2 SYNOPSIS

NAME OF COMPANY **Genzyme Corporation** **500 Kendall Street** **Cambridge, MA 02142** NAME OF FINISHED PRODUCT **Not applicable** NAME OF ACTIVE INGREDIENT **Tolevamer potassium sodium**	SUMMARY TABLE Referring to Part …… of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY:

TITLE OF STUDY:

A randomized, double-blind study of GT267-004 versus vancomycin, and GT267-004 versus metronidazole, in patients with *C difficile*-associated diarrhea

INVESTIGATORS: This was a multisite study.

STUDY CENTER(S):

Twelve sites in Australia, 11 sites in Canada, and 86 sites in Europe recruited patients;

PUBLICATION (REFERENCE):

Bouza E, Dryden M, Mohammed R, et al. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in patients with Clostridium difficile-associated diarrhea (CDAD). Poster session abstract submitted for presentation at the 18th European Society of Clinical Microbiology and Infectious Diseases (ESCMID); 2008 Apr 19-22; Barcelona, Spain.

STUDIED PERIOD:

17 May 2005 (first patient, first visit) to 08 August 2007 (last patient, last visit)

PHASE OF DEVELOPMENT: 3

OBJECTIVES:

1. To compare the safety and tolerability of GT267-004 (known as tolevamer in this study) versus vancomycin and GT267-004 versus metronidazole in patients with *C difficile*-associated diarrhea (CDAD)
2. To compare the effect of tolevamer versus vancomycin, and tolevamer versus metronidazole, on the resolution of CDAD
3. To compare the effect of tolevamer versus vancomycin, and tolevamer versus metronidazole, on the rate of CDAD recurrence during the follow-up period
4. To compare the safety, tolerability, and efficacy of vancomycin versus metronidazole for resolution of CDAD and recurrence rates

METHODOLOGY:

Randomized (2:1:1), double-dummy, double-blind, active-controlled, parallel-design

NUMBER OF PATIENTS (PLANNED AND ANALYZED):

520 patients planned; 544 randomly assigned to treatment, 326 completed study drug regimen, 451 completed study follow up.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION:

INCLUSION:

Patients who met all of the following inclusion criteria were eligible to participate in this study:

1. At least 18 years of age,
2. The presence of CDAD at the time of enrollment with no other likely etiology for the diarrhea,
3. No more than 48 hours of treatment with metronidazole, vancomycin or other antibacterial therapy specific for CDAD within the 5 days before enrollment,
4. Baseline serum potassium (K+) at least 3.0 mmol (mEq)/L,
5. Patient considered clinically stable to probably complete a 6-week study period,
6. No contraindication to oral/enteral therapy, and
7. Absence of fulminant *C difficile* disease

EXCLUSION:

Patients who met any of the following exclusion criteria were not eligible for participation in this study:

1. Patient had any contraindication to oral/enteral therapy (eg, severe nausea or vomiting, ileus, toxic megacolon, severe abdominal pain, or peritoneal signs),
2. Patient had severe hepatic disease (eg, ascites, hepatic encephalopathy, or biliary obstruction),
3. Patient had fulminant *C difficile* disease that required intravenous antibacterial therapy (eg, severe colitis with findings such as peritoneal signs, ileus, megacolon; sepsis with hypotension that, despite adequate fluid resuscitation, required pressor therapy; other contraindications to exclusively oral therapy for CDAD),
4. Patient had any acutely life-threatening medical condition which in the judgment of the investigator precluded completion of the study (patient was considered sufficiently stable clinically to likely complete the 6-week study period),
5. Patient had a baseline serum K+ exclusion criteria:
    - K+ less than 3.0 mmol (mEq)/L or
    - K+ less than 3.5 mmol (mEq)/L and history of cardiac arrhythmias or currently receiving a cardiac glycoside (eg, digoxin or digitoxin)
6. Patient was expected to remain on the CDAD inducing antibiotic(s) for more than 7 days after enrollment,
7. Patient had acute diarrhea of other cause (eg, other stool pathogen, chronic gastrointestinal condition, laxative induced diarrhea, or medications),
8. Patient had chronic diarrhea with onset of diarrhea extending more than 30 days before enrollment,
9. Patient had more than 48 hours of treatment with oral or intravenous metronidazole, oral vancomycin, or other antibacterial therapies specific for CDAD within the 5 days before enrollment. Note: This included antibiotics prescribed for other indications, but which were also effective for treating CDAD (eg, intravenous vancomycin was not effective for CDAD and so would not be exclusionary),

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EXCLUSION: *(continued)*

10. Patient had an allergy to vancomycin, metronidazole, or hypersensitivity to paraben or other ingredients of the formulations,
11. Patient had participated in a clinical study of an investigational (not approved) drug from 30 days before Screening throughout study duration,
12. Female patient was pregnant or breastfeeding,
13. Patient was unable or unwilling to abstain from alcohol during the 14-day treatment period, or
14. Patient had previous exposure to either tolevamer or a previous formulation, GT160-246.

TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:

Oral/enteral loading dose of 9.0 g of tolevamer on Day 1 with subsequent doses of 3.0 g, administered 3 times daily. Batch numbers are available from the study files.

DURATION OF TREATMENT:

Duration of tolevamer therapy = 14 days

Duration of vancomycin therapy = 10 days

Duration of metronidazole therapy = 10 days

Duration of follow-up = 4 weeks

Duration of total participation = 6 weeks

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:

Patients in either the metronidazole or vancomycin groups received a loading dose of tolevamer placebo, equal in volume to a total daily dose, followed by the randomly assigned treatment as follows:

Oral dose of 375 mg of metronidazole, administered 4 times daily. Oral dose of 125 mg of vancomycin, administered 4 times daily. Batch numbers are available from the study files.

CRITERIA FOR EVALUATION: *will be excerpted from finalized text*

EFFICACY:

Efficacy parameters included the resolution of diarrhea, recurrence of CDAD, stool number and consistency, and abdominal pain due to CDAD.

SAFETY:

Safety measures included adverse events, clinical laboratory test results, physical examinations, and vital signs.

STATISTICAL METHODS:

Statistical methods are described in the .

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SUMMARY – CONCLUSIONS

Of the 278 tolevamer patients, 133 (47.8%) completed the regimen, which was significantly lower (P<0.001) than vancomycin patients (74.6%) or metronidazole patients (70.7%). The most common reason for noncompletion was lack of response to the study treatment, which caused patients to voluntarily withdraw from the study.

In the FAS, CDAD was resolved in 105 of 268 (39.2%) tolevamer patients after a median of 12 days. Resolution was noted in 102 of 125 (81.6%) vancomycin patients after a median of 4 days, and in 106 of 135 (78.5%) of metronidazole patients after a median of 4 days. Noninferiority of tolevamer versus vancomycin or versus metronidazole with respect to clinical success was not supported.

Among the tolevamer patients with resolved CDAD, 6 of 105 (5.7%) experienced a recurrence, whereas 18 of 125 (17.6%) vancomycin patients and 20 of 135 (18.9%) metronidazole patients experienced recurrence after CDAD resolved.

SAFETY:

At least 1 treatment-emergent AE was experienced by 89.4% of tolevamer patients, 86.4% of vancomycin patients, and 85.6% of metronidazole patients. The most frequently reported AE was *C difficile* colitis, experienced by at least 20% of patients in each group. The percentages of patients experiencing AEs were similar among treatment groups. The incidence of hypokalemia was similar in the vancomycin and metronidazole treatment groups (11.2% and 12.9%, respectively) and slightly higher in the tolevamer treatment group (18.2%).

There were 58 deaths reported in patients in the Safety Set (SS), including 33 of 274 (manual calculation of 12.0%) tolevamer patients, 15 of 125 (manual calculation of 12.0%) vancomycin patients, and 10 of 139 (manual calculation of 7.2%) metronidazole patients. Fifty-seven of the 58 deaths were judged by the investigator to be unrelated or unlikely related to study drug. However, the investigator indicated that the fatal event of septic shock experienced by Patient 452002 was possibly related to study drug (tolevamer), although he also noted that tolevamer itself did not directly lead to the patient's death.

Overall, there were 148 patients who experienced at least 1 treatment-emergent SAE, including 74 of 274 (27.0%) tolevamer patients, 40 of 125 (32.0%) vancomycin patients, and 34 of 139 (24.5%) metronidazole patients. The most frequently reported SAE was *C difficile* colitis, which was experienced by 21 (7.7%) tolevamer patients, 9 (7.2%) vancomycin patients, and 9 (6.5%) metronidazole patients. Eighteen patients experienced 19 SAEs that were judged by the investigator to be treatment-related (13 of which were experienced by the tolevamer group), including 15 reports of *C difficile* colitis, 1 report of acute myocardial infarction, 1 report of hepatitis, 1 report of septic shock, and 1 report of rash macular.

Overall, there were 40 patients who discontinued before completing the study drug regimen because of AEs including 19 (6.8%) treated with tolevamer, 8 (6.3%) treated with vancomycin, and 13 (9.3%) treated with metronidazole patients.

CONCLUSION:

[redacted]