in the study: 309 subjects were randomized to placebo, and 308 subjects were randomized to each of the Etanercept groups. When the study was closed at the recommendation of the DSMB, 76% of subjects were still participating in the blinded study, and 82% had completed the Week 24 evaluations. The rates of discontinuation were similar in the 3 treatment groups (~23 to 26%). More than half of the discontinuations were for death (~14%), 5% were for patient refusal, and $\leq$ 2% were for other reasons.

RECOVER: A total of 1123 subjects were randomized: 373 were assigned to placebo, 375 were assigned to each of the Etanercept groups (25 mg QW; 25 mg BIW). Across all three treatment groups, approximately 85% of subjects were withdrawn from the study because of the sponsor's decision to discontinue the investigation. Death accounted for 7% of

discontinuations, followed in decreasing frequency by subject request (2%), adverse event (2%), and miscellaneous reasons. There were no imbalances in discontinuations between groups.

Protocol Deviations

Protocol violations were relatively sporadic in both studies, and unlikely to importantly affect the study results or interpretation.

Study Population: Baseline Characteristics

Table 1 and Table 2 provide summaries of baseline demographic characteristics and cardiovascular disease status by treatment group for RENAISSANCE and RECOVER, respectively. Table 3 and Table 4 summarize CHF etiologies and related illnesses for the two studies.

RENAISSANCE: Seventy-eight percent (78%) of subjects were male, and 84% were Caucasian. Mean age was 62 years. The subjects were predominantly NYHA FC III (73%), with two-thirds of these subjects categorized as FC IIIA; one-third classed as FC IIIB. Twenty-four percent (24%) and 5% of subjects categorized as FC II and FC IV, respectively. Median BPs and BPd were 108 and 66 mm Hg, respectively. Median heart rate was 72 beats per minute. Median EF was 23%. The mean duration of CHF was 5.6 years, with 36% of subjects having a history of a hospitalization within the previous 6 months. Beta-blocker use was reported in 61% of subjects. Balance between treatment groups was adequate, with the exceptions of systolic/diastolic BP (lower in the Etanercept groups) and 6-minute walk distance (less in the Etanercept groups).

Reviewer's Comment: Blood pressure and 6-minute walk distance have prognostic implications in CHF, and these imbalances impart a less favorable prognosis in the Etanercept groups.

Sixty-two percent (62%) of subjects were reported to have CHF on an ischemic basis, with a previous myocardial infarction reported in 40% of subjects (Table 3). An idiopathic basis for CHF was reported in 26% of subjects. The next leading etiology was HTN (4%). Of note, 22% of placebo subjects had an implanted cardioverter/ defibrillator, compared to 16% of Etanercept-treated subjects. The frequencies of related illnesses were fairly well-balanced between treatment groups, with the exceptions of HTN, chronic lung disease, and atrial fibrillation/flutter -- all of which were reported more frequently in the Etanercept groups (Table 3).

Reviewer's Comment: The greater percentage of placebo subjects with implanted defibrillators suggests more of a propensity towards arrhythmias in this group. Paradoxically, however, it could be argued that the placebo subjects are better protected against sudden death, because of the presence of the defibrillators.

RECOVER: The vast majority of subjects were white (99%) and male 78% (Table 2). Mean age was 64.6 years. The breakdown with respect to functional classification was very similar to that of the North American study, with excellent balance between treatment arms. Median EF was 24%. Mean systolic and diastolic blood pressures were 120 mm Hg and 75 mm Hg, respectively. Mean heart rate was 72 beats per min. Median duration of CHF was 4.6 years. There was good balance of these parameters across the treatment groups.

The etiologies of CHF in RECOVER were very similar to those of the North American study: 62% of subjects were reported to have CHF on an ischemic basis, 26% were idiopathic, and 5%

were related to HTN. Related illnesses were reasonably well-balanced between treatment groups.

Compared with subjects in the North American study, subjects in RECOVER were, on average, slightly older (64.6 versus 62.3 years) and lighter (79 versus 85 kg), with a higher BP (120/75 versus 108/66 mm Hg), and a shorter duration of CHF (4.6 versus 5.6 years). Eighty-four percent (84%) of North American subjects were Caucasian, compared to 99% in RECOVER. The breakdown of NYHA FC and mean EF were similar in the two studies, and the underlying etiologies of CHF were similar, as above.

Concomitant illnesses were generally similar in frequency, with the exception of HTN (overall reported frequencies of 45% in RECOVER versus 55% in RENAISSANCE), VT/VF (23% in RENAISSANCE versus 11% in RECOVER), and hyperlipidema (61% in RENAISSANCE versus 44% in RECOVER). Differences in the frequencies of VT/VF and hyperlipidema may relate, in part, to differing diagnostic criteria.

Table 1: RENAISSANCE – Demographics and Baseline Status

	Placebo	Etanercept		Total
		BIW	TIW	
	(n = 309)	(n = 308)	(n = 308)	(n = 925)
age (mean)	62.6	61.8	62.4	62.3
range	21 - 85	20 - 85	28 - 83	20 - 85
Race				
Caucasian	254 (82.2)	262 (85.1)	257 (83.4)	773 (83.6)
Black	40 (12.9)	29 (9.4)	37 (12)	106 (11.5)
Hispanic	8 (2.6)	10 (3.2)	10 (3.2)	28 (3)
Asian	3 (1)	2 (0.6)	1 (0.3)	6 (0.6)
Native American	1 (0.3)	1 (0.3)	1 (0.3)	3 (0.3)
Other	3 (1)	4 (1.3)	2 (0.6)	9 (1)
Male	238 (77)	237 (77)	249 (81)	724 (78)
Weight (kg)	85.3	85.7	83.2	84.5
range	45 - 157	41 - 159	45 - 230	41 - 230
BPs	110	108	105	108
BPd	68	66	64	66
HR	72	73.5	72	72
Duration of CHF (years)	5.5	5.7	5.5	5.6
Hospitalization in prior 6 months	114 (37)	111 (36)	108 (35)	333 (36)
NYHA Class				
II	72 (23)	72 (23)	74 (24)	218 (24)
IIIA	144 (47)	144 (47)	144 (47)	432 (47)
IIIB	80 (26)	77 (25)	75 (24)	232 (25)
IV	13 (4)	15 (5)	15 (5)	43 (5)
Beta blocker use	195 (63)	183 (59)	183 (59)	561 (61)
6-minute walk (m)	294.5	292.9	288	292.6
LVEF (%)	23	23	23	23

