2. STUDY SYNOPSIS

Name of Sponsor/Company: Biogen Idec Inc./Biogen Idec Ltd.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use only)***
Name of Finished Product: Tonapofylline	**Name of Active Ingredient:** Tonapofylline	**Study Indication:** Acute Decompensated Heart Failure and Renal Insufficiency (ADHF)

Title of Study:

A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess the Safety and Tolerability of Intravenous Tonapofylline in Subjects with Acute Decompensated Heart Failure and Renal Insufficiency

Principal Investigator/Coordinating Investigator:

[redacted]

Study Period:	**Phase of Development:**
Date of first treatment: 19 August 2008 End of Study Date: 10 November 2009 (last patient last visit) Date of early study termination: 18 August 2009 (date termination notification sent to study sites). The Sponsor terminated the study early based on recommendations of the independent Data Monitoring Committee (iDMC) and Study Oversight Committee.	2b

Study Objective(s):

Primary objective:

- To assess the safety and tolerability of tonapofylline, when added to standard therapy, in subjects hospitalized with acute decompensated heart failure (ADHF) and renal insufficiency.

Secondary objectives:

- To assess the effect of tonapofylline when added to standard therapy in subjects hospitalized with ADHF and renal insufficiency on:
  - Change in body weight at 24 hours following the first dose.
  - Worsening renal function during the double-blind treatment period up to Day 5 (or discharge if prior to Day 5).
  - All-cause mortality or cardiovascular re-hospitalization at Day 30.
  - Days of hospital-free survival (DHFS) over 30 days after the first dose of study treatment.
  - Length of stay during the initial hospitalization.
  - Improvement in Dyspnea Symptom Score at 6 hours following the first dose.

Additional Efficacy Objectives:

- Refer to Section 8.2.

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Study Design:

This was a randomized, double-blind, placebo-controlled, parallel-group study. Subjects were to be randomized evenly into 4 dose groups in a 1:1:1:1 ratio to receive placebo or tonapofylline at 0.03 mg/kg, 0.15 mg/kg, or 0.3 mg/kg. Randomization was stratified by geographic region. Study treatment was to be administered by intravenous (IV) infusion every 12 hours (q12h) for up to 5 days. All subjects were to receive 10 infusions unless they were discharged before Day 5. Efficacy and safety assessments were to be performed at 0 to 2, 6, 12, and 24 hours, Days 2, 3, 4, 5 or discharge, 6, 7, 30, and 60 after initiation of study treatment.

Number of Subjects (Planned and Analyzed):

Planned: 600 subjects; Analyzed: 415 subjects.

Study Population:

Main inclusion criteria:

- Previous diagnosis of heart failure.
- Must have ADHF, requiring hospitalization, with clinical evidence for volume overload.
- Renal insufficiency at the time of screening as defined by estimated glomerular filtration rate (eGFR) ≥20 and ≤70 mL/min/1.73 m^2.

Main exclusion criteria:

- History of an allergic reaction to any xanthine-containing substance.
- History of seizure
- History of stroke
- Myocardial infarction
- Uncorrected hemodynamically significant primary valvular disease or known obstructive or restrictive cardiomyopathy.
- Serious systemic infection
- Major surgical procedures within 30 days
- Acute coronary syndrome
- Cardiogenic shock
- Baseline body weight >150 kg
- Participation in any other investigational study of drugs or devices within 30 days prior to Screening
- Nursing mothers, pregnant women, or women planning on becoming pregnant during the study
- Presence of any clinically significant condition that might interfere with optimal safe participation in this study

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Study Treatment, Dose, Mode of Administration, Batch Number(s):
Tonapofylline 0.03, 0.15, or 0.3 mg/kg IV infusion over 30 minutes, q12h for up to 10 doses. Batch number: Available upon request.

Comparator Therapy/Therapies, Dose, Mode of Administration, Batch Number(s):
Placebo IV infusion over 30 minutes, q12h for up to 10 doses. Batch number: Available upon request.

Duration of Treatment and Follow-Up:
Treatment period: Up to 5 days.

Follow-up period: Follow-up assessments were to be performed at Days 6 and 7, and Days 30 and 60 ± 7 days post study treatment initiation.

Criteria for Evaluation:
Efficacy:

- Body weight
- Days of hospital free survival (DHFS)
- Dyspnea Symptom Score
- Subject Global Clinical Assessment Score
- Physician Global Clinical Assessment Score
- Edema Score Assessment
- Length of hospital stay
- Concomitant medications to treat heart failure
- Cardiovascular and all-cause mortality
- Cardiovascular and all-cause re-hospitalization
- Renal function as reflected by changes in serum creatinine
- Biological markers of cardiac and renal function including BNP and cystatin-C

Tonapofylline and acyl glucuronide (AG) metabolite concentrations measurements:

Plasma samples for tonapofylline and AG concentrations were to be obtained prior to the first infusion, at the end of the first infusion, and 2 hours after the first infusion on each dosing day in all subjects at selected sites.

Safety:

- AEs and SAEs to Day 30 following initial dosing
- Physical examinations
- Vital sign measurements (heart rate, blood pressure, temperature)
- ECG (12-lead)
- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count (with differential), and platelet count
- Blood chemistry will include, but may not be limited to: sodium, potassium, chloride, total bilirubin, calcium, magnesium, phosphate, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), uric acid, creatinine, bicarbonate, and glucose

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Statistical Methods:

Efficacy: Treatment comparisons were to be made between each individual tonapofylline dose level and placebo based on 2-sided tests. In addition, a linear dose-response relationship was to be evaluated. Binary outcomes were to be analyzed by logistic regression, count data by Poisson regression, continuous responses by analysis of variance (ANOVA) or analysis of covariance (ANCOVA), and time to event responses by the Cox proportional hazards model. Each model was to include terms for study treatment and geographic region, regardless of the statistical significance of these terms in the model.

