2. SYNOPSIS

Name of Sponsor/Company: Biogen Idec, Inc.	**Individual Study Table Referring to Part <> of the Dossier** **Volume:** **Page:**	***(For National Authority Use Only)***
Name of Finished Product: Tonapofylline (BG9928)	**Name of Active Ingredient:** Tonapofylline (BG9928)	**Study Indication:** Heart failure associated with renal insufficiency

Title of Study:

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

Study Period:	**Phase of Development:**
Date of first treatment: 24 March 2009 Date of early study termination: 21 January 2010 (date of last subject, last visit). The Sponsor terminated the study early based on a decision not to pursue further development of tonapofylline.	2

Study Population:

Main inclusion criteria:

- 18 years of age or older
- Diagnosis of heart failure (HF) with symptoms of HF present at screening (i.e., subjects were to be graded as New York Heart Association [NYHA] Class II, III, or IV)
- Subjects graded NYHA Class III or IV were required to meet one of the following criteria, and subjects graded NYHA Class II were required to meet both of the following:
    - History of hospitalization for HF >1 month and ≤12 months prior to the screening visit, or documented, unscheduled outpatient treatment with intravenous (IV) diuretics, IV vasodilators, or IV inotropic medications >1 month and ≤12 months prior to the screening visit.
    - Documented brain natriuretic peptide (BNP) ≥150 pg/mL, or N-terminal pro b-type natriuretic peptide (NTproBNP) ≥500 pg/mL within the 12 months prior to Day 1.
- Renal insufficiency defined by estimated glomerular filtration rate ≥20 and ≤70 mL/min/1.73 m^2, as determined by the Modification of Diet in Renal Disease (MDRD) equation (abbreviated version)
- Treatment with oral loop diuretic for at least the 4 weeks prior to Day 1 (introduction or withdrawal of any other class of diuretic was not allowed within the 4 weeks prior to Day 1).
- Subjects with a reduced left ventricular ejection fraction (LVEF; ≤40%) documented during screening were required to be on a pharmacological treatment regimen for HF for at least the 4 weeks prior to Day 1. The HF regimen was to include treatment with a beta blocker **and** treatment with an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). The dose of any of the HF medications could be adjusted once within the 4 weeks prior to Day 1.

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Main exclusion criteria:

- History of an allergic reaction to any xanthine-containing compound
- History of seizure
- History of head injury with loss of consciousness, stroke, or transient ischemic attack
- History of multiple sclerosis, Alzheimer's disease, mental retardation, meningitis/encephalitis, brain surgery, or penetrating head trauma
- History of intracranial pathology known to increase the risk of seizure such as brain tumor, arteriovenous malformation, cerebral cavernous malformation, hydrocephalus, or encephalomalacia
- Serious systemic infection
- Sustained systolic blood pressure >170 or <90 mmHg
- Hospitalization for HF within 30 days of Day 1
- Myocardial infarction within 30 days of Day 1
- Hemodynamically destabilizing arrhythmia within 30 days of Day 1
- Uncorrected hemodynamically significant primary valvular disease
- Known obstructive or restrictive cardiomyopathy
- Currently receiving chronic renal replacement therapy (e.g., hemodialysis or peritoneal dialysis)
- Cardiac surgery within 60 days prior to Day 1
- Likely to undergo cardiac transplantation, device implantation, or other cardiac surgery within next 3 months
- Evidence of malignancy within 6 months prior to Day 1
- Participation in any other investigational study of drugs or devices within 30 days prior to Day 1
- Receiving aminophylline, theophylline, pentoxifylline, dyphylline, or adenosine
- Presence of any clinically significant condition that might interfere with optimal safe participation in this study

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Study Design:

This was a randomized, double-blind, placebo-controlled, parallel-group study of tonapofylline administered orally for 12 weeks in subjects with heart failure associated with renal insufficiency. A total of up to 300 subjects at up to 50 sites in 5 countries were to be randomized to 1 of 6 groups.

Dosing Group	Number of Subjects	Morning Dose	Evening Dose	Total Daily Dose
1	50	Placebo	Placebo	0 mg
2	50	2/7.5 mg*	Placebo	2/7.5 mg
3	50	15 mg	Placebo	15 mg
4	50	75 mg	Placebo	75 mg
5	50	7.5 mg	7.5 mg	15 mg
6	50	37.5 mg	37.5 mg	75 mg

* The low dose was to be 7.5 mg in the United Kingdom and Germany and 2 mg elsewhere.