Table 2: RECOVER – Demographics and Baseline Status

	Placebo	Etanercept		Total
		QW	BIW	
	(n = 373)	(n = 375)	(n = 375)	(n = 1123)
age (mean)	64.8	64.8	64.1	64.6
range	21 - 85	31 - 84	24 - 84	21 - 85
Race				
Caucasian	371 (99.5)	372 (99.2)	373 (99.5)	1116 (99.4)
Other	2 (0.5)	3 (0.8)	2 (0.5)	7 (0.6)
Male	285 (76)	290 (77)	304 (81)	879 (78)
Weight (kg)	76.0	80.0	79.8	79.0
range	41 - 157	45 - 151	35 - 139	35 - 157
BPs	120	120	120	120
BPd	75	76	75	75
HR	72	72	72	72
Duration of CHF (years)	4.1	4.7	4.9	4.6
NYHA Class				
II	103 (28)	102 (27)	102 (27)	307 (27)
IIIA	162 (43)	169 (45)	170 (45)	501 (45)
IIIB	95 (25)	92 (25)	90 (24)	277 (25)
IV	13 (3)	12 (3)	13 (3)	38 (3)
Beta blocker use	239 (64)	233 (62)	232 (62)	704 (63)
6-minute walk (m)	295.1	293.7	302.1	297.0
LVEF (%)	24.3	24.2	24.1	24.2

Table 3: RENAISSANCE – CHF Etiology, Prior Procedures, Related Illnesses

	Placebo	Etanercept		Total
		BIW	TIW	
	(n = 309)	(n = 308)	(n = 308)	(n = 925)
Ischemic etiology	186 (60)	195 (63)	191 (62)	572 (62)
prior MI	118 (38)	123 (40)	127 (41)	368 (40)
CAD	68 (22)	72 (23)	64 (21)	204 (22)
Non-ischemic etiology	123 (40)	113 (37)	117 (38)	353 (38)
mitral valvular disease	3 (1)	2 (1)	2 (1)	7 (1)
aortic valvular disease	3 (1)	3 (1)	3 (1)	9 (1)
alcoholic cardiomyopathy	6 (2)	6 (2)	3 (1)	15 (2)
drug-related	0 (0)	2 (1)	1 (0)	3 (0)
HTN-induced	8 (3)	11 (4)	16 (5)	35 (4)
familial	0 (0)	4 (1)	3 (1)	7 (1)
viral	10 (3)	6 (2)	8 (3)	24 (3)
idiopathic	90 (29)	77 (25)	73 (24)	240 (26)
other	3 (1)	2 (1)	8 (3)	13 (1)
Prior surgeries and procedures				
CABG	103 (33)	129 (42)	126 (41)	358 (39)
PCI	90 (29)	86 (28)	87 (28)	263 (28)
pacemaker	71 (23)	75 (24)	57 (19)	203 (22)
implanted cardioverter	68 (22)	44 (14)	56 (18)	168 (18)
Related illnesses				
HTN	152 (49)	184 (60)	172 (56)	508 (55)
diabetes	105 (34)	125 (41)	114 (37)	344 (37)
atrial fibrillation/flutter	91 (29)	112 (36)	110 (36)	313 (34)
SVT	17 (6)	15 (5)	20 (6)	52 (6)
VF	79 (26)	60 (19)	77 (25)	216 (23)
hyperlipidemia	178 (58)	190 (62)	192 (62)	560 (61)
PVD	30 (10)	35 (11)	42 (14)	107 (12)
thromboembolic disease	17 (6)	19 (6)	25 (8)	61 (7)
stroke	30 (10)	35 (11)	36 (12)	101 (11)
cancer	17 (6)	22 (7)	18 (6)	57 (6)
chronic lung disease	41 (13)	39 (13)	59 (19)	139 (15)

Table 4: RECOVER – CHF Etiology, Related Illnesses

	Placebo	Etanercept		Total
		QW	BIW	
	(n = 373)	(n = 375)	(n = 375)	(n = 1123)
Ischemic etiology	240 (64)	231 (62)	230 (61)	701 (62)
Non-ischemic etiology	130 (35)	143 (38)	144 (38)	417 (37)
idiopathic	83 (22)	96 (26)	98 (26)	277 (25)
HTN-induced	19 (5)	23 (6)	19 (5)	61 (5)
other cardiomyopathy	13 (3)	9 (2)	11 (3)	33 (3)
alcoholic cardiomyopathy	5 (1)	3 (1)	5 (1)	13 (1)
mitral valvular disease	5 (1)	5 (1)	5 (1)	15 (1)
aortic valvular disease	3 (1)	3 (1)	6 (2)	12 (1)
arrhythmia (SVT/Afib/flutter)	1 (0)	4 (1)	0 (0)	5 (0)
arrhythmia: other	1 (0)	0 (0)	0 (0)	1 (0)
Related illnesses				
HTN	173 (46)	169 (45)	160 (43)	502 (45)
atrial fibrillation/flutter	116 (31)	132 (35)	102 (27)	350 (31)
arrhythmia, other	26 (7)	36 (10)	27 (7)	89 (8)
VT/VF	43 (12)	34 (9)	44 (12)	121 (11)
diabetes, diet controlled	50 (13)	52 (14)	55 (15)	157 (14)
diabetes, other treatment	85 (23)	76 (20)	79 (21)	240 (21)
stroke	27 (7)	35 (9)	29 (8)	91 (8)
transient ischemic attack	18 (5)	27 (7)	16 (4)	61 (5)
hyperlipidemia	177 (47)	165 (44)	157 (42)	499 (44)
peripheral vascular disease	52 (14)	34 (9)	42 (11)	128 (11)

Concomitant Medications

RENAISSANCE: Concomitant medication use was similar across treatment groups (Table 5), with the exception of antiarrhythmics (21% in the Etanercept groups versus 15% in the placebo group). Virtually all subjects were taking an ACE inhibitor or angiotensin II antagonist, although use of angiotensin II antagonists was slightly greater in the Etanercept groups, and use of ACE inhibitors was correspondingly less. Beta-blocker use was recorded in 61% of subjects overall. Digoxin use was recorded in 82% of subjects, with nitrate use in 44%. Spironolactone use was reported in approximately one-third of subjects overall, with calcium channel blocker use and vasodilator use reported in 7% and 6% of subjects, respectively.

RECOVER: There was good balance across treatment groups with respect to recorded concomitant medication use (Table 6). Virtually all subjects were taking a diuretic and an ACE inhibitor or angiotensin II antagonist; 91% of subjects were taking a potassium-sparing diuretic; 63% of subjects were taking beta-blockers; and 54% of subjects were taking digitalis compounds.

Compared to subjects in the North American study, subjects in RECOVER were more likely to be using a potassium-sparing diuretic, and slightly more likely to be taking an ACE inhibitor in favor of an angiotensin II antagonist. In addition, subjects in RECOVER were more likely to be taking nitrates (52% versus 44% in RENAISSANCE), and less likely to be taking digitalis compounds (54% versus 82%) and lipid lowering agents (37% versus 55%). Use of antiarrhythmics, beta-blockers, and antithrombotic agents was similar in the two studies overall.