Safety: Analyses were descriptive, using summary statistics (mean, standard deviation, and range), frequency distributions, shift tables, and listings.

Results:

Subject disposition:

A total of 420 subjects were randomized into the study, with 104 subjects in the placebo group, 105 in the 0.03 mg/kg tonapofylline group, 106 in the 0.15 mg/kg tonapofylline group, and 105 in the 0.3 mg/kg tonapofylline group, of whom 415 received at least one dose of study treatment. All 415 subjects were included in the efficacy and safety analyses.

Of the 415 subjects dosed, 320 (77%) completed study treatment (defined as completing 10 doses of study treatment or receiving adequate study treatment at the discretion of the Investigator). The major reasons for discontinuation of study treatment were discharge prior to Day 5 and early study termination.

Demographics and baseline disease characteristics:

- Demographics of the subjects were comparable across the 4 groups. Of the 415 subjects dosed, the mean (SD) age was 71.6 (11.0) years (ranging from 20 to 96 years), 248 (60%) subjects were males. The majority of the subjects (366 [88%]) were White. The mean (SD) body weight was 84.3 (20.6) kg (ranging from 39.4 to 142.2 kg). The mean (SD) Body Mass Index (BMI) was 30.0 (7.1) kg/m^2 (ranging from 17.1 to 69.8 kg/m^2).
- Baseline general medical history, as well as cardiovascular and renal history appeared comparable across the 4 treatment groups. Neurological history is summarized.
- Baseline ADHF characteristics appeared comparable across the 4 treatment groups.
- Baseline use of IV loop diuretic use was comparable across the 4 treatment groups. Baseline use of angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), beta blockers, and renin inhibitors is summarized.

Efficacy:

- Tonapofylline produced statistically significant dose-dependent improvement in dyspnea at 6 and 24 hours following initiation of treatment.
- No statistically significant effect was observed in body weight, worsening renal function, or mortality/hospitalization clinical outcome measures.

Pharmacokinetics:

- Summary statistics of tonapofylline concentration and AG metabolite concentration by timepoint and treatment group are provided.

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Safety:

Overall, tonapofylline at 0.03, 0.15, and 0.3 mg/kg was generally well tolerated; however, there was an apparent increased seizure risk and 2 subjects who experienced seizures died (one who experienced status epilepticus and one who experienced transient loss of consciousness [initially reported by the Investigator as seizure]). Below is a summary of the safety results:

- The overall incidences of AEs and SAEs were similar to placebo across the tonapofylline dose groups. Among the most common AEs, the incidence of the following AEs appeared to be slightly higher in the tonapofylline groups than in the placebo group: hypotension (<1% for placebo, 6% for 0.03 mg/kg, 3% for 0.15 mg/kg, and 8% for 0.3 mg/kg), dyspnea (<1%, 6%, 4%, and 3%, respectively), cough (<1%, 3%, 4%, and 5%, respectively), and diarrhea (0, 2%, 3%, and 5%, respectively).
- AEs of interest specified in the protocol, including convulsion (status epilepticus) [0.15 mg/kg], transient loss of consciousness (initially reported by the Investigator as seizure) [0.15 mg/kg], simple partial seizures (0.3 mg/kg), and syncope (0.03 mg/kg), were each reported in 1 (<1%) subject in the tonapofylline dose groups and none in the placebo group.
- A total of 35 deaths occurred during the study (7 in placebo, 8 in 0.03 mg/kg, 14 in 0.15 mg/kg, and 6 in 0.3 mg/kg), 2 of which were judged by the Investigator to be related to study treatment: one in the 0.03 mg/kg group (cause of death: complications from myocardial infarction/acute coronary syndrome) and one in the 0.15 mg/kg group (sudden cardiac death).
- No clinically significant changes or differences were observed in vital signs, physical examination findings, and 12-lead ECG findings.

Study-specific subgroups:

- Subgroup analyses of selected efficacy endpoints by region, eGFR at screening, baseline serum B-type natriuretic peptide (BNP), left ventricular ejection fraction (LVEF), and time from first dose of diuretic for the current episode of ADHF to study treatment are presented.

Conclusion(s):

In conclusion, the study data suggest that when added to standard therapy for ADHF, including high-dose IV diuretics, tonapofylline may have a beneficial effect on dyspnea symptoms. The improvements in dyspnea observed were numerically largest in subjects receiving the highest dose of tonapofylline studied (0.3 mg/kg). However, no dose of tonapofylline studied was associated with a positive effect on renal function, clinical morbidity outcomes (such as the need for hospitalization), or short-term mortality. Further, tonapofylline was associated with an apparent increase in the risk for seizure. Overall, 3 subjects who received tonapofylline (0.15 or 0.3 mg/kg) reported seizures: 2 cases of seizure (1 status epilepticus and a second case in the setting of profound hypoglycemia that was initially reported as seizure and later changed to transient loss of consciousness by the Investigator) and 1 case of simple partial seizure. Two of the subjects died, and the other subject with simple partial seizure recovered fully.

The study was terminated early based on interim review of risk/benefit ratio: there was no apparent positive signal for efficacy or dose-related pharmacodynamic response in the face of an apparent increased risk for seizure associated with tonapofylline. These observations are consistent with available data from other compounds of the same class in patients with ADHF and do not support further development of tonapofylline in acute heart failure.

Publication(s) Based on the Study: There is no publication based on this study to date.

Date of Report: 14 July 2010