The study period was to consist of Screening (up to 28 days), a Treatment Period (12 weeks), and a Post-Treatment Follow-up Visit (at Week 16). During the Treatment Period, visits were scheduled at Weeks 2, 4, 8, and 12 for assessments of efficacy and tolerability.

Number of Subjects (Planned and Analyzed):

Up to 300 subjects were planned, and 33 subjects were analyzed.

Study Treatment, Dose, Mode of Administration, Batch Number:

Subjects were treated with oral tonapofylline and/or placebo as 2 capsules taken twice daily in the dosing groups indicated above. Tonapofylline and placebo batch numbers are available upon request.

Duration of Treatment and Follow-Up:

The planned Treatment Period was 12 weeks, and a Follow-Up visit was planned for 4 weeks after the end of treatment.

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Results:

Subject disposition:

Thirty-three subjects were randomized into the study, of whom 7 received placebo, 5 received 2/7.5 mg tonapofylline once daily (QD), 7 received 15 mg tonapofylline QD, 5 received 75 mg tonapofylline QD, 4 received 7.5 mg tonapofylline twice daily (BID), and 5 received 37.5 mg tonapofylline BID. All subjects received at least one dose of study treatment.

Sixteen subjects (48%) completed treatment with study drug, while 17 subjects (52%) discontinued study drug prematurely; the reason for discontinuation was adverse event (AE) for 7 subjects (21%), other for 9 subjects (27%; this included the Sponsor's termination of the study for 7 subjects, 21%), and consent withdrawn for 1 subject. Twenty-two subjects (67%) completed study participation, while 11 subjects (33%) withdrew from the study prematurely; the reason for withdrawal was AE for 2 subjects (6%), other for 8 subjects (24%; this included the Sponsor's termination of the study for 7 subjects, 21%), and consent withdrawn for 1 subject. With the exception of Subject [redacted] who completed study treatments before withdrawing from the study prematurely, the 11 subjects who withdrew from the study early are contained within the 17 subjects who discontinued study drug treatment prematurely.

The study was prematurely terminated by the Sponsor after an internal decision in December 2009 to discontinue the tonapofylline program.

Efficacy and pharmacokinetic analyses were not conducted due to the early termination of the study and the small size of the study population.

Safety:

Of the 26 subjects treated with tonapofylline, 22 subjects (85%) reported an AE; 11 subjects (42%) reported a severe AE; 8 subjects (31%) reported a related AE; 13 subjects (50%) reported an SAE (4 subjects reported a related SAE); 5 subjects (19%) reported an AE leading to treatment discontinuation; and 4 subjects (15%) reported an AE leading to study withdrawal. Of the 7 subjects treated with placebo, 5 subjects (71%) reported an AE; 3 subjects (43%) reported a severe AE; 3 subjects (43%) reported a related AE; 3 subjects (43%) reported an SAE; 2 subjects (29%) reported an AE leading to treatment discontinuation; and 1 subject (14%) reported an AE leading to study withdrawal.

Study-specific AEs were also examined. Syncope and/or loss of consciousness were reported in 4 subjects who received active study drug; 2 of the 5 events were considered related to study treatment, and none of the events were considered to be related to seizure activity. Acute or chronic renal failure was reported for 4 of 26 subjects who received tonapofylline and for 0 of 5 placebo subjects. The majority of these events were considered unrelated to the study drug by the Investigator and occurred in subjects with other contributing factors. The clinical relevance of these events is not clear.

Common treatment-emergent AEs among subjects treated with tonapofylline included cardiac failure

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congestive (5 subjects, 19%), headache (4 subjects, 15%), and pneumonia, syncope, and hypotension (each 3 subjects, 12%). In the placebo group, nausea was the only event reported for more than 1 subject (2 subjects, 29%).

No clinically significant trends with respect to laboratory results, vital signs, physical examination findings, or electrocardiograms were evident.

Conclusions:

The study was terminated in December 2009, after about one-tenth of the planned study population had been enrolled, based on a decision by Biogen Idec not to pursue further development of tonapofylline. No particular safety signal (such as seizure activity) was observed in this patient population, and there was no evidence of poor tolerability of the study drug. Although the numbers of subjects in each group were low, the incidence of AEs and particular categories of AEs in the combined tonapofylline groups was comparable to the incidence in the placebo group. Because of the early termination of the study and the consequent small size of the study population, efficacy and pharmacokinetic data were not analyzed. In this regard, it is not possible to draw conclusions about the activity of the study drug.

Publications Based on the Study:

None

Date of Report: 13 July 2010