Table 5: RENAISSANCE – Concomitant Cardiovascular Medications

	Placebo	Etanercept		Total
		BIW	TIW	
	(n = 309)	(n = 308)	(n = 308)	(n = 925)
ACE inhibitors	253 (82)	236 (77)	243 (79)	732 (79)
angiotensin II antagonists	49 (16)	71 (23)	60 (19)	180 (19)
alpha blockers	2 (1)	2 (1)	2 (1)	6 (1)
antiarrhythmics	47 (15)	68 (22)	64 (21)	179 (19)
antithrombotic agents	264 (85)	278 (90)	271 (88)	813 (88)
platelet inhibitors	171 (55)	160 (52)	167 (54)	498 (54)
beta-blockers	195 (63)	183 (59)	183 (59)	561 (61)
diuretics	305 (99)	303 (98)	307 (100)	915 (99)
spironolactone	104 (34)	110 (36)	95 (31)	309 (33)
inotropes (digoxin)	249 (81)	251 (81)	255 (83)	755 (82)
lipid lowering agents	164 (53)	166 (54)	175 (57)	505 (55)
nitrates	127 (41)	143 (46)	141 (46)	411 (44)
other vasodilators	23 (7)	19 (6)	16 (5)	58 (6)
calcium channel blockers	18 (6)	27 (9)	22 (7)	67 (7)

Table 6: RECOVER – Concomitant Cardiovascular Medications

	Placebo	Etanercept		Total
		QW	BIW	
	(n = 373)	(n = 375)	(n = 375)	(n = 1123)
ACE inhibitors	316 (85)	312 (83)	326 (87)	954 (85)
angiotensin II antagonists	48 (13)	52 (14)	44 (12)	144 (13)
alpha blockers	5 (1)	3 (1)	0 (0)	8 (1)
antiarrhythmics	71 (19)	71 (19)	75 (20)	217 (19)
antithrombotic agents	323 (87)	325 (87)	324 (86)	972 (87)
platelet inhibitors	165 (44)	174 (46)	186 (50)	525 (47)
beta-blockers	239 (64)	233 (62)	232 (62)	704 (63)
diuretics	369 (99)	373 (99)	373 (99)	1115 (99)
potassium sparing	340 (91)	339 (90)	348 (93)	1027 (91)
loop	139 (37)	166 (44)	164 (44)	469 (42)
digitalis compounds	198 (53)	209 (56)	197 (53)	604 (54)
lipid lowering agents	138 (37)	131 (35)	144 (38)	413 (37)
nitrates	201 (54)	199 (53)	186 (50)	586 (52)
other vasodilators	23 (6)	21 (6)	18 (5)	62 (6)
calcium channel blockers	32 (9)	36 (10)	36 (10)	104 (9)

Overall, the subject populations in the two studies were generally similar. There were no substantial differences between studies in the etiology of CHF, baseline NYHA functional classification, or LVEF. Key differences between the subject populations are summarized in Table 7. Of note, despite a higher mean weight and a greater frequency of HTN in the North American subjects, the mean BP was actually substantially *lower* in RENAISSANCE. This suggests more aggressive use of ACE inhibitors, beta-blockers, and/or diuretics in the North American subjects. In addition, the North American study is notable for a much lower rate of potassium-sparing diuretic use, and higher rates of use of digitalis and lipid-lowering agents (statins).

Table 7: Disparities Between Subject Populations of RENAISSANCE and RECOVER

	RENAISSANCE	RECOVER
age (years)	62.3	64.6
Caucasian (%)	83.6	99.4
weight (kg)	84.5	79.0
BPs (mm Hg)	108	120
BPd (mm Hg)	66	75
VT/VF (%)	23	11
HTN (%)	55	45
hyperlipidemia (%)	61	44
use of K+ sparing diuretic (%)	33	91
use of digitalis compounds (%)	82	54
use of lipid lowering agents (%)	55	37
use of nitrates (%)	44	52

Study Agent Dosing

RENAISSANCE: Compliance was similar between treatment groups. The 70% of subjects who prematurely discontinued study agent did so because of the sponsor's decision to close the study. There were no important differences in the numbers of subjects who discontinued study agent prematurely because of adverse events, death, or worsening CHF.

RECOVER: All subjects prematurely discontinued the study agent, largely because of the sponsor's decision to close the investigation. Study closure accounted for discontinuation in 85% of subjects. Aside from study closure and death, other reasons for discontinuation were uncommon and similar in the three treatment groups. Adverse events led to discontinuation in 5 subjects (1%) in the placebo group, and 18 subjects (2%) in the combined Etanercept groups.

Efficacy Results

Clinical Composite Score

RENAISSANCE: The clinical composite score data are summarized in Table 8. There were no statistically significant differences between groups. In general, relative to control subjects, a larger fraction of Etanercept-treated subjects experienced worsening of clinical status.

Table 8: RENAISSANCE – Clinical Composite Score

	Placebo	Etanercept		
		BIW	TIW	BIW + TIW
	(n = 309)	(n = 308)	(n = 308)	(n = 616)
Improved	137 (44%)	121 (39%)	128 (42%)	249 (40%)
Unchanged	110 (36%)	98 (32%)	97 (31%)	195 (32%)
Worsened	62 (20%)	89 (29%)	83 (27%)	172 (28%)

RECOVER: Fifty-six percent (56%) underwent the protocol-specified evaluation of clinical status at Week 24, or reached a protocol-defined endpoint (death or CHF hospitalization) while on study. Ninety-five percent (95%) of subjects achieved at least 16 weeks of study, and 78% of subjects achieved at least 20 weeks. Clinical composite data for all subjects are summarized in Table 9.

Table 9 : RECOVER – Clinical Composite Score

	Placebo	Etanercept		
		QW	BIW	QW + BIW
	(n = 373)	(n = 375)	(n = 375)	(n = 750)
Improved	118 (32%)	122 (33%)	141 (38%)	263 (35%)
Unchanged	185 (50%)	175 (47%)	161 (43%)	336 (45%)
Worsened	70 (19%)	78 (21%)	73 (19%)	151 (20%)

There were no significant differences in outcome among treatment groups. Results were similar across NYHA functional classes. Though there was a statistically significant difference in favor of Etanercept in NYHA FC IV patients, the number of subjects with FC IV CHF was very limited

(3% of the total), and the relevance of this observation is questionable (data not shown). There was a trend in favor of Etanercept in patients who did not report beta blocker use at baseline; however, the trend was observed only in the BIW dosing group (data not shown).

All-Cause Mortality and CHF Hospitalizations (Combined Studies)

Results of all-cause mortality and CHF hospitalizations for "RENEWAL," the combined analysis over "RENAISSANCE" and "RECOVER" and the co-primary endpoint for both studies, are shown in Table 10. The data must be interpreted cautiously, however, because of the disparity between the two investigations with respect to time-on-study. There were no significant differences between groups, although there was a trend towards higher mortality in the Etanercept BIW + TIW group.

