Evaluation of Bezlotoxumab in Prevention of Recurrent *C. Difficile* Infection: A Multicenter Single-Arm Study in Office Infusion Centers

Richard L. Hengel[1] ,Timothy E. Ritter[2], Ramesh V. Nathan[2], Lucinda J. Van Anglen[4], Claudia P. Schroeder[4], Stephen W. Marcella[5], Kevin W. Garey[6]

[1]Atlanta ID Group, Atlanta, GA; [2]Luminal Research Division, Texas Digestive Disease Consultants, Southlake, TX; [3]Mazur, Statner, Dutta, Nathan PC, Thousand Oaks, CA; [4]Healix Infusion Therapy, Sugar Land, TX; [5]Center for Observational and Real World Evidence, Merck & Co., Inc., Kenilworth, NJ, USA; [6]University of Houston College of Pharmacy, Houston, TX

INTRODUCTION

Bezlotoxumab (BEZ, Zinplava™) was approved by the FDA in October 2016 for prevention of *C. difficile* infection (CDI) in adults receiving standard-of-care (SoC) therapy and are deemed at high risk for recurrent disease.[1]

The MODIFY trials have demonstrated significantly lower rates of rCDI in patients (pts) receiving BEZ plus SoC compared to those with SoC alone.[2,3]

Presently, little is known about CDI recurrence rates and factors associated with recurrence in patients (pts+ receiving BEZ in the real-world. This study describes characteristics of pts receiving a single dose of BEZ in U.S. outpatient infusion centers (OICs) and analyzes CDI recurrences.

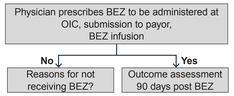
OBJECTIVES

- To characterize study cohort and utilization of BEZ in OICs
- To evaluate CDI recurrence rate after 90 days following BEZ dose
- To determine potential risk factors associated with CDI recurrence

METHODS

- **Study design:** retrospective multicenter single-arm
- **Data source**: pharmacy and electronic health records from March 2017 through December 2017 for treated patients and through March 2018 for follow-up patients
- **Index CDI definition**: episode of CDI (ICD-10 code A04.7) resulting in referral for BEZ
- **Patient population**: CDI pts ≥18 years from 24 OICs in the U.S.
- **Study parameters**: demographics, clinical characteristics, reasons for not receiving BEZ and CDI risk factors. Utilization characteristics include time from positive *C. difficile* test to initiation of BEZ, time from initiation of SoC to BEZ, laboratory test confirming toxigenic *C. difficile*, and type/duration of SoC antibiotic
- **CDI recurrence**: assessed 90 days post BEZ by MD visit or phone call defined as:
  - recurrence of diarrhea lasting ≥2 days and
  - medical intervention (SoC antibiotic, FMT) with or without positive stool test for toxigenic *C. difficile*
- **Statistical analysis**: continuous data are reported as mean or medians, categorical data as counts and percentages. Risk factors for rCDI were assessed using Pearson Chi-square test. Kaplan-Meier method was used to describe time to CDI recurrence stratified by previous number of CDI episodes and analyzed using the log-rank Chi-Square test. A p<0.05 was considered significant.

Figure 1. Study Design



STUDY COHORT

Table 1. Demographics of Patients Referred for BEZ

Characteristics	Results (N=137)
Age (mean years±SD)	63±17
Gender female, n (%)	87 (64)
Hospital stay within 4 weeks of current CDI episode, n (%)	61 (44)
length of stay, days (mean±SD)	6±4
Primary payor, n (%)	
federally funded	91 (67)
commercial	44 (32)
private	2 (1)

Table 2. Reasons for Patients Not Receiving BEZ

Specific Reason	Results (N=57)
Payor denial	24 (42%)
outside SoC therapy window	9
positive *C. difficile* test outside window	13
negative *C. difficile* test	2
Competing problem	11 (20%)
treatment of other infection or disease	8
expired prior to infusion	2
history of congestive heart failure	1
Patient financial hardship	8 (14%)
Physician decision	7 (12%)
continued SoC	5
fecal microbiota transplant	2
Patient decision	4 (7%)
Transfer of care	3 (5%)

