

# Faster Time to Resolution of Diarrhea with Fidaxomicin vs. Vancomycin in Patients with *Clostridium difficile* Infection (CDI).

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## Abstract

**Background** A phase 3 trial of fidaxomicin (FDX; formerly OPT-80) vs. vancomycin (VAN) for treatment of *Clostridium difficile* infection (CDI) has been used to explore the differential effect of these therapies on the time to resolution of diarrhea (TTROD). FDX was previously shown to be equivalent to VAN for achieving clinical cure but superior to VAN in reducing the relapse rate and achieving global cure (= cure + no relapse).

**Methods** The database of the completed phase 3 FDX/VAN comparative trial was used to analyze the effect of these 2 treatments on the TTROD. The analyses were conducted on the "per protocol" (PP) study population. Prospectively-collected daily bowel movement diaries were the source of data.

**Results** 629 patients were enrolled into the study, of whom 548 were in the PP study group. At 60 hours after start of therapy, more FDX patients were free of diarrhea compared with VAN patients (PP: 67.6% vs. 61.5% P=0.038). Survival curve analysis showed no difference in the first 24 hours of therapy, but thereafter FDX led to significantly faster resolution of diarrhea than VAN (P=0.056). This difference was even more marked in the subgroup of patients with albumin levels > 35 g/L (P=0.047), who accounted for approximately 26% of the study population.

**Conclusions** In this trial, fewer patients had diarrhea at 60 hours after start of FDX therapy when compared to VAN. For subjects with more pronounced diarrhea (i.e. diarrhea continuing more than 24 hours on therapy), it resolved faster with FDX than with VAN. This differential effect in TTROD may result in less environmental contamination with *C. difficile*, less cross-transmission of CDI, and earlier discharge from hospital of CDI inpatients.

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## Background

*Clostridium difficile* infection (CDI) is the most common cause of healthcare-associated infectious nosocomial diarrhea. Despite the existence of two widely-accepted therapeutic medications for CDI (i.e. oral metronidazole and oral vancomycin) and other potentially useful pharmaceutical agents (e.g. rifaximin, nitazoxanide), no therapy has shown a difference in the rate of resolution of CDI symptoms. Faster resolution of diarrhea would be of great benefit to the patient and would also theoretically reduce contamination of the environment by *C. difficile* spores and could limit spread of this pathogen. Faster resolution of diarrhea could also lead to earlier discharge from hospital and reduced healthcare-associated costs.

Fidaxomicin, a novel antibacterial agent in the macrocyclic class, targets bacterial RNA polymerase and is extremely potent against all strains of *C. difficile*. There is no known cross-resistance with other antibacterials.<sup>1</sup>

The recently-presented results of the North American Phase 3 clinical trial of fidaxomicin (FDX) vs. vancomycin (VAN) for the treatment of CDI showed that FDX was non-inferior to VAN for cure of CDI at end-of-therapy. However, FDX therapy was associated with a statistically and clinically significant reduction in relapse rate and global cure rate (cure plus no relapse) following CDI treatment.<sup>2,3</sup>

The results of the North American Phase 3 fidaxomicin/vancomycin trial were used to calculate whether there was a difference in "Time To Resolution Of Diarrhea" (TTROD) between the 2 treatment groups.

## Methods

The study was a Phase 3, randomized, double-blind, comparative clinical trial of FDX 200 mg orally BID vs. VAN 125 mg orally QID.

Administration of the study drug was for 10 days, and patients were then followed for an additional 4 weeks post-therapy for assessment of relapse.

Bowel movements were assessed and recorded daily in a patient diary, along with the time and consistency.

### Resolution of diarrhea

- a study subject experiences 3 or fewer unformed stools for 2 consecutive days, sustained through the end of therapy (or through study drug discontinuation for subjects who withdraw early)
- the time of resolution will be the time of the last unformed bowel movement on the day prior to the first of 2 consecutive days of < 3 unformed bowel movements sustained through the end of therapy (or through study drug discontinuation)

### Time To Resolution Of Diarrhea (TTROD) was defined as follows:

- the time elapsing (in hours, rounded up when minutes are > 30) from the start of treatment until resolution of diarrhea
- For this TTROD analysis, the "per protocol" (PP) population was examined. The PP group included subjects who had toxin-positive diarrhea and received at least one dose of study medication.

## Results

The TTROD results, shown graphically in a "survival curve" analysis, can be seen in figure 1. There was little difference among the "per protocol" treatment groups in the first 24 hours of therapy, during which approximately 20% of patients resolved their diarrhea.