Table 10: Combined Analysis ("RENEWAL") All-cause Mortality and CHF Hospitalizations

	Placebo	Etanercept		RR (95% CI)	
		BIW	BIW + TIW		
	n = 682	n = 683	n = 991	placebo vs. BIW	placebo vs. BIW + TIW
All-cause mortality	77 (11.3%)	82 (12.0%)	143 (14.4%)	1.07 (0.78, 1.46)	1.13 (0.86, 1.50)
All-cause mortality/CHF	166 (24.3%)	172 (25.2%)	288 (29.1%)	1.08 (0.87, 1.33)	1.10 (0.91, 1.33)
CHF hospitalizations	89 (13.0%)	90 (13.2%)	145 (14.6%)		

Of note, the trend towards higher all-cause mortality/CHF in the Etanercept BIW + TIW group is driven almost entirely by the difference in all-cause morality. For CHF hospitalizations alone, shown at the bottom of Table 10, the rates are fairly similar.

The interpretation of this trend is also confounded by imbalances in a few prognostically important variables, specifically BP, 6-minute walk, and baseline use of antiarrhythmics, all of which favor placebo.

Figure 1 shows the Kaplan-Meier survival curves for "RENEWAL." The pre-specified endpoint compares the placebo group to the combined BIW and TIW Etanercept groups. The log-rank p-value for this analysis is 0.35. The survival curves are superimposable thorough week 48, with a clear divergence developing thereafter, favoring survival in the placebo group. At week 48, however, roughly only 37% of the original subjects in each group remain at risk.

The Kaplan-Meier curves for all-cause mortality and CHF hospitalizations are shown in Figure 2. again comparing placebo to combined BIW and TIW Etanercept. The log-rank p-value is 0.15.

Figure 1: All-cause Mortality – "RENEWAL" ("RENAISSANCE" + "RECOVER")

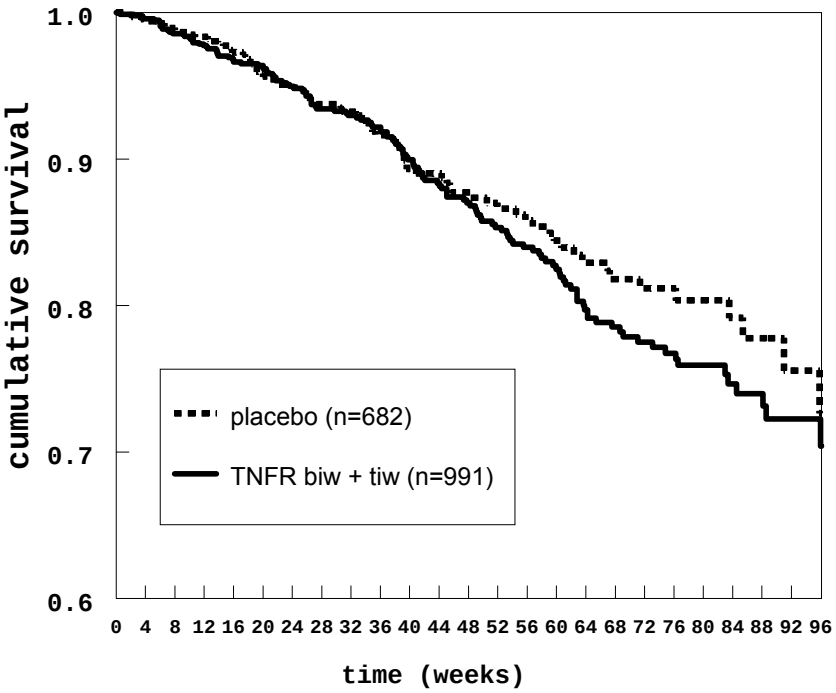
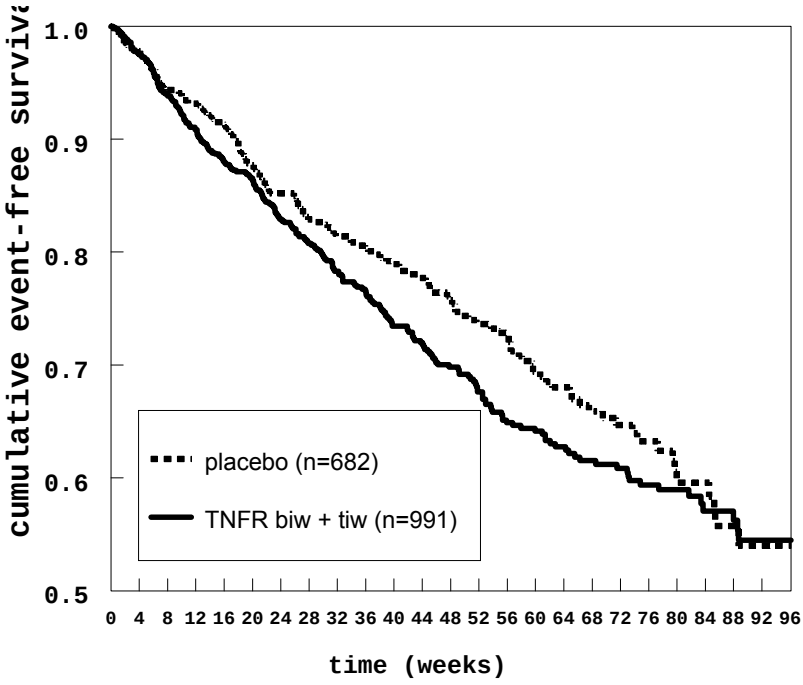


Figure 2: All-cause Mortality and CHF Hospitalizations ("RENEWAL")



NYHA Functional Classification

RENAISSANCE: For the categorical change from baseline to Week 24, there was no significant difference across treatment groups with respect to improvement. There was, however, a significant difference in the proportions of subjects with worsened NYHA FC at Week 24. Six percent (6%) of placebo-treated subjects experienced worsening of their NYHA FC, compared to 11% of subjects in each of the Etanercept-treated groups.

RECOVER: There were no significant differences among treatment groups with respect to either the final distributions of NYHA FC, or the changes in NYHA FC.

Global Assessment of Heart Failure

There were no significant differences across treatment groups with respect to patient or physician global assessments of heart failure at Week 24.

MLWHF Quality of Life Questionnaire

There were no significant differences across treatment groups in change from baseline for the MLWHF questionnaire scores.

Safety

Mortality and CHF Hospitalizations

RENAISSANCE: The mean duration of exposure to study agent was 10.8 months. Table 11 (top) summarizes results for all-cause mortality, all-cause mortality or CHF hospitalization, and CHF hospitalization. Though morality rates for the three groups are statistically indistinguishable, there is a trend towards greater mortality in the Etanercept groups, as well as a trend suggesting a dose-response. The rates of CHF hospitalizations are virtually the same in each group, such that the trend in all-cause mortality/CHF hospitalizations is driven entirely by differences in mortality.

RECOVER: RECOVER was initiated after RENAISSANCE and discontinued at the same time. As a result, the mean duration of exposure in RECOVER was approximately 60% of that of RENAISSANCE - - 6.4 months. Table 11 (bottom) shows all-cause mortality and CHF hospitalizations for RECOVER. Mortality and CHF hospitalizations tended to be less frequent in RECOVER than in RENAISSANCE. Much but not all of this difference can be accounted for by the difference in time on-study.