Table 3. Clinical Characteristics of Patients Receiving BEZ

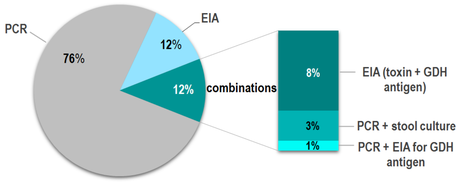
Variables	Results (N=80)
Age (mean years±SD)	65±16
Charlson score (mean±SD)	4.3±3.2
Setting of care, n (%)	
hospital stay within 4 weeks	33 (41)
community	47 (59)
CDI risk factor, n (%)	
prior 6-month CDI episode	59 (74)
age ≥65 years	50 (63)
immunocompromised*	38 (48)
gastric acid suppressant use	36 (45)
severe CDI on presentation†	25 (31)
chronic renal diseae	21 (26)
Non-CDI antibiotic use 4 weeks prior to CDI	20 (25)
prior fecal microbiota transplant	11 (22)
inflammatory bowel disease	10 (13)
No. of CDI risk factors per patient	
mean±SD	3.7±1
>2 CDI risk factors, n (%)	62 (78)
No. of CDI episodes per patient	
mean±SD	3.1±1
>2 CDI episodes, n (%)	54 (68)

*; due to medication use (steroid, PD-L1 inhibitor, chemotherapy) or condition (immune deficiency, transplant solid organ or HSCT/autologous or allogeneic, absolute neutrophil count <500 cells/mL).

†; defined by any of the following: albumin ≤3.0 g/dl, colectomy related to CDI, creatinine ≥1.5x baseline, hypotension or shock, ICU stay related to CDI, toxic megacolon, WBC ≥15,000 cells/mL.

RESULTS

Figure 2. Diagnostic Method for Detection of *C. difficile*

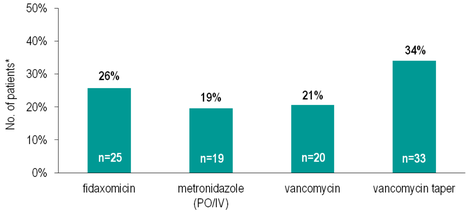


Abbreviations: EIA; enzyme immunoassay for toxins A, B, GDH; glutamate dehydrogenase, PCR; polymerase chain reaction

Table 4. Utilization Characteristics of BEZ in the Outpatient Setting

Variable	Results
Time from *C. difficile* test to BEZ (n=80)	
mean days±SD	22±20
median days (range)	14 (3 to 97)
Time from hospital discharge to BEZ (n=33)	
mean days±SD	11±8
median days (range)	10 (1 to 34)

Figure 3. Overall Use of SoC Antibiotics for Current CDI Episode



- A total of 17 pts (21%) received concomitant (n=13) and sequential (n=5) SoC antibiotics during the course of CDI therapy
- Metronidazole was administered to 16 pts as short-term IV therapy during prior hospitalization

Table 5. SoC Antibiotic Therapy at Time of BEZ

Primary SoC antibiotic at time of BEZ	No of pts (percent)	Time from initiation of SoC to BEZ (days)	
		Mean ± SD	Median (range)
Fidaxomicin	25 (31%)	12 ± 6	10 (9-32)
Metronidazole (PO)	3 (3%)	20 ± 10	14 (14-32)
Vancomycin fixed dose	20 (25%)	18 ± 7	14 (10-34)
Vancomycin tapered regimen	33 (41%)	49 ± 26	42 (15-142)