However, after the initial 24-hour period of therapy, there was significantly faster resolution of diarrhea with FDX than with VAN. (P = 0.056) – figure 2. This difference was even more marked in the sub-group of patients with serum albumin levels > 35 g/L (P = 0.047), this group making up 26% of the study population – figure 3.

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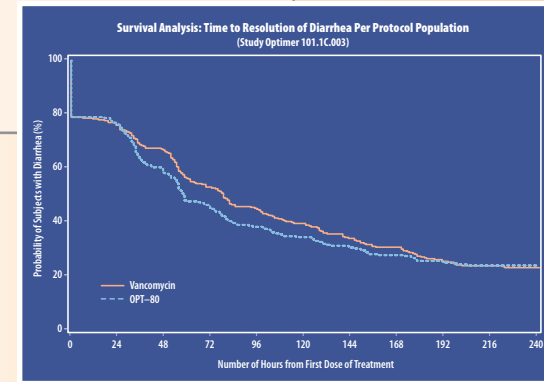


Figure 1. "Survival curve" analysis of time to resolution of diarrhea (TTROD) among all Per Protocol (PP) study subjects, by treatment group.

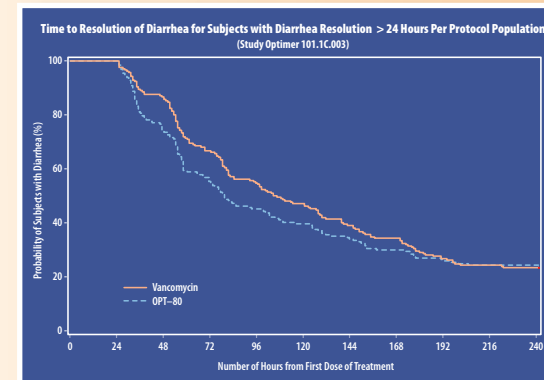


Figure 2. "Survival curve" analysis of time to resolution of diarrhea (TTROD) among those "per protocol" (PP) study subjects with "pronounced" diarrhea (i.e. whose diarrhea resolved >24 hours after start of study drug), by treatment group.

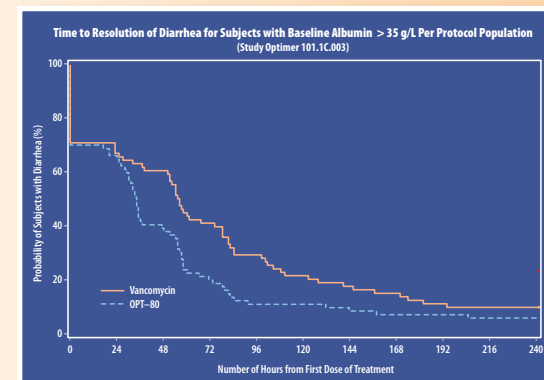


Figure 3. "Survival curve" analysis of time to resolution of diarrhea (TTROD) among those "per protocol" (PP) study subjects with baseline albumin level >35 gm/L, by treatment group.

## Conclusions

The Phase 3 clinical trial of FDX vs. VAN has been useful in assessing differences in TTROD between the 2 therapies studied.

In patients with more pronounced diarrhea (i.e. not resolving in the first 24 hours of therapy), FDX was associated with a faster TTROD than VAN.

In patients with albumin levels > 35 g/L, the difference in TTROD between FDX and VAN was even more marked.

## Discussion

This is the first study to show a difference in TTROD among two therapeutic agents for the treatment of CDI. Although both FDX and VAN appeared equivalent in resolving diarrhea in the first 24 hours of therapy, those study subjects with more pronounced diarrhea (i.e. diarrhea lasting longer than 24 hours on therapy) manifested a faster resolution of their diarrhea with FDX than with VAN.

Since symptomatic diarrhea due to CDI has been associated with higher *C. difficile* spore counts in the environment,<sup>4</sup> it is possible that decreasing the duration of diarrhea may have a direct impact on the spread of CDI in healthcare facilities. Reduction in the total days of diarrhea due to CDI in a healthcare facility may result in lower overall environmental spore contamination and decreased CDI rates. Faster resolution of diarrhea may also lead to earlier discharge of nosocomial CDI patients from hospital. Most importantly for the patient, shorter duration of diarrhea is an important clinical parameter which benefits their health and quality of life.

## References

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## Author Disclosure Information

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