Table 11: All-Cause Mortality and CHF Hospitalization

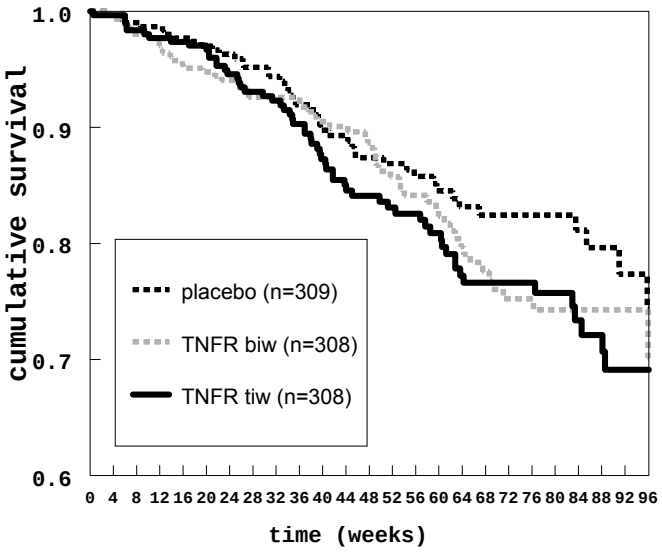
		Placebo	Etanercept	
			BIW	TIW
		n = 309	n = 308	n = 308
"RENAISSANCE"	All-cause mortality	44 (14.2%)	55 (17.9%)	61 (19.8%)
	All-cause mortality/CHF	100 (32.4%)	112 (36.4%)	116 (37.7%)
	CHF	56 (18.1%)	57 (18.5%)	55 (17.9%)

		Placebo	Etanercept	
			QW	BIW
		n = 373	n = 375	n = 375
"RECOVER"	All-cause mortality	33 (8.8%)	22 (5.9%)	27 (7.2%)
	All-cause mortality/CHF	65 (17.4%)	68 (18.1%)	60 (16.0%)
	CHF	32 (8.6%)	46 (12.3%)	33 (8.8%)

Figure 3 shows the Kaplan-Meier curves for all-cause mortality for RENAISSANCE (top) and RECOVER (bottom). In RENAISSANCE, there is a trend toward lower risk with placebo (log-rank p =0.236). In RECOVER, the trend is towards minimally lower risk with Etanercept: at Week 27, a point in time at which 40% of the subjects are still at risk, survival rates are 93.0%, 95.0%, and 94.5% for the placebo, Etanercept QW, and Etanercept BIW groups, respectively.

Figure 3: All-Cause Mortality

"RENAISSANCE"



"RECOVER"

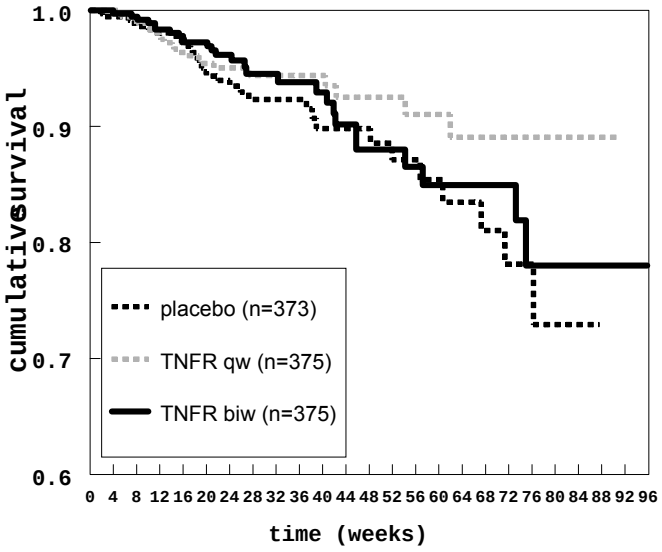
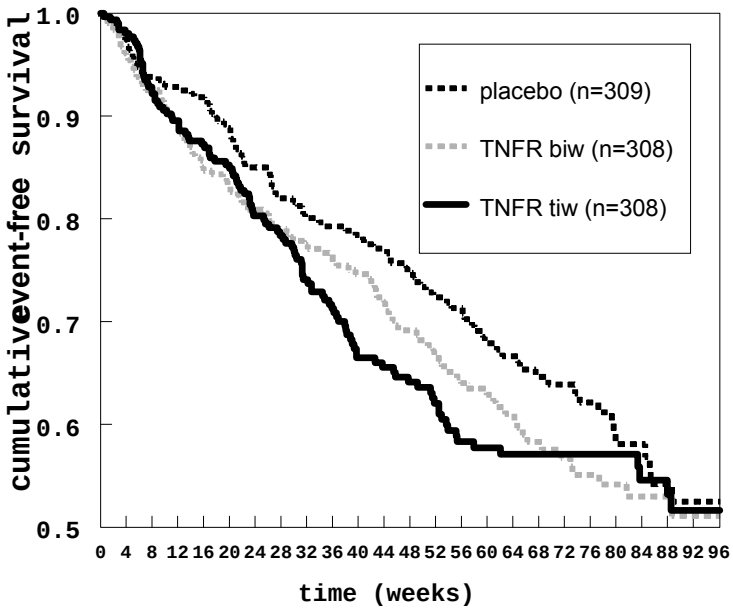


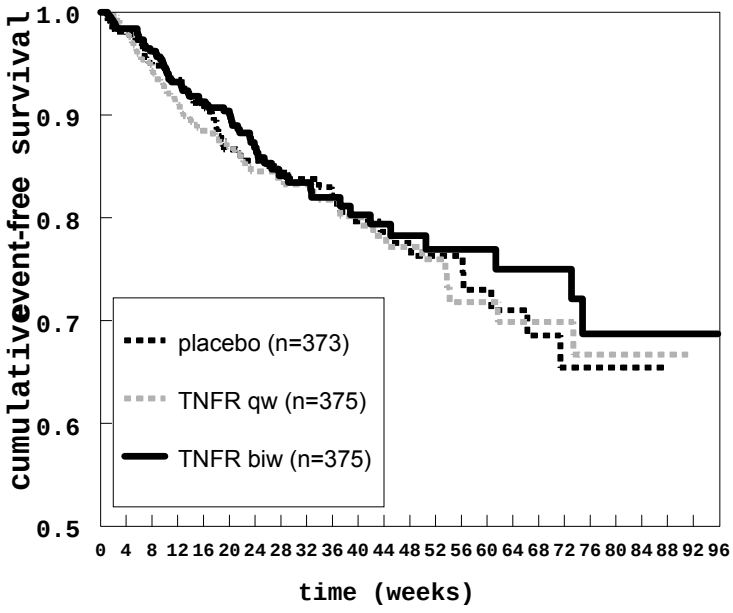
Figure 4 shows the Kaplan-Meier curves for all-cause mortality and CHF hospitalizations for RENAISSANCE (top) and RECOVER (bottom). For RENAISSANCE, there is some separation between the placebo group and the two Etanercept groups, favoring the placebo group. After Week 30, the Etanercept groups diverge, with less favorable outcomes in the TIW versus the BIW group. In RECOVER, there is no appreciable sustained separation of the curves.