Figure 4. CDI Recurrence Rate at 90 Days post BEZ

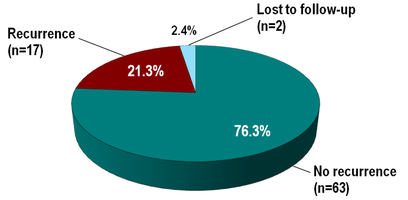
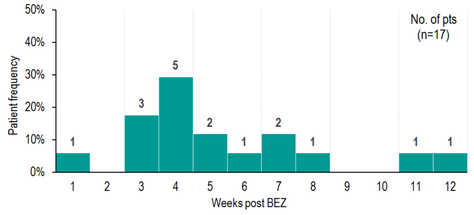
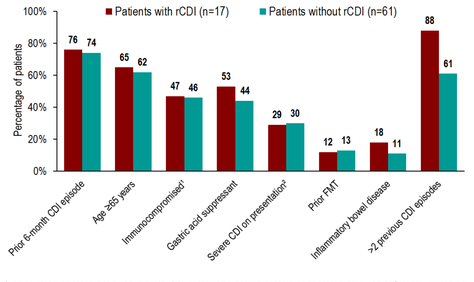


Figure 5. Distribution of CDI Recurrences over Time



- Mean and median times to recurrence were 34±20 and 28 days, respectively
- 6 pts were hospitalized due to rCDI. 3 pts with rCDI received subsequent FMT

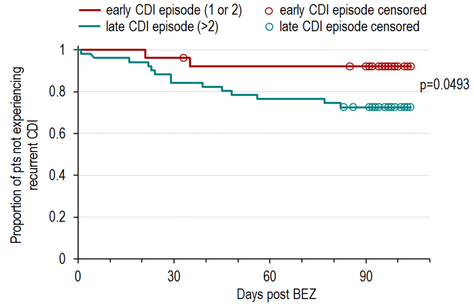
Figure 6. Assessment of Risk Factors of CDI Patients Receiving BEZ



†; determined by medication use (steroid, PD-L1 inhibitor, chemotherapy) or condition (immune deficiency, transplant solid organ or HSCT/autologous or allogeneic, absolute neutrophil count <500 cells/mL)

‡; defined by any of the following: albumin ≤3.0 g/dl, colectomy related to CDI, creatinine ≥1.5x baseline, hypotension or shock, ICU stay related to CDI, toxic megacolon, WBC ≥15,000 cells/mL

Figure 7. Kaplan Meier Plot of CDI Recurrence Following BEZ



CONCLUSIONS

- **This study provides real-world data on pt characteristics and use of BEZ in the outpatient setting.**
  - all patients received BEZ in OICs
  - the referral-to-treatment rate was 58% with payor denial being the primary reason for non-treatment
  - patient population was highly comorbid including multiple CDI risk factors
  - diagnosis of CDI was confirmed primarily using PCR assay
  - the majority of patients received vancomycin as SoC antibiotic
- **BEZ administered as single infusion in OICs demonstrated 76.3% efficacy in the prevention of recurrent CDI at 90 days.**
- **Patients with >2 prior CDI episodes had a significantly higher risk of CDI recurrence (p=0.049).**
- **Results were comparable with data reported for MODIFY trials[2,3], despite a highly comorbid patient population with multiple CDI risk factors and prior CDI episodes.**
- **BEZ during SoC therapy for CDI provides an effective treatment option for adults, especially for patients at high risk recurrence.**

Disclosures

- This study was sponsored by Merck & Co., Inc., Rahway, NJ, USA

References

1. Wilcox MH, Gerding DN, Poxton IR et al. Bezlotoxumab for prevention of *Clostridium difficile* infection, N Engl J Med 376:305-17, 2017
2. Gene KM, Colleen MB et al. Increasing incidence of multiply recurrent *Clostridium difficile* infection in the United States. Ann Intern Med 167:152-58, 2017
3. Gerding DN, Kelly CP et al. Bezlotoxumab for prevention of recurrent *Clostridium difficile* infection in patients at increased risk for recurrence. Clin Infect Dis https://doi.org/10.1093/cid/ciy171, 10 March 2018

https://bit.ly/2ByNIAO

Presented at IDWeek®, San Francisco, CA, USA, October 3-7, 2018