Figure 4: All-Cause Mortality and CHF Hospitalizations

"RENAISSANCE"



"RECOVER"



Exploratory Analyses on Mortality and CHF Hospitalizations

Given the trend in favor of excess mortality for Etanercept-treated subjects in RENAISSANCE and the absence of a similar trend in RECOVER, CBER focused on disparities between the patient populations of the two studies that might contribute to the difference in outcome. Such analyses had the potential to define particular subgroups at heightened risk of Etanercept-related morbidity. The primary differences, summarized in Table 7, include race, BP (lower in NA), use of potassium-sparing diuretics (less frequent in NA), use of digitalis compounds (more frequent in NA), and use of lipid lowering agents (more frequent in NA).

Race

Overall, 11.5% of subjects in RENAISSANCE were of African ancestry, compared to <1% of subjects in RECOVER. For the RENAISSANCE study, CBER performed time-to-event mortality analyses by race. There were no apparent differences in mortality trends between Caucasians and African Americans.

Blood Pressure

On average, BP was ~10 mmHg lower in RENAISSANCE subjects than in RECOVER subjects. Therefore, it is reasonable to hypothesize that lower BP might make patients more susceptible to deleterious effects of Etanercept, which could explain the differences in study outcomes. CBER analyzed all-cause mortality and CHF hospitalizations by treatment and BP tertile, across both studies. Mean arterial pressure (MAP) was defined as: 1/3 X systolic pressure + 2/3 X diastolic pressure. Tertile 1 was defined as a MAP < 80 mmHg; tertile 2 was defined as: 80 mmHg $\leq$ MAP <91.67 mmHg; and tertile 3 was defined as a MAP $\geq$ 91.67 mmHg. Because MAP tertiles were constructed over the combined studies, and because MAP tended to be lower in the NA study, roughly half of the patients in RENAISSANCE fell into the lowest MAP tertile. If a lower BP imparted a heightened sensitivity to deleterious effects of Etanercept, this would be most apparent in subjects in RENAISSANCE within the lowest BP tertile. In fact, subjects in this tertile had similar results, irrespective of whether or not they received Etanercept. Thus, the data for the lowest BP tertile do not support a particular susceptibility to harmful effects of Etanercept. The disparity in outcomes (i.e., greater frequency of mortality and CHF hospitalizations with Etanercept) was primarily evident in the two upper MAP tertiles, i.e., patients with MAP $\geq$ 80 mmHg. In RECOVER, the lines crossed fairly frequently within each MAP tertile, and there was no apparent interaction between treatment and MAP.

Overall, differences in BP between the two studies do not appear to account for the disparate outcome trends.

Use of Potassium-Sparing Diuretics

Given that roughly a third of subjects in RENAISSANCE reported potassium-sparing diuretic use at baseline, compared with ~90% of subjects in RECOVER, the two-thirds of subjects in RENAISSANCE who were not using potassium-sparing diuretics at baseline represent a subgroup of interest. CBER analyzed mortality and CHF hospitalizations by treatment group, separately for subjects with and without reported use of potassium-sparing diuretics at baseline. The analysis showed consistent outcomes with respect to Etanercept, for subjects with and without baseline use of potassium-sparing diuretics.

Use of Digitalis Agents

In both studies, there was a negative association between digoxin use and outcome. This was particularly evident in RECOVER.

Digitalis glycoside use was reported in 82% of subjects in RENAISSANCE. Thus, the results in these subjects were entirely consistent with those of the study as a whole. For the 18% of subjects wherein digoxin use was not reported, the trend was also similar to that of the study as a whole.

Digoxin use was reported in 54% of subjects in RECOVER. For these subjects, outcomes tended to be better in the Etanercept groups. For subjects wherein digoxin use was not reported, outcomes tended to be worse with Etanercept. Considered together, these data do not suggest a unifying hypothesis regarding digoxin and Etanercept use in patients with CHF

Use of Lipid Lowering Agents
There was no apparent association between the use of lipid-lowering agents and outcome in either study, and no apparent interaction between the use of these agents and Etanercept.

In summary, these analyses fail to identify factors predictive of a negative outcome in patients with CHF who received Etanercept - - factors that might be of value in labeling.

Functional Class and Mortality

In light of the prognostic importance of NYHA FC, CBER examined mortality data for possible interactions between treatment group and NYHA FC.

Figure 5 shows all-cause mortality within NYHA FC by treatment group. Because so few NYHA FC IV subjects were enrolled (5% in Renaissance; 3% in Recover), only the Kaplan-Meier plots for NYHA FC II, IIIa, and IIIb are shown. The curves for Renaissance are shown in the left panels; curves for Recover are shown in the right panels.

For Renaissance, the trend towards greater mortality in the Etanercept groups is most evident in the FC II subjects. The major importance of this observation is that it suggests that the risk of Etanercept in the CHF patient population is not restricted to patients who are most severely affected with CHF. The results suggest that it would not be appropriate to provide reassurance in labeling regarding the risk of Etanercept in patients with only mild CHF (i.e., NYHA FC II). For Recover, there are no clear trends, and it is important to note that only half of the total number of subjects remain at risk after 23 weeks.

Figure 6 shows the complementary analysis - - the relation between NYHA FC and mortality by treatment group. Again, the Kaplan-Meier curves for Renaissance and Recover are depicted on the left and right, respectively. Note that the NYHA FC IV subjects are included in these plots. Associations between more advanced FC and mortality are generally apparent for each treatment group in both studies.

Figure 5: All-cause Mortality Within NYHA Functional Classification by Treatment Group

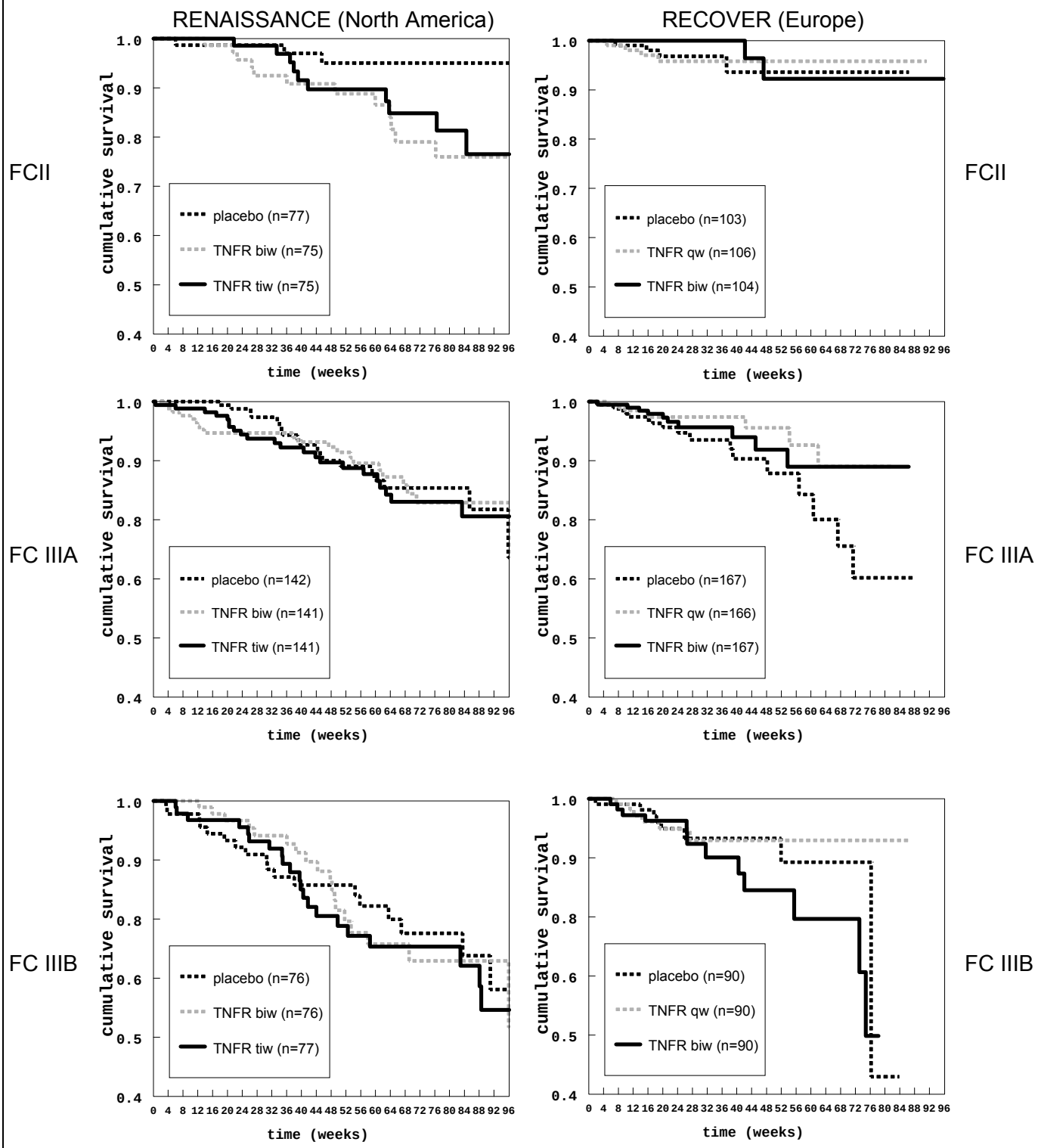
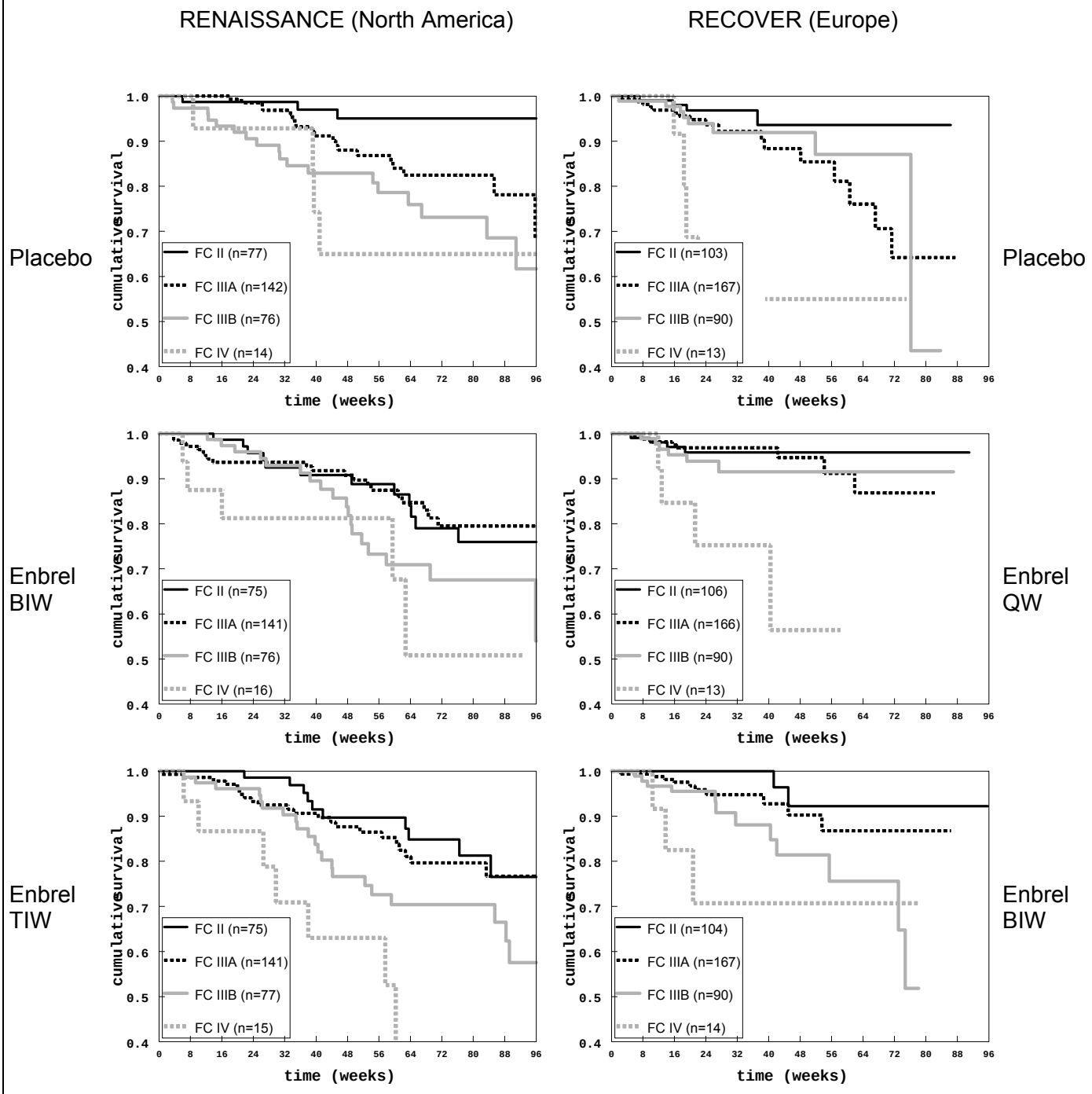


Figure 6: All-cause Mortality Within Treatment Groups by NYHA Functional Classification



Cardiovascular Adverse Events

Analysis of cardiovascular adverse event rates has the potential to provide supportive evidence regarding deleterious effects of Etanercept in the CHF patient population, as well as to provide clues to help elucidate mechanism of action. Major factors to consider in the CHF patient population include: 1) genesis of arrhythmias; 2) hemodynamic effects; 3) exacerbation of ischemia; and 4) negative inotropism.

RENAISSANCE: Adverse events most relevant to CHF are summarized in Table 12. There is a trend towards excess chest pain in the Etanercept groups, as well as a dose response trend. Although this trend might suggest Etanercept-induced ischemia in the setting of CHF, the reverse trend is apparent for angina pectoris. Thus, if chest pain and angina are construed as essentially the same phenomenon, the percentage of subjects reporting either event is essentially the same in all 3 treatment groups. The rates of adverse events suggestive of dysrhythmias (syncope, atrial fibrillation, ventricular tachycardia, and palpitations) were very similar in all three treatment groups. Hypotension tended to be reported less commonly in the Etanercept groups.

Table 12: Adverse Events with Mechanisms Relevant to Heart Failure - RENAISSANCE

	Placebo	Etanercept	
		BIW	TIW
	n = 307	n = 305	n = 307
dizziness	52 (17%)	62 (20%)	71 (23%)
pain chest	37 (12%)	42 (14%)	56 (18%)
angina pectoris	20 (7%)	17 (6%)	10 (3%)
hypotension	33 (11%)	32 (10%)	24 (8%)
syncope	18 (6%)	21 (7%)	21 (7%)
atrial fibrillation	14 (5%)	19 (6%)	16 (5%)
ventricular tachycardia	18 (6%)	16 (5%)	18 (6%)
palpitations	16 (5%)	5 (2%)	12 (4%)

Cardiovascular severe adverse events are summarized in Table 13. Of note, the frequencies of these events were similar across all three treatment groups.

Table 13: Cardiovascular Serious Adverse Events - RENAISSANCE

	Placebo	Etanercept	
		BIW	TIW
	n = 307	n = 305	n = 307
increased CHF	67 (22%)	81 (27%)	77 (25%)
cardiac arrest	6 (2%)	12 (4%)	10 (3%)
ventricular tachycardia	10 (3%)	7 (2%)	12 (4%)
angina pectoris	13 (4%)	12 (4%)	6 (2%)
syncope	9 (3%)	10 (3%)	7 (2%)
atrial fibrillation	5 (2%)	6 (2%)	7 (2%)
acute MI	7 (2%)	0	4 (1%)
coronary artery disease	5 (2%)	0	1 (<1%)
any cardiovascular SAE	113 (37%)	122 (40%)	113 (37%)

RECOVER: Adverse events relevant to CHF are summarized in Table 14. There is a trend towards excess aggravated CHF in the Etanercept groups, as well as trends towards excess hypotension and postural hypotension. Incidences of ischemic symptoms and rhythm disturbances are similar in the three treatment groups.

Overall, these data do not suggest a specific mechanism of action leading to Etanercept-related adverse consequences in the CHF patient population.

Table 14: Adverse Events with Mechanisms Relevant to Heart Failure - RECOVER

	Placebo	Etanercept	
		QW	BIW
	n = 373	n = 375	n = 375
CHF			
CHF aggravated	**86 (23%)**	**108 (29%)**	**103 (27%)**
dyspnea	**15 (4%)**	**27 (7%)**	**15 (4%)**
heart failure	**7 (2%)**	**6 (2%)**	**5 (1%)**
Total CHF	**108 (29%)**	**141 (38%)**	**123 (33%)**
Ischemia			
pain chest	**23 (6%)**	**23 (6%)**	**24 (6%)**
angina pectoris	**24 (6%)**	**23 (6%)**	**19 (5%)**
myocardial infarction	**5 (1%)**	**3 (1%)**	**4 (1%)**
Total ischemia	**52 (14%)**	**49 (13%)**	**47 (13%)**
Hypotensive symptoms			
dizziness	**23 (6%)**	**24 (6%)**	**25 (7%)**
syncope	**11 (3%)**	**10 (3%)**	**12 (3%)**
hypotension	**3 (1%)**	**6 (2%)**	**12 (3%)**
postural hypotension	**3 (1%)**	**1 (0%)**	**6 (2%)**
Total hypotension	**40 (11%)**	**41 (11%)**	**55 (15%)**
Rhythm disturbances			
atrial fibrillation	**9 (2%)**	**6 (2%)**	**7 (2%)**
palpitation	**7 (2%)**	**10 (3%)**	**8 (2%)**
cardiac arrest	**6 (2%)**	**7 (2%)**	**7 (2%)**
ventricular tachycardia	**10 (3%)**	**9 (2%)**	**0 (0%)**
arrhythmia	**3 (1%)**	**8 (2%)**	**3 (1%)**
sudden death	**8 (2%)**	**2 (1%)**	**1 (0%)**
atrial flutter	**1 (0%)**	**3 (1%)**	**3 (1%)**
ventricular fibrillation	**3 (1%)**	**1 (0%)**	**2 (1%)**
tachycardia	**1 (0%)**	**2 (1%)**	**3 (1%)**
tachycardia supraventricular	**1 (0%)**	**1 (0%)**	**1 (0%)**
Total rhythm	**49 (13%)**	**49 (13%)**	**35 (9%)**

Vital Signs

RENAISSANCE and RECOVER: For the comparisons between Etanercept and placebo treatment groups, there were no clinically significant differences in heart rate or blood pressure. There were no notable changes in vital signs with respect to time in the Etanercept groups. There was no suggestion of a hemodynamic effect of Etanercept that might account for the study results.

Summary and Recommendations

Both Renaissance and Recover were fairly large, multicenter, randomized, double-blind, placebo-controlled "add-on" studies of Etanercept in CHF. The investigations enrolled patients who were NYHA FC II-IV with an EF of $\leq$ 30%. Both studies failed on their primary efficacy endpoint.

For the Renaissance study, the key finding was a trend towards higher mortality in Etanercept-treated subjects, a concern heightened by the apparent dose-response relation. Specifically, mortality rates were 14.2%, 17.9%, and 19.8% in the placebo, Etanercept BIW, and Etanercept TIW treatment groups. There were imbalances in baseline characteristics (BP, 6-minute walk distance, and antiarrhythmic use) that favored the placebo group. To some extent, these imbalances call into question the magnitude of the concern; however, they do not eliminate it.

The results of Recover do not substantiate the findings of Renaissance with respect to Etanercept-induced mortality in CHF. The mortality rate for the placebo, Etanercept QW, and BIW groups were 8.8%, 5.9%, and 7.2%, respectively. In terms of labeling, when all of the results are considered together, the level of concern probably rises to that of a warning. Because the risk can not be considered definitive, either a boxed warning or contraindication seems unwarranted at present.

Of note, exploratory analyses did not identify specific factors associated with increased risk of adverse outcomes in CHF patients. In particular, patients in Renaissance with milder CHF (NYHA FC II) or higher BP did not appear to be at a lower risk of adverse outcomes. Thus, there is no basis to provide a measure of reassurance for patients with mild forms of CHF.